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*Research Article*

# The Incidence of, and Patterns of Antibiotic Resistance among Culture-Proven Bacterial Neonatal Sepsis in Developing Countries

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***Abstract***

***Aim:*** *The menace of antimicrobial resistance, especially in neonatal sepsis, is growing at an alarming rate. The situation is aggravated more in developing countries; it is estimated that neonatal infection incidence ranges from 5.5 -170 cases /1,000 live births for blood culture-proven infections in developed. Also, it is estimated neonatal sepsis account for approximately 50% of neonatal deaths in developing countries.*

*This systematic review aims to look at studies describing antibiotic resistance in positive blood cultures among neonatal populations in developing countries.*

***Methods:*** *The author searched Two major scientific databases (Ovid Medline & Embase), and other WHO regional online sites.*

*The search was initially conducted on April 1, 2019, and repeated on June 11, 2020.*

*Studies were included if they defined how sepsis cases were diagnosed or identified and provided information about the total number of blood cultures obtained, the number of bacterial isolates with details, and the number of patients enrolled. Only studies that complied with the minimum requirements for data inclusiveness described in the inclusion criteria were included.*

***Results:*** *The total sample size was 4,490 neonates with suspected sepsis that were analyzed in seven selected studies from the first search. The positive culture percentage was 45.3%; the predominant organisms were gram-negative with 76.1% of the total positive cultures*

*The mean resistance rate was 37.8% for all tested antibiotics.*

*In general, the highest resistance rate were for amoxicillin (69.1%), ceftazidime (72.0%), ampicillin (74.6%), aztreonam (76.9%) and clarithromycin (83.2%), with the lowest being for linezolid (0.0%), meropenem (4.3%), ampicillin/sulbactam (4.8%), rifampicin (5.0%), Cefepime (7.7%), and imipenem (8.4%).*

*As for antibiotics resistance analyzed in the second search, all four papers revealed a high percentage resistance against most commonly used antibiotics (amoxicillin, ampicillin, and gentamicin)*

***Conclusion:*** *The presented data only views bacterial AMR rates in developing countries, which raises particular concern about the high level of resistance reported among gram-negative pathogens, especially Klebsiella and E. coli to gentamicin, ampicillin to third-generation cephalosporins.*

*The implication of this search for clinical practice is crucial. Rigorous clinical and epidemiological surveillance based on proficient and inexpensive microbiology is required to deliver precise data on AMR, which, in turn, can enable the updating of local treatment guidelines and antibiotic stewardship programs.*

## 1. Introduction

The burden of maternal and child mortality is a leading problem worldwide, and developing countries account for over 99% of this weight. (1)

It is estimated that neonatal infection incidence ranges from 5.5 cases/1,000 live births for blood culture-proven infections in developed countries too high as 170 cases/1,000 births for clinically diagnosed bacterial infections in developing countries. It is Also estimated that infections account for approximately 23% of neonatal deaths in developed countries and 50% in developing countries. (2)

The menace of antimicrobial resistance is growing at an alarming rate, and the situation is aggravated more in developing countries. (3) The strain that antimicrobial resistance inflicts on neonatal health, mortality, morbidity, and quality of life is significant but difficult to measure with precision, especially in developing countries where surveys and available data do not fulfill objective quantitative evaluation standards. (4). The atypical localized statistics, unreliable laboratory quality, and limited microbiological investigative amenities pose other kinds of difficulty. (5)

The resistance rate bacteria show to keystone antibiotics used in neonatal sepsis was estimated in developing countries` hospital settings to reach as high as 97% against ampicillin in Klebsiella species and 72% in E. coli species. Against gentamicin, on the other hand, resistance reaches 60% in Klebsiella species and 13% in E. coli species. Furthermore, the Staphylococcus aureus resistance to methicillin has reached 38%. (6) Resistance escalation is widely noticed among reserved regimens for the second- or third-line treatment (such as third-generation cephalosporins, carbapenems, and piperacillin/tazobactams) without reliable bacteriological

capacities, professional guidance, or passable prescription regulators. (7)

Antimicrobial resistance (AMR) develops through several mechanisms, such as a modified antimicrobial target, enzymatic hydrolysis/degradation, efflux, and impermeability. Furthermore, very recently, scientists discovered cell-wall deficient (L-form changing) bacteria. (8) This resistance is interceded by various resistance genes that develop because of antimicrobial selection compression due to the improper use of antimicrobial drugs and is heightened by the new antimicrobial agents in the current therapeutic era. (9) however, some reports suggest that antibiotic resistance is a natural (ancient) phenomenon that preludes the contemporary irresponsible antimicrobial use. (10)

Hence, it is essential to investigate antibiotic resistance in developing countries to measure the rate of changes in the pattern of resistance across time and geographical differences.

| authors | Akindolire et al. | Amin, A. J. et al. | Macharashvili, Nino et al. | Mohammed, Doaa et al. | Nikkhoo et al. | Yadav, Nikita. Et al. | Ullah, Obaid. Et al. | Sum of All Organisms Tested |
|---|---|---|---|---|---|---|---|---|
| **positive culture** | 25 | 101 | 126 | 161 | 30 | 59 | 1534 | 2036 |
| **sample size** | 202 | 163 | 200 | 418 | 472 | 350 | 2685 | 4490 |
| **positive culture ratio** | 12.4% | 62.0% | 63.0% | 38.5% | 6.4% | 16.9% | 57.1% | 45.3% |
| **Total BACTERIAL isolates** | 25 | 101 | 120 | 161 | 30 | 59 | 1534 | 2030 |
| **Staphylococcus aureus nonspecific** | 13 | 13 | 15 | 42 | | 21 | 300 | 404 |
| **CoNS** | | 4 | 7 | | 8 | 6 | 28 | 53 |
| **Staphylococcus aureus MRSA** | 4 | | | | | | | 4 |
| **Staphylococcus aureus MSSA** | 9 | | | | | | | 9 |
| **Group B streptococci** | | | 6 | 6 | 1 | | | 13 |
| **Group D streptococci/Enterococcus** | 1 | | | | | | | 1 |
| **All gram positives** | 16 | 30 | 28 | 48 | 9 | 27 | 328 | 486 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Klebsiella species** | 3 | 28 | 45 | 55 | 6 | 9 | 102 | 248 |
| **E. COLI** | 1 | 12 | 11 | 18 | 3 | 4 | 811 | 860 |
| **Pseudomonas** | | 8 | 6 | 24 | | 4 | 199 | 241 |
| **Enterobacter** | 2 | | 23 | | 11 | 6 | | 42 |
| **Serratia species** | | | | | 1 | | | 1 |
| **Proteus species** | | | | 12 | | | 87 | 99 |
| **Salmonella species** | | | | | | 1 | 7 | 8 |
| **Citrobacter species** | | | | 4 | | 1 | | 5 |
| **Acinetobacter species** | | 23 | 7 | | | 7 | | 37 |
| **other gram-negative bacteria** | 3 | | | | | | | 3 |
| **All gram negatives** | 9 | 71 | 92 | 113 | 21 | 32 | 1206 | 1544 |

Table 1: distribution of bacterial isolates in all selected studies

## 2. Materials and Methods

As a systematic review, this review follows a strict and standard method of searching and appraising evidence in selected papers; the Cochrane criteria for systematic review synthesis were applied. (11)

### 2.1. Search Strategy

The search for available evidence was conducted by systematic scrutiny commensurate with the PRISMA prerequisites (12) to identify studies relevant to the search question. Keyword searches were performed by combining Medical Subject Heading (MeSH) in Medline, Index Terms Subject Heading, and search-field descriptors like [tiab] and [tw]. Additionally, truncation with an asterisk after the word endings was used.

The identified keywords are listed initially in the logic grid term (13) with search-field descriptors and wildcard characters beside each term in the grid. The grid was continuously updated after each search.

The relevant articles were also searched for citations to retrieve any related papers. Boolean logic search terms and synonyms were connected by the Boolean operators OR, AND, and NOT to combine the keywords in each search field.

| Antimicrobial Resistance Rates of All Gram Positives [A] | | |
|---|---|---|
| Antibiotic Agents | Resistance Rate (%) As Reported in Different Studies [B] | Mean Resistance Rate (%) [C] |
| Penicillin | 0.0%[1], 30.0%[2], 100.0%[4] Median 30.0% | 57/94 (60.6%) |
| Piperacillin/Tazobactam | 28.6%[3], 50.0%[4] Median 39.3% | 32/76 (42.1%) |
| Amoxicillin-Clavulanic Acid | 81.3%[1], 46.4%[3], 29.2%[4], 59.8%[7] Median 53.1% | 236/420 (56.2%) |
| Amoxicillin | 75.0%[1], 57.1%[3], 29.6%[6] Median 57.1% | 36/71 (50.7%) |
| Amikacin | 25.0%[1], 62.5%[4], 11.1%[6], 25.3%[7] Median 25.2% | 120/419 (28.6%) |
| Gentamicin | 43.8%[1], 30.0%[2], 50.0%[4], 88.9%[5], 7.4%[6] , 55.8%[7] Median 46.9% | 233/458 (50.9%) |
| Cefotaxime | 50.0%[1], 3.6%[3], 100.0%[4], 55.6%[5], 37.0%[6], 49.4%[7] Median49.7% | 234/456 (51.3%) |
| Cefuroxime | 37.5%[1] | 6/16 (37.5%) |
| Ceftazidime | 93.8%[1], 6.7%[2], 68.3%[7] Median 68.3% | 241/374 (64.4%) |
| Cephalothin | 10.0%[2], 66.7%[5] Median 38.3% | 9/39 (23.1%) |
| Cefixime | 12.5%[1], 66.7%[5] Median 39.6% | 8/25 (32.0%) |
| Meropenem | 50.0%[1], 3.6%[3] Median 26.8% | 9/44 (20.5%) |
| Vancomycin | 6.3%[1], 0.0%[2], 3.6%[3], 60.4%[4], 45.4%[7] Median 6.3% | 180/450 (40.0%) |
| Ampicillin | 31.3%[1], 60.0%[2], 62.5%[4], 88.9%[5], 77.8%[6], 46.3%[7] Median 61.3% | 234/458 (51.1%) |
| Erythromycin | 0.0%[1], 76.7%[2], 46.4%[3], 48.1%[6] Median 47.3% | 49/101 (48.5%) |
| Cotrimoxazole | 21.4%[3], 44.4%[5] Median 32.9% | 10/37 (27.0%) |
| Ciprofloxacin | 43.8%[1], 10.0%[2], 21.4%[3], 62.5%[4], 22.2%[5], 29.6%[6], 40.9%[7] Median 29.6% | 190/486 (39.1%) |
| Chloramphenicol | 12.5%[1] | 2/16 (12.5%) |
| Ampicillin/Sulbactam | 31.3%[1] | 5/16 (31.3%) |
| Ampicillin-Cloxacillin | 50.0%[1] | 8/16 (50.0%) |
| Ofloxacin | 25.0%[1], 14.8%[6], 24.4%[7] Median 24.4% | 88/371 (23.7%) |
| Levofloxacin | 23.3%[2] | 7/30 (23.3%) |
| Oxacillin | 68.8%[1], 26.7%[2], 35.7%[3] Median 35.7% | 29/74 (39.2%) |
| Piperacillin | 3.3%[2], 0.0%[3] Median 1.7% | 1/30 (3.3%) |
| Clindamycin | 26.7%[2], 39.3%[3] Median 33.0% | 19/58 (32.8%) |
| Tetracycline | 3.3%[2], 35.7%[3], 100.0%[5] Median 35.7% | 20/67 (29.9%) |
| Linezolid | 0.0%[2] | 0/30 (0.0%) |
| Doxycycline | 33.3%[2], 53.4%[7] Median 43.3% | 185/358 (51.7%) |
| Ceftriaxone | 6.7%[2], 14.3%[3], 33.3%[5], 61.0%[7] Median 23.8% | 209/395 (52.9%) |
| Moxifloxacin | 21.4%[3] | 6/28 (21.4%) |
| Rifampicin | 21.4%[3] | 6/28 (21.4%) |
| Imipenem | 3.6%[3], 50.0%[4], 6.7%[7] Median 6.7% | 47/404 (11.6%) |
| Aztreonam | 100.0%[4], 86.9%[7] Median 93.4% | 333/376 (88.6%) |
| Azithromycin | 100.0%[4] | 48/48 (100.0%) |

| | | |
|---|---|---|
| Cefoperazone | 48.8%[7] | 160/328 (48.8%) |
| Cefpirome | 28.0%[7] | 92/328 (28.0%) |
| Cephradine | 51.8%[7] | 170/328 (51.8%) |
| Clarithromycin | 64.9%[7] | 213/328 (64.9%) |
| Enoxacin | 40.5%[7] | 133/328 (40.5%) |
| Nalidixic Acid | 73.8%[7] | 242/328 (73.8%) |
| Tobramycin | 46.6%[7] | 153/328 (46.6%) |
| Positive Cultures | 25[1], 101[2], 120[3], 161[4], 30[5], 59[6], 1534[7] | Total 2030 |
| Sample Size | 202[1], 163[2], 200[3], 418[4], 472[5], 350[6], 2685[7] | Total 4490 |
| No. Of Isolates | 16[1], 30[2], 28[3], 48[4], 9[5], 27[6], 328[7] | Total 486 |

[A] (7/7 Studies)[1]Akindolire, Abimbola. et. al., [2]Amin, A. et. al., [3]Macharashvili, et. al., [4]Mohammed, et al., [5]Nikkhoo, Bahram et al., [6]Yadav, Nikita. et al., [7]Ullah,Obaid. et al.,

[B] Number of Resistant Strains / Total Number of Strains in Each Study, Expressed As %.

[C] Mean Resistance Rate (%) = Sum of All Resistant Organisms / Sum of All Organisms Tested.

Table 2: Antimicrobial Resistance Rates of All Gram Positives

| Antimicrobial Resistance Rates of All Gram Negatives [A] | | |
|---|---|---|
| Antibiotic Agents | **Resistance Rate (%) As Reported in Different Studies [B]** | **Mean Resistance Rate (%) [C]** |
| Penicillin | 0.0%[1], 92.0%[4] **Median** 46.0% | 104/122 (85.2%) |
| Piperacillin/Tazobactam | 2.8%[2], 21.7%[3], 58.4%[4] **Median** 21.7% | 88/276 (31.9%) |
| Amoxicillin-Clavulanic Acid | 11.1%[1], 15.2%[3], 69.0%[4], 8, 0.2%[7] **Median** 42.1% | 1060/1420 (74.6%) |
| Amoxicillin | 77.8%[1], 78.3%[3], 81.3%[6] **Median** 78.3% | 105/133 (78.9%) |
| Amikacin | 0.0%[1], 42.3%[2], 6.5%[3], 57.5%[4], 57.1%[5], 15.6%[6], 47.2%[7] **Median** 42.3% | 687/1544 (44.5%) |
| Gentamicin | 0.0%[1], 25.4%[2], 15.2%[3], 86.7%[4], 71.4%[5], 15.6%[6], 73.5%[7] **Median** 25.4% | 996/1544(64.5%) |
| Cefotaxime | 0.0%[1], 9.9%[2], 22.8%[3], 100.0%[4], 57.1%[5], 71.9%[6], 78.6%[7] **Median** 57.1% | 1124/1544 (72.8%) |
| Cefuroxime | 33.3%[1] | 3/9 (33.3%) |
| Ceftazidime | 0.0%[1], 35.2%[2], 22.8%[3], 71.9%[6], 76.9%[7] **Median** 35.2% | 997/1410 (70.7%) |
| Cefixime | 0.0%[1], 61.9%[5] **Median** 31.0% | 13/30 (43.3%) |
| Meropenem | 0.0%[1], 5.6%[2], 0.0%[6] **Median** 0.0% | 4/112 (3.6%) |
| Vancomycin | 33.3%[1], 79.6%[4] **Median** 56.5% | 93/122 (76.2%) |
| Ampicillin | 33.3%[1], 76.1%[4], 90.5%[5], 62.5%[6], 88.1%[7] **Median** 76.1% | 1191/1381 (86.2%) |
| Erythromycin | 1.4%[2] | 1/71 (1.4%) |
| Cotrimoxazole | 42.4%[3], 47.6%[5], 56.3%[6] **Median** 47.6% | 67/145 (46.2%) |
| Ciprofloxacin | 0.0%[1], 29.6%[2], 7.6%[3], 70.7%[4], 28.6%[5], 59.4%[6], 33.6%[7] **Median** 29.6% | 538/1544 (34.8%) |

| | | | |
|---|---|---|---|
| Chloramphenicol | 44.4%[1], 49.3%[2] | **Median** 46.9% | 39/80 (48.8%) |
| Levofloxacin | 5.6%[2] | | 4/71 (5.6%) |
| Ampicillin/Sulbactam | 0.0%[1], 2.2%[3] | **Median** 1.1% | 2/101 (2.0%) |
| Ampicillin-Cloxacillin | 88.9%[1] | | 8/9 (88.9%) |
| Ofloxacin | 11.1%[1], 18.8%[6], 24.5%[7] | **Median** 18.8% | 302/1247 (24.2%) |
| Oxacillin | 11.1%[1] | | 1/9 (11.1%) |
| Imipenem | 25.4%[2], 6.5%[3], 10.6%[4], 0.0%[6], 6.8%[7] | **Median** 6.8% | 118/1514 (7.8%) |
| Aztreonam | 32.4%[2], 94.6%[4], 76.1%[7] | **Median** 76.1% | 1048/1390 (75.4%) |
| Piperacillin | 53.5%[2], 0.0%[6] | **Median** 26.8% | 38/103 (36.9%) |
| Tetracycline | 40.8%[2], 26.1%[3], 90.5%[5] | **Median** 40.8% | 72/184 (39.1%) |
| Cefepime | 4.2%[2], 15.2%[3] | **Median** 9.7% | 17/163 (10.4%) |
| Tobramycin | 10.9%[3], 74.5%[7] | **Median** 42.7% | 909/1298 (70.0%) |
| Ceftriaxone | 7.0%[2], 21.7%[3], 57.1%[5], 71.4%[7] | **Median** 39.4% | 898/1390 (64.6%) |
| Moxifloxacin | 7.6%[3] | | 7/92 (7.6%) |
| Ticarcillin/Clavulanic Acid | 14.1%[3] | | 13/92 (14.1%) |
| Cefazolin | 12.0%[3] | | 11/92 (12.0%) |
| Nalidixic Acid | 52.9%[7] | | 638/1206 (52.9%) |
| Enoxacin | 21.4%[7] | | 258/1206 (21.4%) |
| Clarithromycin | 88.1%[7] | | 1063/1206 (88.1%) |
| Cephradine | 30.5%[7] | | 368/1206 (30.5%) |
| Cefpirome | 64.3%[7] | | 776/1206 (64.3%) |
| Azithromycin | 79.6%[4], 0.0%[5], 0.0%[6] | **Median** 0.0% | 90/145 (62.1%) |
| Cephalothin | 81.0%[5] | | 17/21 (81.0%) |
| Cefoperazone | 60.9%[7] | | 734/1206 (60.9%) |
| Doxycycline | 69.1%[7] | | 833/1206 (69.1%) |
| Positive Cultures | **25[1], 101[2], 120[3], 161[4], 30[5], 59[6], 1534[7]** | | **Total 2030** |
| Sample Size | **202[1], 163[2], 200[3], 418[4], 472[5], 350[6], 2685[7]** | | **Total 4490** |
| No. Of Isolates | **9[1], 71[2], 92[3], 113[4], 21[5], 32[6], 1206[7]** | | **Total 1544** |

[A] (7/7 Studies) [1]Akindolire. et al., [2]Amin, A et al., [3]Macharashvili. et al[*]., [4]Mohammed, [4]Doaa. et al., [5]Nikkhoo, Bahram. et al., [6]Yadav, Nikita . et al., [7]Ullah, Obaid. et al.

[B] Number of Resistant Strains / Total Number of Strains in Each Study, Expressed As %.

[C] Mean Resistance Rate (%) = Sum of All Resistant Organisms / Sum of All Organisms Tested.

[*] Susceptibilities for Acinetobacter lwoffi (N = 2), Burkholderia cepacia (N = 2), Serratia marcescens (N = 1), and Salmonella choleraesuis (N = 1) were not tested because of small numbers of isolates. Total 6 isolates.

Table 3: Antimicrobial Resistance Rates of All Gram Negatives

### 2.2. Literature review and data sources

Two major scientific databases Ovid (Medline & Embase) and Ebsco, were searched, in addition to WHO local index sites. The databases were carefully searched according to the predefined search criteria.

The subject headings and keywords are use,d as shown in table 3. This strategy of searching for terms was simplified when simple database engines, such as WHO, Index Medicus sites, were used.

The Endnote X9 software (Clarivate Analytics) was used for referencing and citation.

| Antimicrobial Resistance Rates Of total bacterial strains [A] | | |
|---|---|---|
| Antibiotic Agents | **Resistance Rate (%) As Reported in Different Studies** [B] | **Mean Resistance Rate (%)** [C] |
| Penicillin | 0.0%[1], 8.9%[2], 94.4%[4] **Median** 8.9% | 161/287 (56.1%) |
| Piperacillin/Tazobactam | 2.0%[2], 23.3%[3], 55.9%[4] **Median** 23.3% | 120/382 (31.4%) |
| Amoxicillin-Clavulanic Acid | 56.0%[1], 22.5%[3], 57.1%[4], 75.8%[7] **Median** 56.6% | 1296/1941 (66.8%) |
| Amoxicillin | 76.0%[1], 73.3%[3], 57.6%[6] **Median** 73.3% | 141/204 (69.1%) |
| Amikacin | 16.0%[1], 29.7%[2], 5.1%[3], 59.0%[4], 40.0%[5], 13.6%[6], 42.5%[7] **Median** 29.7% | 807/2030 (39.8%) |
| Gentamicin | 28.0%[1], 26.7%[2], 11.6%[3], 50.3%[4], 76.7%[5], 11.9%[6], 69.8%[7] **Median** 28.0% | 1229/2030(60.5%) |
| Cefotaxime | 32.0%[1], 6.9%[2], 18.3%[3], 100.0%[4], 56.7%[5], 55.9%[6], 72.4%[7] **Median** 55.9% | 1358/2030 (66.9%) |
| Cefuroxime | 36.0%[1] | 9/25 (36.0%) |
| Ceftazidime | 60.0%[1], 26.7%[2], 16.7%[3], 39.0%[6], 75.1%[7] **Median** 39.0% | 1238/1719 (72.0%) |
| Cefixime | 8.0%[1], 63.3%[5] **Median** 35.7% | 21/55 (38.2%) |
| Cephalothin | 3.0%[2], 76.7%[5] **Median** 39.8% | 26/101 (25.7%) |
| Meropenem | 32.0%[1], 4.0%[2], 0.8%[3], 0.0%[6] **Median** 2.4% | 13/305 (4.3%) |
| Vancomycin | 16.0%[1], 0.0%[2], 0.8%[3], 73.9%[4], 9.7%[7] **Median** 9.7% | 273/1941 (14.1%) |
| Ampicillin | 32.0%[1], 17.8%[2], 72.0%[4], 90.0%[5], 69.5%[6], 79.2%[7] **Median** 70.8% | 1425/1910 (74.6%) |
| Erythromycin | 0.0%[1], 23.8%[2], 10.3%[3], 22.0%[6] **Median** 16.2% | 50/305 (16.4%) |
| Cotrimoxazole | 35.7%[3], 46.7%[5], 30.5%[6] **Median** 35.7% | 77/209 (36.8%) |
| Ciprofloxacin | 28.0%[1], 23.8%[2], 10.3%[3], 68.3%[4]M 26.7%[5], 45.8%[6], 35.1%[7] **Median** 28.0% | 728/2030 (35.9%) |
| Chloramphenicol | 24.0%[1], 34.7%[2] **Median** 29.3% | 41/126 (32.5%) |
| Levofloxacin | 10.9%[2] | 11/101 (10.9%) |
| Clindamycin | 7.9%[2], 8.7%[3] **Median** 8.3% | 19/221 (8.6%) |
| Oxacillin | 48.0%[1], 7.9%[2], 7.9%[3] **Median** 7.9% | 30/246 (12.2%) |
| Imipenem | 17.8%[2], 5.6%[3], 22.4%[4], 0.0%[6], 6.8%[7] **Median** 6.8% | 165/1975 (8.4%) |
| Aztreonam | 22.8%[2], 96.3%[4], 78.4%[7] **Median** 78.4% | 1381/1796 (76.9%) |
| Piperacillin | 38.6%[2], 0.0%[6] **Median** 19.3% | 39/160 (24.4%) |
| Tetracyclines | 29.7%[2], 27.0%[3], 93.3%[5] **Median** 29.7% | 92/251 (36.7%) |
| Tobramycin | 7.9%[3], 68.6%[7] **Median** 38.3% | 1062/1654 (64.2%) |
| Ceftriaxone | 6.9%[2], 19.0%[3], 50.0%[5], 69.2%[7] **Median** 34.5% | 1107/1785 (62.0%) |
| Linezolid | 0.0%[2] | 0/101 (0.0%) |
| Moxifloxacin | 10.3%[3] | 13/120 (10.8%) |
| Rifampicin | 4.8%[3] | 6/120 (5.0%) |
| Ofloxacin | 20.0%[1], 16.9%[6], 24.4%[7] **Median** 20.0% | 390/1618 (24.1%) |
| Nalidixic Acid | 57.4%[7] | 880/1534 (57.4%) |

| | | |
|---|---|---|
| Enoxacin | 25.5%[7] | 391/1534 (25.5%) |
| Clarithromycin | 83.2%[7] | 1276/1534 (83.2%) |
| Cephradine | 35.1%[7] | 538/1534 (35.1%) |
| Cefpirome | 56.6%[7] | 868/1534 (56.6%) |
| Cefoperazone | 58.3%[7] | 894/1534 (58.3%) |
| Ampicillin/Sulbactam | 20.0%[1], 1.6%[3] **Median** 10.8% | 7/145 (4.8%) |
| Ampicillin-Cloxacillin | 64.0%[1] | 16/25 (64.0%) |
| Doxycycline | 9.9%[2], 65.7%[7] **Median** 37.8% | 1018/1635 (62.3%) |
| Cefepime | 3.0%[2], 11.6%[3] **Median** 7.3% | 17/221 (7.7%) |
| Ticarcillin/Clavulanic Acid | 10.8%[3] | 13/120 (10.8%) |
| Cephazolin | 9.1%[3] | 11/120 (9.2%) |
| Azithromycin | 85.7%[4], 0.0%[6] **Median** 42.9% | 138/220 (62.7%) |
| Positive Cultures | **25[1], 101[2], 120[3], 161[4], 30[5], 59[6], 1534[7]** | **Total 2030** |
| No. Of Isolates | **25[1], 101[2], 120[3], 161[4], 30[5], 59[6], 1534[7]** | **Total 2030** |
| Sample Size | **202[1], 163[2], 200[3], 418[4], 472[5], 350[6], 2685[7]** | **Total 4490** |

[A] (7/7 Studies) [1]Akindolire. et al., [2]Amin, A. et al., [3]Macharashvili. et al.[*], [4]Mohammed, Doaa .et al.[5]Nikkhoo. et al., [6]Yadav, Nikita. et al,[7] Ullah, Obaid. et al.

[B] Number of Resistant Strains / Total Number of Strains in Each Study, Expressed As %.

[C] Mean Resistance Rate (%) = Sum of All Resistant Organisms / Sum of All Organisms Tested.

[*] Susceptibilities for Acinetobacter lwoffi (N = 2), Burkholderia cepacia (N = 2), Serratia marcescens (N = 1), and Salmonella choleraesuis (N = 1) were not tested because of small numbers of isolates. Total 6 isolates.

Table 4: Antimicrobial Resistance Rates Of total bacterial strains

**2.3. Selection of studies:**

Every article identified in this manner was considered a candidate for inclusion and retrieved as full text. All cited references from included articles were also screened for inclusion. The search was conducted on Februar20, 201919, and again on Apri1, 201919.

The included studies were required to identify a well-accepted or acknowledged standard for antibiotic susceptibility testing (?) such as the Clinical and Laboratory Institute (CLSI) (14). Studies were included if they defined how sepsis cases were diagnosed or identified and provided information about the total number of blood cultures obtained, the number of bacterial isolates with details, and the number of patients enrolled. Only studies that complied with the minimum requirements for data inclusiveness described in the inclusion criteria were included.

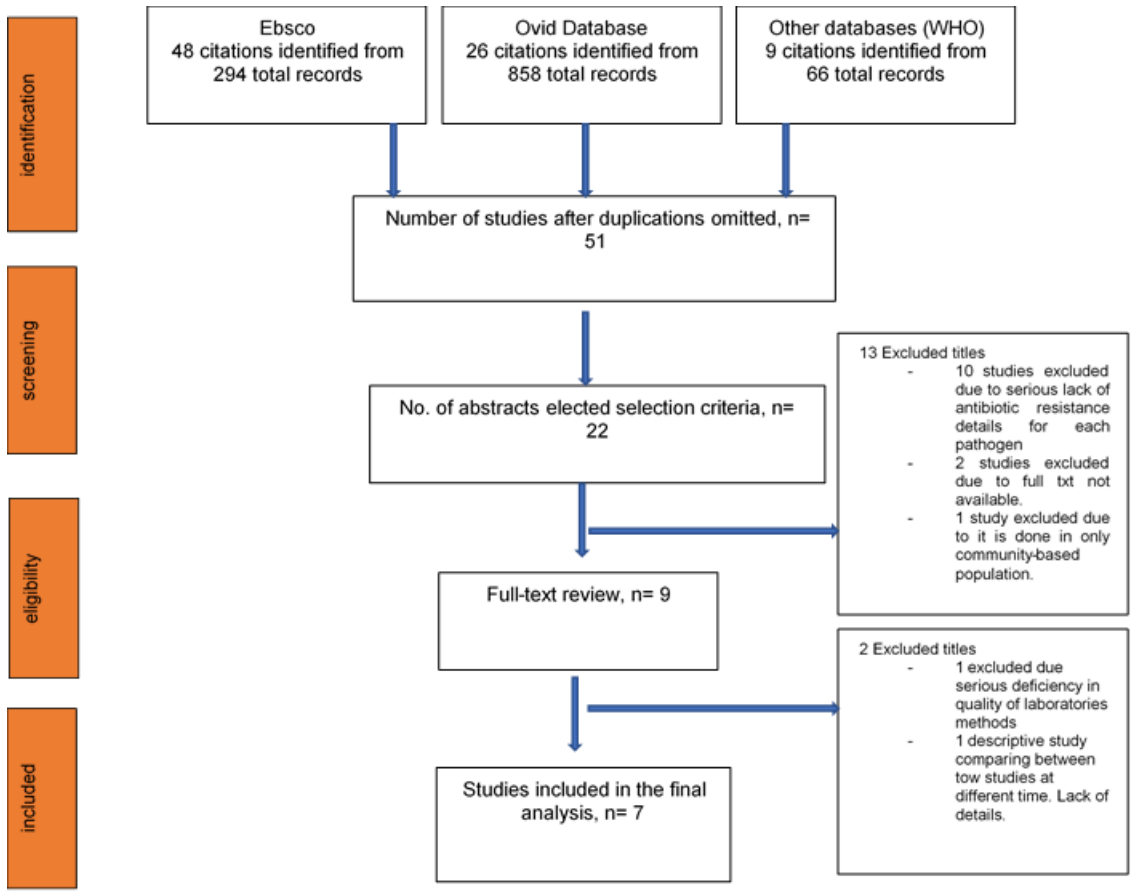


Figure 1: Prisma Flowchart depicting stages of article selection from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10

### 2.4. Data abstraction

Relevant data from the selected papers were extracted and transferred into an Excel file. The details of excluded titles listed in the table criteria of excluded studies are on supplementary file.

### 2.5. Study validity and quality assessment

Qualitative description and ranking of studies were initially done after the selection of full article reviews. By applying essential codes from the Working Group for Grading of Recommendations Assessment, Development, and Evaluation (GRADE)(15), with some adjustments and modifications were explained in the Child Health Epidemiology Reference Group reviews. (16) Critical Appraisal Skills Programme

### 2.6. Characteristics of the Selected Studies

Seven studies were selected for the final analysis. (17-23) All were conducted in hospital settings between 2003 and 2014. One was a prospective cohort study(20), another was a nested case-control study (21), and the remaining were cross-sectional analytical studies. The GRADE level of selected studies ranged from very low to moderate grade.

Four studies discussed all types of neonatal sepsis. (18, 19, 22, 23) Meanwhile, two studies examined nosocomial neonatal sepsis (20, 21), and one reviewed only early neonatal sepsis. (17)

The selected papers represented Asia (18, 19, 21-23) and Africa (17, 20), but none were set for South America. All studies were assessed for their quality of laboratory methods.

#### 2.6.1. Statistical analysis

Data were entered onto an Excel spreadsheet and summarized using descriptive data analysis with AnalystSoft Inc.'s Stat Plus:mac, version 7, a statistical analysis program for macOS® http://www.analystsoft.com/en/. Categorical and continuous variables and frequency tables were obtained. Since some studies only contained data about antibiotic susceptibility, the data were manually transformed into antibiotic-resistant form.

## 3. Results and Data analysis

Seven papers were selected for the final analysis. The total sample size was 4,490 neonates with suspected sepsis. There was a noticeable variation in sample size between the studies (sample size median of 350, range 163_2,685 neonates).

The studies were performed in the in-hospital setting. Of these, 2,036 (only 2,030 isolates are counted, as six isolates are dropped from Macharashvili. et al.) positive blood cultures were identified, With a positive culture percentage of 45.3%. (the median was 38.5%, and the average was 6.5% – 63%). The gram-negative bacteria represent the majority of isolates at 1,544.

Missing data was only identified in a single study. (19) (because in six cases, the data was dropped due to a small number of isolates). All studies, except one, discussed the geographical and demographic data of the studied samples. (18)

All selected studies, except one, met the recommendations of the National Committee for Clinical Laboratory Standards (CLSI) breakpoint values. (17) Also, only one study declared that its laboratories were accredited by a specific accreditation institute. (18) None of the studies discussed timing, duration, dose provided, and DDD (defined daily dose) of antibiotics given to septic neonates. Two studies utilized automated culture

techniques (17, 19)

### 3.1.1. Antibiotic resistance of Gram-positive bacteria

Overall, for gram-positive organisms, 486 isolates (23.9%) of 2,030 positive cultures were examined by all seven studies (Akindolire, Abimbola, et Al.; Amin, A., et Al.; Macharashvili et al.; Mohammed et al.; Nikkhoo, Bahram, et al.; Yadav, Nikita, et al.; and Ullah, Obaid, et al.).

Aztreonam and azithromycin hit the highest resistance rate (88.6% and 100%), while piperacillin (3.3), linezolid (0%), and vancomycin (6.3%) hit the lowest.

All other agents were shown to have a low to moderate resistance rate, as demonstrated in from a clinical perspective, the widely used antibiotics for gram-positive bacteria, such as penicillin, ampicillin, and second-generation cephalosporins, show a moderate to high resistance pattern. And that was noticed not only for the general population of gram-positive pathogens but also for most subpopulations of gram-positive ones, such as staphylococcus and group B streptococcus.

On the other hand, there is insufficient data on specific anti-staphylococcus agents such as teicoplanin and linezolid. Researchers relied mainly on vancomycin (which has moderate resistance) in most papers tested in this review.

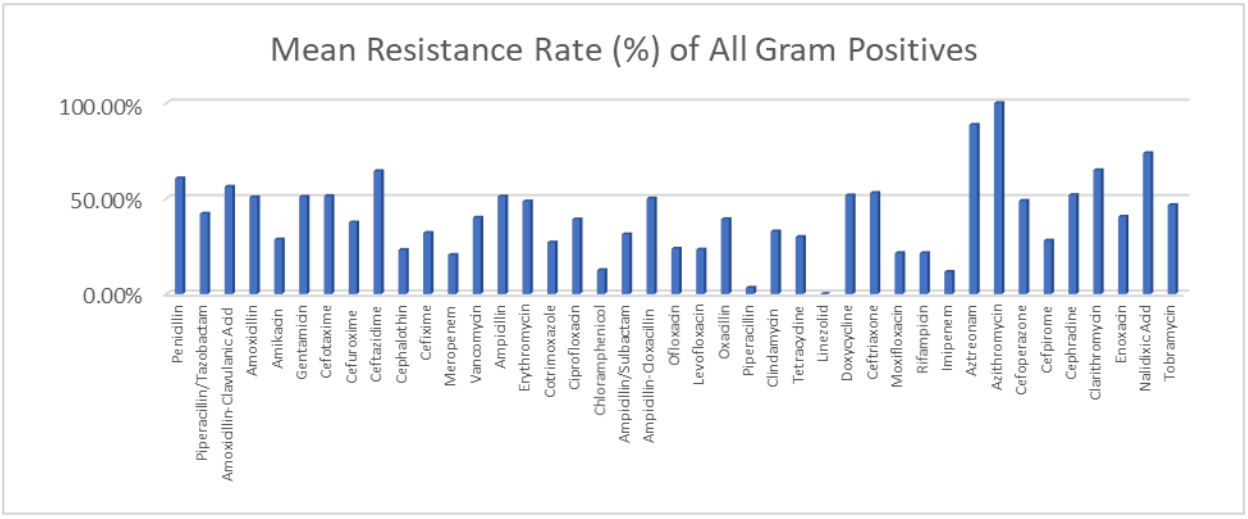


Figure 2: All Gram-Positive Bacteria's Antibiotic Resistance Rates

**3.1.2.Staphylococcus Aureus Species identified in** (20.2%) and was highly resistant to Penicillins and azithromycin.

Methicillin-resistant Staphylococcus aureus (MRSA) was isolated (30.7%) positive blood cultures. In comparison, Methicillin-sensitive Staphylococcus aureus (MSSA) was isolated in (69.2%) positive staphylococcus cultures with moderate resistance rate to most of the antibiotics.

**3.1.3.On the other hand, Coagulase-Negative Staphylococci (CoNS)** identified to have a low incidence rate (2.8%).

Group B streptococcus (4.1%) positive cultures were identified and showed a very high resistance rate among penicillin, amikacin, gentamicin, cefixime, and cotrimoxazole (100%).

Group D Streptococci/Enterococcus (11.9%) were identified. Enterococcus Had a very high resistance rate profile to most of the drugs examined. And similar resistant rates were determined for Streptococcus Pneumoniae.

### 3.2. Antimicrobial Resistance Rates of All Gram-negative Organisms

The data were collected from all seven studies (Akindolire. et al., Amin, A. et al., Macharashvili. et al., Mohammed. et al., Nikkhoo, Bahram. et al., Yadav, Nikita. et al., and Ullah, Obaid. Et. In a total of 2,030 positive cultures, 1,544 isolates (76.1%) of all gram-negative species, representing the majority of neonatal sepsis pathogens as expected.

The reported and mean resistance rates were very high for all commonly used antibiotics like penicillin, amoxicillin, ampicillin, ampicillin-cloxacillin, and moderately high for aminoglycosides. Both amikacin and gentamicin were examined in all seven studies (44.5% and 67.2%, respectively).

Resistance remained much lower for meropenem, levofloxacin, ampicillin/sulbactam, imipenem, and moxifloxacin. Noticing the moderate to the high prevalence of resistance for widely used antibiotics against gram-negative pathogens in daily clinical practice such as gentamycin, amikacin, ampicillin, and piperacillin is essential. In contrast, the new preparations of carbapenems are examined in only some studies, including Meropenem, which appeared in 3/7 reviews (67.2%), and imipenem, which appeared in 5/7 studies with resistance rate (7.8%).

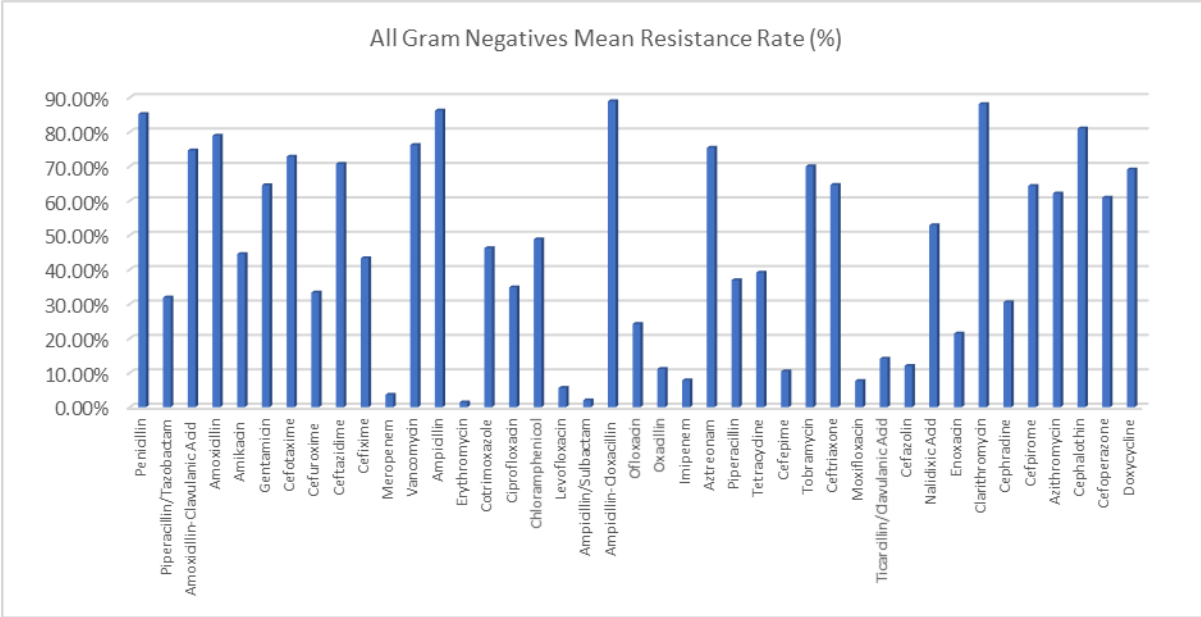


Figure 3: All Gram-Negative Antibiotic Resistance Rates

Klebsiella species were at the top of commonly isolated bacteria in three studies (Al, Amin, A. et al., Macharashvili, et al., Mohammed. et al.) at a rate of 27.7%, 35.7%, and 34.1%, respectively.

Cefixime, cephalothin, and ampicillin-cloxacillin reached the highest resistance rate (100%) compared to Cefuroxime and meropenem (0%).

**E. Coli** 860 isolates (42.3%) out of the 2,030 positive cultures identified with minimal resistance to both meropenem and imipenem.

Other subgroups revealed a different pattern of resistance. Pseudomonas incidence rate was 12.2% with a very high percentage resistance to Penicillin, Amoxicillin, Cotrimoxazole and Vancomycin.

While Enterobacter was slightly higher resistant (17.9%), on the other hand, Acinetobacter (13.2%), Serratia (3.3%), Citrobacter (2.2%), Salmonella (0.5%), and Proteus species (5.8%) revealed minimum incidence rate with variable antibiotics resistance pattern.

### 3.3. Antimicrobial Resistance Rates of Total Bacterial Strains

From the reviewed seven articles with a total sample size of 4,490 neonates, 2,036 positive blood cultures were identified (a total of six isolates dropped out from Macharashvili. et al., as the susceptibilities for Acinetobacter lwoffi (N = 2), Burkholderia cepacia (N = 2), Serratia marcescens (N = 1), and Salmonella choleraesuis (N = 1) were not tested because of the small numbers of isolates) with a positive blood culture

rate of 45.3%.

The predominant organisms were gram-negative with 76.1% of the total positive cultures, while the remaining were gram-positive bacteria.

Forty-four different antimicrobial agents were tested for susceptibility and resistance in different studies with different methods, technologies, and laboratory specifications. The average or mean resistance rate was 37.8% for all tested antibiotics. The median was 35.9% with a range of 0.0%_83.2% [Percentile 25% (Q1) _ Percentile 75% (Q3) (11.4%-62.4%)] The highest resistance rate was for amoxicillin (69.1%), ceftazidime (72.0%), ampicillin (74.6%), aztreonam (76.9%) and clarithromycin (83.2%), with the lowest being for linezolid (0.0%), meropenem (4.3%), ampicillin/sulbactam (4.8%), rifampicin (5.0%), Cefepime (7.7%), and imipenem (8.4%).

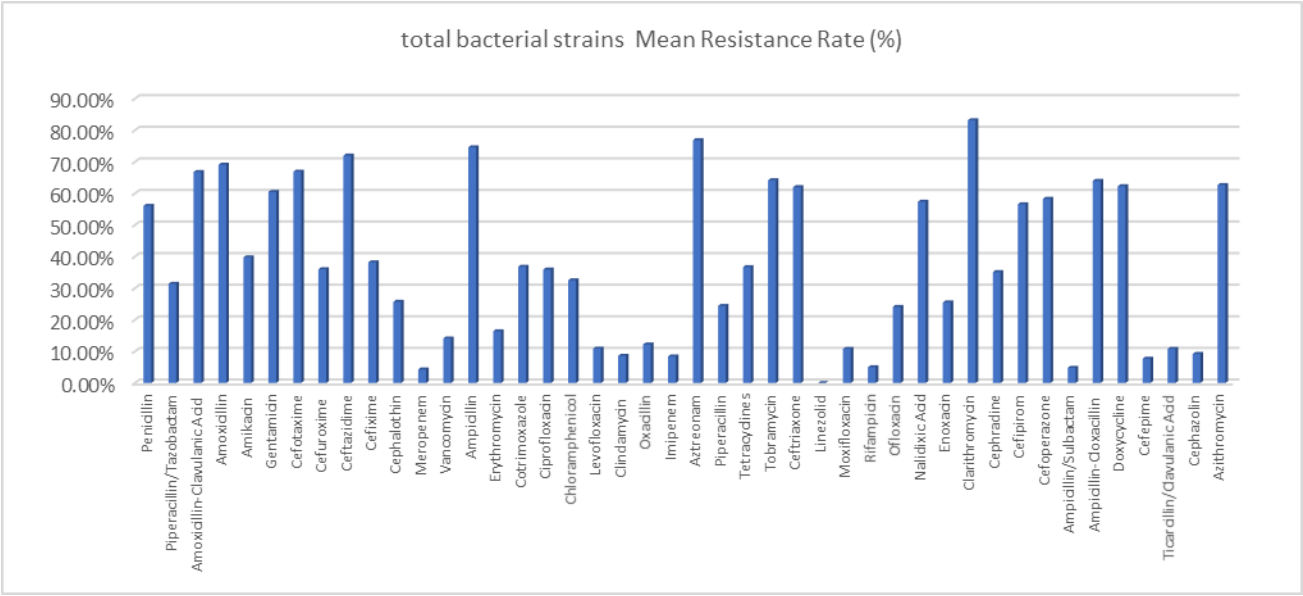


Figure 4: total bacterial strains Antibiotic Resistance Rate

## 4. Update (second search) section

To ensure the study is updated, A new search process is conducted with the same preliminary parameters on OVID and OBESCO on June 11, 2020

The search revealed 674 total number of records. Only four papers (Bhishma Pokhrel(24), Yongmei Jiang(25), Eman M. Rabie Shehab El-Din,(26) and Nisel Ozkalay Yilmaz(27)) are compiled for appraisal after submitting of enrolling criteria.

The total sample size of all selected studies was 1040 neonates from four countries (Egypt(26), Nepal(24),

turkey(27), and china(25)). The positive blood culture done was 569 cultures with a positive blood culture rate of 54.7% where it is 10% higher than positive cultures found in the preliminary study.

Coagulase-negative staphylococcus was the most frequent microorganisms in three papers {Yongmei Jiang(25), Eman M. Rabie Shehab El-Din(26) and Nisel Ozkalay Yilmaz(27)} and Klebsiella was the most frequent in Bhishma Pokhrel (24). These findings opposite the preliminary study where the gram-negative was the leading pathogen, which could be explained by the high possibility of contamination with skin microflora, as noticed in the low to a middle-quality score of laboratories method in all four papers.

As for antibiotics resistance, all four papers revealed high percentage resistance against most commonly used antibiotics (amoxicillin, ampicillin, and gentamicin) With low resistance rate for vancomycin, linezolid, and teicoplanin among Staphylococcus spp.

Multidrug resistance was identifying in two studies (Eman M. Rabie Shehab El-Din (26) and Bhishma Pokhrel (24)) with a high incidence among studies samples (70.1%) and (73.9%), respectively.

While Yilma Z (27) demonstrates a trend of increasing the resistance isolates' rate of all antibiotics in 2008, those in 2004.

This update shade some light on increasingly noted antibiotics resistance in developing countries. However, these results counteract the preliminary study in bacterial isolates prevalence among selected studies. But, after adding the total number of isolates, the final result will favor a high prevalence of klebsiella spp.

## 5. Discussion and Recommendations

There is an astronomical burden of bacterial sepsis in the neonate in developing countries, with restrictions in diagnostic constructs; efficient empirical antibiotic guidelines and therapy must be available. WHO's clinical guidelines for managing common childhood illnesses consider the constraints of low resources, set the review, and emphasize the lack of data regarding antibiotics resistance among dominant bacteria-causing sepsis in neonates in developing countries. The review also highlights the low quality of most papers reviewed (in both study design and laboratory quality).

Numerous data in both developed and developing countries associate the increased mortality and morbidity with an antibiotic-resistant bacterial infection in neonates (OR 2.8341, 95% CIs; 2.2180–3.6213; P = 0.000). (28) Unfortunately, only two studies recorded mortality due to neonatal sepsis (19, 20) with a mortality rate of 34% and 26.7% ( both had Klebsiella pneumonia as major bacteria), respectively.

This result harmonized with the last WHO Antimicrobial Resistance report, which revealed a significant increase in mortality due to resistant Klebsiella pneumonia and S. aureus in hospitals. (5)

The high rate of positive cultures of 45.3%. (median 38.5%, average 6.5%–63%) With a large heterogeneity in reviewed papers may be explained by large variations between different centers (both in geography, study population, in hospital settings and laboratory quality, differences in study methods of detecting sepsis and previous antibiotics used) across countries that participated in the review. Also, tertiary centers have more serious septic cases to transfer. That may increase the bias level in the results. Worldwide differences between different studies are also reported to be as big as 6.2% (29) to 54%. (30). Furthermore, this review will not discuss negative sepsis, which may reach 21% of sepsis in some studies. (31)

The predominant organisms were gram-negative, with 76.1% of total positive cultures. They correlate well with data from both hemispheres of the globe. (32-34).

E. coli represents the dominant bacteria identified with a total of 860 isolates (42.3%) out of the 2,030 positive cultures done. This review is for in-hospital settings, where Staphylococcus aureus, Klebsiella spp. and E. coli accounted for 74.7% of all pathogens in contrast to 55% in community-acquired neonatal sepsis in developing countries. (35) Which was much more apparent than studies from developed countries where group B streptococcus and E. coli reflect the majority of the isolates. However, this is partially counteracted by the lower rates of GBS (4.1%) and CoNS (2.8%), which are rationalized by different methods of GBS assessment and intrapartum antibiotic prophylaxis (IAP) practice in these nations. (36, 37) A similar distribution of gram-positive isolates (23.9%) is identified by UK neonIN and German NeoKISS studies, (36) (38) with a dominance of Staphylococcus aureus (20.2% from all gram-positive pathogens). Regrettably, only one study Addressed the resistance of methicillin-resistant Staphylococcus aureus (MRSA) (17) with a low profile of clinical significance. In general, the pathogen distribution is comparable to research in most developing countries (32, 39).

Regarding microbiological techniques, few studies mentioned the application of quality assurance in the identification and susceptibility testing, and MICs or inhibition diameters were never available. Likewise, none of the studies reported a distinction between intermediate and high-level resistances.

The susceptibility and resistance test included 44 different antimicrobial agents. However, none of the selected studies reported details of an empirical antibiotic regimen (what and when to start, duration, rate of coverage, and dosage) with different methods, technology, and laboratory specifications. The average or mean resistance rate was 37.8% for all tested antibiotics.

Since the targeted population is neonates, it is expected to see antibiotics certified for neonates—the enclosure of adults-only licensed agents (as tetracyclines, quinolones, aztreonam). The absence of specified agents from susceptibility (teicoplanin, methicillin, vancomycin, and linezolid as anti-staphylococcus) from some studies did not give any applicable clinical information to the referred studies.

The most commonly used and cheapest antibiotics in developing countries, amoxicillin and ampicillin, strike the highest resistance rate at 69.1% and 74.6%, respectively. Both aminoglycosides and third-generation cephalosporines posed a moderate to a high level of resistance, as these agents constitute the main component of empirical antibiotics for treatment of neonatal sepsis by different recognizable guidelines for clinical practice (ampicillin/amoxicillin plus aminoglycosides or third-generation cephalosporines), which will pose a serious question about dangerous future AMR in developing countries.

Low resistance in vitro reported to an agent does not mean that it is commended to treat that bacterium (cephalosporins for Enterobacter or doxycycline for gram-positive bacteria). Contrariwise, the resistance to one agent in a combination may not compare to the resistance of the whole combination as some of these regimens act synergistically together (ampicillin and gentamicin). Furthermore, in vitro low susceptibility does not inescapably associate with a lack of clinical therapeutic effect. It highlights the importance of enhanced research in clinical and epidemiological areas and makes individualization of results for every case. The best solution is not to generalize results for all patients.

Of particular concern is the high level of resistance reported among Klebsiella and E. coli showing gentamicin resistance since these agents are uniformly resistant to ampicillin. Also, increasing resistance to third-generation cephalosporins among Klebsiella and E. Coli is remarkable. The newsworthy broad-spectrum antibiotics as meropenem and piperacillin/tazobactam pose a low resistance profile, making them an excellent alternative regimen, but at the expense of a higher cost. It demands availability and the likelihood of developing future resistance among these rescue agents.

An apparent policy gap remains between evidence-based empiric antibiotics guidelines and prospective and local surveillance to monitor AMR,s varying patterns within and between different zones in developing areas. These outcomes highlight many significant zones for future research. Until new antimicrobial strategies are revealed and verified, the attention must remain on adherence to tailored local guidelines, educating practitioners on appropriate drug-prescribing practices, and refining laboratory substructures. Forthcoming research should emphasise identifying suitable and applicable local empirical treatments with enhanced susceptibility profiles, delivering perfect clinical indicators for improved second-line therapy when the primary empirical regimen fails, and adapting strategies for primary antimicrobial therapy's phasedown and

termination. Moreover, this finally adheres to the Standardised research schemes of the WHO's Global Antimicrobial Resistance Surveillance System (GLASS). (40)

In conclusion, although the present data only gives a view of bacterial AMR rates in developing countries, which shares the worldwide trend of increasing AMR, rigorous clinical and epidemiological surveillance based on proficient and inexpensive microbiology is required to deliver precise data on AMR, which, in turn, can enable the updating of local treatment guidelines and antibiotic stewardship programs.

## 6. Study Limitations

The primary strength of this review is its size, and geographic distribution over seven developing countries representing three different continents.

The potential limitations anticipated include the paucity of published neonatal data related to developing countries. This review targeted several search engines and sources of the WHO data to assure that these concerns are overcome. Still, geographical publication bias will likely to be an issue, as some papers published may not have been captured by the search terms of this review.

Other sources of limitation may be a defectiveness in the quality of laboratory methods concerning culture and antibiotic susceptibility detection in developing countries. Therefore, the review applied exclusive criteria for evaluating and assessing the quality of microbiological methods in chosen papers to decrease this limitation risk.

This review did not differentiate between early and late sepsis, which over-or underestimates the incidence rate of bacteria.

**Ethical approval:** This study needs no ethical approval due to the inherent design of the systematic review.

**Declaration of Interests:** The author declares that he has no conflicts of interest.

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