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High reported rates of antimicrobial resistance in Indian neonatal and pediatric blood stream infections.

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TITLE PAGE

Manuscript title

High reported rates of antimicrobial resistance in Indian neonatal and pediatric blood stream infections.

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SUMMARY:

In the absence of a national data on antimicrobial resistance in pediatric population in India, this work serves as a first large pooled data review highlighting the extremely high resistance in the commonly isolated blood-borne pathogens in Indian neonates and children against all routinely used antibiotics.

ABSTRACT

Background

There is real shortage of national data on antimicrobial resistance rates in Indian neonates and children. A descriptive review was conducted to determine the patterns of antimicrobial resistance in isolates of bloodstream infection among hospitalised children in India

Methods

Published and grey literature on antibiotic resistance in children was searched using "Google Scholar", "Scopus" and "Pubmed" databases between January 2000 and July 2015. Studies were included if they were original articles that reported a minimum of 10 pathogenic bacterial isolates from the bloodstream within a pediatric population in India, and excluded if they reported studies done during an outbreak or epidemic.

Results

A total of 1,179 studies were screened, and 82 papers were identified as eligible for inclusion. Most studies (78.7%) were reported from neonatal intensive care units. Among a total of 50,545 reported blood cultures, 14,704(29.1%) were positive. *Staphylococcus aureus*, (median:14.7%;IQR7.4%-25.6%) and *Klebsiella pneumoniae* (median:26%;IQR16.7**%**-35.4**%**) were the commonest reported gram-positive and gram-negative pathogens respectively. Around half of all *Staphylococcus aureus* isolates were reported as methicillin resistant *Staphylococcus aureus* (median:50%;IQR31.4**%**-65.1**%**). After age stratification, the median rate of resistance of common gram-negative pathogens to ampicillin and gentamicin/amikacin were extremely high. (*Klebsiella pneumoniae*/ampicillin 95.9% ; *Klebsiella pneumoniae*/gentamicin 75% ; *Escherichia coli*/ampicillin 92.9% ; *Escherichia coli*/gentamicin 55.6%) .Similarly the median resistance of common gram-negative blood stream isolates to cephalosporins were also high (*Klebsiella pneumoniae*/cefotaxime 62.6% ; *Escherichia coli*/cefotaxime 47.5%).

Conclusions

High rates of resistance to WHO recommended first-line treatment options for neonates and children have been identified in blood stream infections across India. There is an urgent need to both enhance antibiotic stewardship and infection prevention and control measures and consider urgently how to repurpose older antibiotics back into routine care in India.

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Introduction

There has been a relentless rise in antimicrobial resistance globally. Concerns about this serious threat have been raised since late 1990s as evident by the Global Strategy for Containment of Antimicrobial Resistance of the World Health Organisation (WHO) in 2001[1]. The WHO in its recent global surveillance report states that this reality of antimicrobial resistance is "far from an apocalyptic fantasy", is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country[2].

Due to lack of a national robust surveillance system for Antimicrobial Resistance (AMR) in India, there is currently no centrally reported AMR national database. Earlier initiatives to generate AMR data include those carried out by the India clinical epidemiological network (INCLEN) and Indian network for surveillance of antimicrobial resistance (INSAR)[3,4]. In 2011, the Indian Council of Medical Research (ICMR) launched the national policy for containment of antimicrobial resistance which includes sentinel surveillance of AMR phase wise across the country[5]. This surveillance has not defined any age stratification. The Jaipur Declaration in 2011[6] and Chennai declaration[7] in the subsequent year framed consensus roadmaps to tackle AMR.

AMR patterns can significantly differ in adult and children[8]. It is estimated that India has the highest neonatal mortality due to neonatal sepsis caused by bacteria resistant to first-line antibiotics[9]. Nearly one-fifth of neonates with sepsis die in the hospital and the mortality rises to 50% for those with culture-proven sepsis[10]. In the absence of any recent national data of AMR rates in blood stream infections in the Indian neonatal or pediatric population, this study aimed to review the published and unpublished data on AMR during 2000-2015 from India.

Methods:

The published and grey literature on antibiotic resistance in children in English literature was searched using the databases "Google Scholar" "Scopus" and Pubmed using keywords "India" AND "children" OR "pediatrics" OR "neonates" OR "infants" AND "antimicrobial resistance" OR "antibiotic resistance" OR "antibiotic susceptibility" OR "antibiotic sensitivity" AND "blood culture" (see supplementary material 1). Grey literature sources such as pediatric conference proceedings and national reports were examined individually. The period between 1 January 2000 and 1st July 2015 was chosen to access maximum information of published abstracts and full text articles. A single reviewer assessed the study quality and performed data extraction.

Inclusion criteria included original articles describing studies performed in well described health centres in India, published between January 2000 and July 2015 that described blood culture-derived bacterial isolates from children from birth to 18 years, with determination of antimicrobial susceptibility patterns. Excluded studies were those that described less than 10 pathogenic isolates, or those that did not distinguish bloodstream and non-bloodstream sources, and those performed in adult populations. Studies performed during outbreaks or epidemics were also excluded. Bacterial isolates of interest reviewed here included gram-positive bacteria (*Staphylococcus aureus,* coagulase-negative *Staphylococcus , Enterococcus fecalis*) and gram- negative bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* , *Enterobacter species* ,*Citrobacter* species, *Acinetobacter baumannii* , *Proteus* species and *Salmonella typhi*).

Statistical Analysis

The proportions (%) and ranges of individual blood-borne pathogens in infants and children, resistant to various drugs mentioned in Table 1, 2 and 3 were calculated. As the total number of reported blood cultures varied markedly between studies, proportions and ranges for pathogens were weighted by total sample size of blood cultures and given as weighted median of proportions (%) and inter-quartile ranges (IQRs). Similarly, median and inter-quartile ranges (IQRs) of resistance rates attributable to a pathogen to recommended antibiotics were reported [11].

Results

Search Analysis

Electronic search on 9th July 2015 identified 298 articles in Pubmed, 4,980 articles in the database of "Google scholar" and 243 articles in Scopus. Of the 4,980 articles, Google scholar engine displays only the first 1,000. Individual search of abstracts from national conferences of Indian Academy of Pediatrics identified 8 abstracts. 72 articles were common in both search engines. So, in total, 1,179 abstracts were reviewed. Most of the articles were excluded because the studies were done in children living outside India or in the adult population (Figure 1). Among the remaining 484 articles, those that met the exclusion criteria were excluded.

Thus, 82 papers (see supplementary material 2) were included for analysis. Among these 82 papers, some papers had multiple data sets covering multiple years. Since the data set belonging to a particular year was considered as a separate study, the total number of studies obtained was 89. The positive blood culture rate was calculated using 78 of the 89 studies, as the total number of blood cultures analysed were not available in the remaining 11 studies.

Study characteristics

Among the 89 eligible studies that had provided data about positive blood cultures, 78.7% data were from neonates, 14.6% from children older than 1 month, and 6.7% studies were

done in both neonate and pediatric ages. Studies were spread across India, with 36% reports from North India, 31.5% from South, 16.9% from Western India, 12.4% from the East and 3.4% from Central India. Out of the 89 studies, 98.9% had been conducted at a tertiary level health care centre and only one study (i.e. 1.1%) had been reported from a secondary level health care centre. The great majority of studies (78.7%) had been reported from NICU and a small percentage (<5%) from PICU ward, IPD, or their combinations. One study had screened enteric cases using blood cultures from the outpatient department[12].

Blood Culture positivity

Data were available from a total of 16,777 positive blood cultures from 89 studies, which were used to examine the drug resistance of the isolates. The number of total blood cultures reported was available only in 78 of the 89 studies, which summed to a total 50,545 blood cultures. The positive blood culture rate was calculated from the 78 studies that, varied from 7.2% to 88.5% with a median of 35.4% (IQR= 21.2% - 46.6%).

Pathogens identified

Among 72 studies that reported gram-positive bacteria the median of percentage gram-positive bacteria was 29.2% (IQR=15.8%-36.8%). Among gram-positive bacteria, *Staphylococcus aureus* was found to be the most common isolate (median 14.7%; IQR 7.4%-25.6%) followed by *coagulase negative Staphylococcus* (CONS) (median 10.4%; IQR 4.2%-15.9%) and *Enterococcus faecalis* (median 0.9%;IQR 0%-4.4%) (Table 1). It was not possible to distinguish true pathogens of CONS from contaminants in this review.

Gram-negative bacteria were reported in 81 studies. The median percentage gram-negative bacteria identified among all reported positive cultures was 61.0% (IQR=34.6% -67.9%). Among gram-negative bacteria, *Klebsiella pneumoniae* was found to be the most common isolate (median 26%; IQR 16.7%-35.4%) followed by *Escherichia coli* (Median 9.3%; IQR

4.7%-14.5%), *Acinetobacter baumanii* (median 5.9%; IQR 2.1%-10.8%) and *Pseudomonas aeruginosa* (median 4.8%; IQR 2.4%-9.4%)

Resistance of Gram-positive bacteria:

50% of the *Staphylococcus aureus* isolates were methicillin resistant Staphylococcus aureus (MRSA). High resistance was also noted for *Staphylococcus aureus* to erythromycin (53%), cefotaxime (57%) and cotrimoxazole (57.7%) (Table1). Lower resistance pattern was shown by CoNS except to cotrimoxazole (69.9%). However *Enterococcus faecalis* showed very high resistance to antibiotics including penicillins (88.5%), gentamicin (68.5%) and ciprofloxacin (50%). No resistance was found to vancomycin, linezolid and teicoplanin in all the gram-positive bacteria reported.

Resistance of Gram-negative bacteria:

Details of the gram-negative resistance rates are provided in Table 2. High levels of resistance was reported in *Klebsiella pneumoniae* to ampicillin (95.2%) and cephalosporins (over 60%). The rates of reported resistance to tigecycline were 8.2%, colistin, 3.8% and meropenem, 1%. Reported resistance in *Enterobacter* spp. was 100% to ceftriaxone and aztreonam. Resistance to piperacillin-tazobactam was 16.7%, ciprofloxacin (39%) and meropenem (16.7%). There were very high resistance rates identified in *Escherichia coli* (Table 2) to ampicillin (92.3%), chloramphenicol (63.9%) and ciprofloxacin (40%) and relatively lower resistance to amikacin (22.4%) and piperacillin-tazobactam (16.7%). Resistance to meropenem of 9.0% and colistin of 8.8% was noted. As seen in Table 2, high resistance of *Pseudomonas aeruginosa* was noted to ceftazidime (58.7%) which is often used empirically for *Pseudomonas aeruginosa* infections. There was high resistance (16.7%) noted of *Pseudomonas aeruginosa* to meropenem.

In case of resistance of *Acinetobacter baumanii* and *Citrobacter spp.* (table 2), though the resistance to cephalosporins are high, there was relatively less resistance to ciprofloxacin and

beta-lactam antibiotics including piperacillin-tazobactam and cefoperazone-sulbactam. *Acinetobacter baumanii* infections were reported to have 11.5% resistance to meropenem. *Salmonella typhi* (Table 3) displayed a median resistance of 50% to ampicillin, 35% to nalidixic acid and 17.9% to chloramphenicol. However 6.3% resistance to ceftriaxone and 16% to second-line antibiotics like azithromycin were also noted.

Age-based stratification for commonly used pathogen-drug combinations (Table 4)

Using age as criterion, the data was then split by age into neonatal (less than 1 month) and pediatric populations (age greater than 1 month) for commonly used pathogen-drug combinations.

a. *Gram-positive resistance in neonates vs pediatric population*

The overall resistance was found to be greater in neonatal age than pediatric age. However, this difference was not statistically significant. There was no resistance noted of isolates of *Staphylococcus aureus and* CONS to vancomycin, and linezolid, in both age groups.

b. *Gram-negative resistance in neonates vs pediatric population*

The median resistances of common gram negative pathogens to the WHO recommended combination of ampicillin and gentamicin for the empiric treatment of neonatal sepsis were extremely high (*Klebsiella pneumoniae* /ampicillin 95.9% ; *Klebsiella pneumoniae* /gentamicin 75% ; *Escherichia coli*/ampicillin 92.9% ; *Escherichia coli*/gentamicin 55.6%) and median resistance to cephalosporins were also high (*Klebsiella pneumoniae* /cefotaxime 62.6% ; *Escherichia coli*/cefotaxime 47.5%).

Discussion

Main findings

This literature review provides a comprehensive analysis on the antimicrobial resistance pattern of bacterial blood stream infection (BSI) in the pediatric population of India over the past 15 years. This study found higher reports of bacteraemia caused by gram-negative bacteria (53.3%) compared to gram-positive bacteria (30.9%).

The majority of the BSI identified in this study (78.7%) were reported from tertiary NICU's. These NICUs reported very high rates of MRSA BSI (53.6%). WHO recommends ampicillin plus an aminoglycoside (gentamicin or amikacin) as empirical treatment for community acquired neonatal sepsis[13]. Very high levels of resistance of more than 90% to ampicillin was noted among the majority of the gram-negative isolates and the median resistance to amikacin ranged from 22.4% to 50%. Cephalosporins contribute to over 50% of prescribed antibiotics in paediatrics in India[14,15]. Cephalosporins are recommended as first line antibiotics in various community acquired infections like enteric fever, meningitis and severe pneumonia. The high rates of resistance to cephalosporins in gram-negative BSI isolates of both the neonatal and pediatric population is concerning (*Klebsiella pneumoniae*/cefotaxime 62.6% in neonates and 70% in children; *Escherichia coli*/cefotaxime 47.5% in neonates and 50% in children). In addition, this study noted an emerging resistance to carbapenems.

Comparison to other studies

Despite concern about the high resistance reported from India, it is surprising to note the lack of published data from India. In a study from a mixed population of adults and children across 15 centres in India, the prevalence of MRSA was 42 per cent in 2008 and 40 per cent in 2009. However 60% of the isolates were from skin and soft tissue infections, while the present study reported only on blood culture isolates. No isolate was found to be resistant to vancomycin and linezolid similar to the present study[4].

A high incidence of MRSA BSI in neonates was also reported from a large prospective multisite cohort study by the Delhi Neonatal Infection Study (DeNIS) collaboration (38%)

[16]. Though the rate of gram-negative sepsis and the most common gram-negative pathogens isolated in this study were similar to ours, the proportion of *Acinetobacter* spp identified (22%) was much higher than ours (5.9%). On comparing our data with a systematic review of gram-negative antimicrobial resistance in sepsis in resource limited countries, the figures from Asian studies show a similar resistance pattern for gram-negative isolates except for a lower resistance to cotrimoxazole and chloramphenicol[11].

Since 1990s, *Salmonella typhi* had acquired resistance to the former first line drugs recommended by WHO, ampicillin, chloramphenicol and fluoroquinolones[17]. In the present study, one third of invasive *Salmonella* isolates (35%) in children had resistance to nalidixic acid similar to the resistance of 37.3% found in the systematic review of Asian studies[10]. Ceftriaxone and azithromycin are currently recommended as first line and second line therapy for multidrug resistant typhoid fever, (MDRTF). However the resistance rates reported here were significant with ceftriaxone (6.3%) and azithromycin (16%). A recent review on multi drug resistant typhoid fever in India had similarly noted isolated reports of ceftriaxone resistance[18].

Study limitations

This study has several biases and limitations such as:

Selection bias

Over 80% of studies were reported from tertiary Intensive Care Units where children have prolonged length of stay and underlying medical conditions. Most of the studies in the data were laboratory based, with very limited clinical information, and it was not possible to determine if the infections were community or hospital acquired. Despite the exclusion of any study reporting an outbreak, it is probable that some studies had unrecognised outbreaks.

Surveillance bias

The data was largely contributed by tertiary medical centres. It is noted from CDC's surveillance on antimicrobial resistance [19, 20] that expansion of surveillance to include smaller community hospitals (<200 beds) resulted in reduction in the pooled mean percent resistance for certain resistance phenotypes like MRSA.

Reporting bias

The heterogeneity in data showed the lack of any uniform protocol being followed for reporting key drug bug combination data in a standardised manner. There were no formal national guidelines on reporting antimicrobial resistance until February 2015 when the Indian Council of Medical Research announced the Standard Operating Procedure (SOP)[21].

Next steps

Although there are many limitations and biases, this study clearly highlights the concerning level of antimicrobial resistance in serious infections within the tertiary neonatal and pediatric setting in India. It is important to differentiate between hospital acquired and community acquired infections to develop appropriate empirical therapy choices. Guidelines on regional empirical treatment cannot be made on the basis of the present study as it is not representative of the resistance in the community [22]. Improved multi-centre, prospective studies using a standardised protocol such as the DeNIS study, are required, with data on underlying disease, treatment and clinical outcomes, which are essential to give a more accurate assessment of the true burden of disease, especially in relation to the clinical outcome.

The factors contributing to antimicrobial resistance in India are complex and diverse and range from unregulated use of antibiotics in the community and hospital settings, poor infection control policies and the unavailability of culture facilities or point of care tests. The stewardship programmes recommended by the developed countries require time, personnel and resources which are currently completely lacking in the Indian health care system. It is

very important to develop simple, easy to implement antimicrobial stewardship programme adapted to resource poor settings.

In 2016, the Government of India launched the national treatment guidelines for antimicrobial use in infectious diseases [23]. While this is a major step to ensure a uniform rational practice in the country, there is a need to formulate a similar guideline for neonates and children. In addition, participation of paediatricians should be encouraged in active surveillance for antibiotic resistance by bodies like ICMR, Indian Academy of Pediatrics and international networks. More importantly, the awareness about the magnitude of antibiotic resistance and the essence of rational antibiotic use needs to be highlighted more urgently among practicing physicians and families. Resistance rates to current antibiotics are now so high, that there is an urgent need to consider how to re-introduce older antibiotics back into routine clinical practice and determine how the very few new antibiotics under development can be introduced into high risk clinical care in a rational and affordable manner.

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Figure Legend

Figure 1: Flow Chart of selection of studies based on PRISMA 2009 flow chart

Listing of Supplementary Material

Supplementary material 1

Supplementary material 2

TABLES

Table 1: Median and IQR of percentage resistance of gram-positive bacteria: *Staphylococci aureus, CONS* and *Enterococcus faecalis*

	Staphylococcus aureus **14.7%(7.4%-25.6%) [n=70]**	***CONS*** **10.4%(4.2%-15.9%) [n=68]**	***Enterococcus faecalis*** **0.9%(0%-4.4%) [n=44]**
Penicillin	NS	NS	88.5% (41.7%-100.0%) [n=9]
Ampicillin	NS	NS	100.0% (77.5%-100.0%) [n=4]
Erythromycin	53.0% (39.5%-65.9%) [n=31]	43.3% (30.5%-67.1%) [n=26]	53.2% (44.6%-61.9%) [n=8]
Cloxacillin	50.0% (31.4%-65.1%) [n=33]	42.5% (19.1%-66.7%) [n=24]	NS
Amikacin	25.8% (14.2%-48.7%) [n=40]	28.6% (0.0%-41.0%) [n=35]	NS
Gentamicin	44.9% (24.9%-69.7%) [n=42]	50.0% (29.2%-66.7%) [n=36]	68.5% (41.7%-77.5%) [n=13]
Cephelexin	34.3% (27.3%-66.6%) [n=11]	27.3% (0.0%-51.5%) [n=10]	NS
Cefotaxime	57.1% (25.0%-66.0%) [n=23]	35.4% (18.4%-64.1%) [n=22]	NS
Ceftriaxone	40.0% (21.4%-60.0%) [n=11]	33.0% (9.0%-47.9%) [n=9]	NS
Cotrimoxazole	57.7% (30.0%-72.7%) [n=19]	69.9% (60.6%-87.3%) [n=16]	75.0% (12.5%-100.0%) [n=4]
Ciprofloxacin	40.0% (25.0%-59.0%) [n=39]	38.9% (16.7%-53.6%) [n=31]	50.0% (0.0%-64.4%) [n=10]
Amoxiclav	25.0% (16.0%-53.6%) [n=9]	11.1% (0.0%-40.3%) [n=11]	20.0% (0.0%-40.0%) [n=2]
Clindamycin	29.3% (15.9%-40.2%) [n=14]	27.5% (6.1%-37.1%) [n=14]	NS
Vancomycin	0.0% (0.0%-0.0%) [n=37]	0.0% (0.0%-0.0%) [n=35]	0.0% (0.0%-13.7%) [n=12]
Linezolid	0.0% (0.0%-12.5%) [n=19]	0.0% (0.0%-0.0%) [n=17]	0.0% (0.0%-5.0%) [n=6]
Teicoplanin	0.0% (0.0%-10.5%) [n=5]	0.0% (0.0%-0.0%) [n=5]	0.0% (0.0%-16.6%) [n=3]
Doxycycline	-NS	-NS	40.0% (40.0%-40.0%) [n=1]

* Data is presented in the form [median, (Inter quartile range:Q1-Q3), n=number of studies

NS : Not Studied.

Table 2: Median and IQR of percentage resistance of Gram-negative bacteria: *Klebsiella pneumoniae, Enterobacter spp, Escherichia coli, Acinetobacter baumannii, Citrobacter spp and Pseudomonas aeruginosa*

	Klebsiella pneumoniae 26%(16.7%-35.4%) [n=74]	**Enterobacter spp 3.2%(0%-8.4%) [n =43]**	***Escherichia coli* 9.3%(4.7%-14.5%) [n =72]**	***Acinetobacter baumannii* 5.9%(2.1%-10.8%) [n =62]**	***Citrobacter spp* 1.5%(0%-3%) [n =44]**	***Pseudomonas aeruginosa* 4.8%(2.5%-9.4%) [n =65]**
Ampicillin	95.2% (74.0%-100.0%) [n=47]	100.0% (94.7%-100.0%) [n=19]	92.3% (67.7%-100.0%) [n=32]	42.9% (7.0%-63.2%) [n=35]	99.0% (79.2%-100.0%) [n=10]	NS
Cephalexin	73.7% (49.5%-95.2%) [n=4]	100.0% (95.2%-100.0%) [n=3]	58.4% (58.3%-100.0%) [n=3]	NS	NS	NS
Cefazolin	76.5% (53.8%-100.0%) [n=3]	NS		NS	NS	NS
Cefotaxime	63.7% (40.9%-80.5%) [n=52]	70.4% (55.2%-90.3%) [n=22]	50.0% (40.0%-66.0%) [n=37]	60.0% (42.2%-90.6%) [n=29]	60.0% (0.0%-69.1%) [n=13]	NS
Ceftriaxone	65.0% (28.7%-90.4%) [n=31]	100.0% (58.8%-100.0%) [n=11]	50.0% (33.3%-66.7%) [n=19]	68.9% (49.6%-97.1%) [n=14]	50.0% (0.0%-62.5%) [n=11]	NS
Ceftazidime	64.3% (44.4%-88.6%) [n=34]	67.0% (51.9%-97.6%) [n=13]	NS	77.8% (50.0%-100.0%) [n=19]	NS	58.7% (33.3%-73.7%) [n=26]
Amikacin	41.0% (18.8%-50.5%) [n=65]	37.9% (20.6%-66.2%) [n=26]	22.4% (0.0%-40.0%) [n=43]	NS	50.0% (18.6%-63.5%) [n=16]	40.0% (25.0%-50.0%) [n=39]
Gentamicin	75.7% (54.8%-86.8%) [n=64]	83.3% (65.8%-93.6%) [n=25]	55.6% (33.3%-83.3%) [n=43]	64.0% (45.0%-79.6%) [n=37]	50.0% (33.4%-83.3%) [n=15]	65.8% (50.0%-75.0%) [n=36]
Ciprofloxacin	46.2% (28.4%-62.0%) [n=57]	39.0% (8.3%-62.1%) [n=23]	40.0% (22.9%-67.0%) [n=37]	52.8% (32.5%-63.2%) [n=34]	33.4% (0.0%-64.8%) [n=16]	50.0% (32.5%-62.6%) [n=38]
Chloramphenicol	59.2% (9.8%-77.3%) [n=14]	91.1% (51.7%-100.0%) [n=6]	63.9% (28.8%-84.9%) [n=8]	88.9% (65.3%-100.0%) [n=9]	71.9% (37.5%-93.8%) [n=4]	NS
Amoxiclav	64.7% (33.0%-90.0%) [n=19]	NS	74.5% (34.4%-87.8%) [n=12]	NS	52.3% (12.5%-88.6%) [n=4]	NS
Piperacillin-tazobactam	42.0% (1.6%-61.4%) [n=22]	16.7% (0.0%-68.8%) [n=8]	16.7% (0.0%-40.0%) [n=11]	22.3% (0.0%-53.2%) [n=17]	0.0% (0.0%-37.5%) [n=4]	21.0% (1.2%-33.3%) [n=17]
Cefoperazone-sulbactam	23.6% (9.5%-53.9%) [n=12]	23.8% (1.5%-85.4%) [n=4]	NS	20.0% (9.4%-23.2%) [n=5]	1.0% (0.0%-1.9%) [n=2]	NS
Cotrimoxazole	62.5% (50.1%-80.7%) [n=25]	NS	63.2% (50.0%-78.3%) [n=17]	NS	33.4% (0.0%-50.0%) [n=7]	NS
Aztreonam	71.9% (19.0%-84.1%) [n=9]	100.0% (50.0%-100.0%) [n=3]	30.9% (2.9%-57.5%) [n=4]	22.2% (0.0%-86.1%) [n=4]	0.0% (0.0%-100.0%) [n=3]	45.0% (6.3%-83.3%) [n=5]
Meropenem	1.0% (0.0%-17.4%) [n=17]	16.7% (0.0%-83.4%) [n=4]	9.0% (0.0%-27.0%) [n=11]	11.5% (0.0%-47.5%) [n=12]	0.0% (0.0%-0.0%) [n=3]	16.7% (0.0%-30.0%) [n=11]
Colistin	3.8% (0.0%-21.4%) [n=3]	NS	8.8% (0.0%-17.6%) [n=2]	NS	NS	0.0% (0.0%-0.0%) [n=2]
Tigecycline	8.2% (1.0%-18.9%) [n=4]	NS	0.0% (0.0%-0.0%) [n=1]	NS	NS	NS

* Data is presented in the form [median, (Inter quartile range:Q1-Q3), n=number of studies]

NS : Not Studied

Table 3: Median and IQR of percentage resistance of *Salmonella Typhi*

	Salmonella typhi **0%(0%-6.8%)** **[n=37]**
Ampicillin	50.0% (16.6%-87.1%) [n=9]
Cefotaxime	0.0% (0.0%-13.6%) [n=7]
Ceftriaxone	6.3% (0.0%-14.2%) [n=7]
Ceftazidime	0.0% (0.0%-0.0%) [n=2]
Ciprofloxacin	14.3% (0.0%-21.4%) [n=11]
Chloramphenicol	17.9% (0.9%-62.1%) [n=8]
Amoxiclav	0.0% (0.0%-14.3%) [n=3]
Cotrimoxazole	12.2% (0.0%-45.1%) [n=8]
Azithromycin	16.0% (0.0%-31.2%) [n=3]
Nalidixic acid	35.5% (0.0%-81.3%) [n=5]

* Data is presented in the form [median,(Inter quartile range:Q1-Q3), n=number of samples]

NS : Not Studied

Table 4: Age based pathogen resistance in common drug combinations

Pathogen-Antibiotic combination	Neonate [Median(Q1-Q3) number of samples]	Pediatric [Median(Q1-Q3) number of samples]	P[$]
***Staphylococcus aureus* - Cloxacillin**	53.6% (39.8%-66.2%) [#22]	33.3% (29.3%-64.3%) [#11]	0.08
***Staphylococcus aureus* - Clindamycin**	33.0% (20.0%-45.7%) [#11]	27.7% (0.0%-30.0%) [#3]	ns
***Staphylococcus aureus* - Vancomycin**	0.0% (0.0%-0.0%) [#30]	0.0% (0.0%-0.0%) [#7]	ns
***Staphylococcus Aureus* - Linezolid**	0.0% (0.0%-12.5%) [#14]	0.0% (0.0%-13.2%) [#5]	ns
***Klebsiella pneumoniae*- Ampicillin**	95.9% (76.2%-100.0%) [#42]	93.9% (44.6%-100.0%) [#5]	ns
***Klebsiella*- Gentamicin**	75.0% (54.8%-86.2%) [#56]	83.6% (31.3%-98.5%) [#8]	ns
***Klebsiella pneumoniae*- Cefotaxime**	62.6% (42.8%-80.2%) [#46]	70.0% (14.3%-89.0%) [#7]	ns
***Klebsiella pneumoniae*– Piperacillin-tazobactam**	42.0% (5.1%-62.1%) [#20]	25.0% (0.0%-50.0%) [#2]	ns
***Klebsiella pneumoniae* - Imipenem**	0.0% (0.0%-8.0%) [#27]	0.0% (0.0%-0.0%) [#5]	ns
***Escherichia coli*- Ampicillin**	92.9% (66.7%-100.0%) [#27]	83.3% (62.0%-100.0%) [#5]	ns
***Escherichia coli*- Gentamicin**	55.6% (33.3%-83.3%) [#38]	50.0% (0.0%-79.4%) [#5]	ns
***Escherichia coli*- Amikacin**	22.3% (2.3%-40.0%) [#38]	38.8% (0.0%-50.0%) [#5]	ns
***Escherichia coli*- Cefotaxime**	47.5% (40.0%-66.3%) [#32]	50.0% (45.0%-74.3%) [#5]	ns
***Pseudomonas* - Amikacin**	39.4% (23.5%-50.0%) [#32]	40.0% (25.0%-66.3%) [#7]	ns
***Pseudomonas*- Ceftazidime**	50.0% (33.3%-73.3%) [#19]	67.0% (33.3%-75.0%) [#7]	ns
***Pseudomonas aeruginosa*- Ciprofloxacin**	43.0% (30.0%-60.0%) [#31]	63.0% (40.0%-80.0%) [#7]	ns
***Enterobacter* spp-**	100.0% (97.4%-100.0%)	97.1% (94.2%-0.0%)	ns

Ampicillin	[#17]	[#2]	
***Enterobacter spp*-Gentamicin**	88.0% (61.7%-97.4%) [#21]	76.5% (67.6%-83.0%) [#4]	ns
***Citrobacter* spp-Ampicillin**	95.3% (62.5%-100.0%) [#6]	99.0% (87.0%-100.0%) [#4]	ns
***Citrobacter spp*-Gentamicin**	52.8% (39.8%-80.3%) [#12]	0.0% (0.0%-0.0%) [#3]	ns
***Acinetobacter baumannii*-Gentamicin**	63.6% (45.0%-78.9%) [#33]	77.1% (18.8%-94.8%) [#4]	ns

* Data is presented in the form [Median,(Inter quartile range:Q1-Q3), #number of samples]

$: significance levels using Mann-Whitney test ; ns – not significant

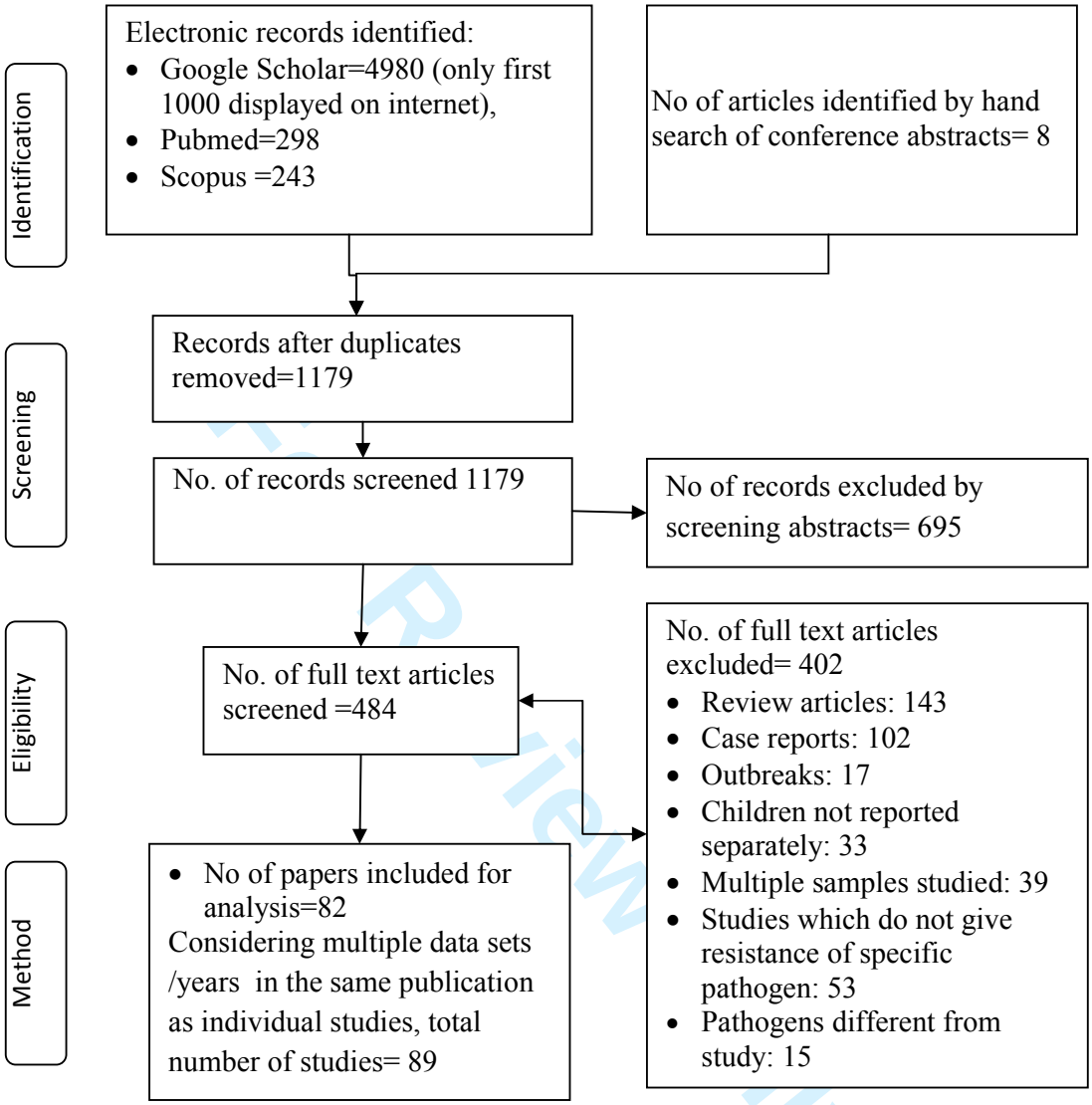

Figure 1: Flow Chart of selection of studies based on PRISMA 2009 flow chart

eAppendix 1

Search strings used

For Scopus

ALL ("India" AND "Children" OR "Pediatrics" OR "Neonates" OR "Infants" AND "Antimicrobial resistance" OR "Antibiotic Resistance" OR "Antibiotic Susceptibility" OR "Antibiotic sensitivity" AND "Blood Culture") AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 1999 AND PUBYEAR < 2015 AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "no")) AND (EXCLUDE (SUBJAREA , "AGRI") OR EXCLUDE (SUBJAREA , "ENVI") OR EXCLUDE (SUBJAREA , "DENT") OR EXCLUDE (SUBJAREA , "HEAL") OR EXCLUDE (SUBJAREA , "NURS") OR EXCLUDE (SUBJAREA , "VETE")) AND (EXCLUDE (LANGUAGE , "French") OR EXCLUDE (LANGUAGE , "Turkish") OR EXCLUDE (LANGUAGE , "Portuguese") OR EXCLUDE (LANGUAGE , "Spanish")) AND (EXCLUDE (SRCTYPE , "b") OR EXCLUDE (SRCTYPE , "k")) AND (LIMIT-TO (AFFILCOUNTRY , "India"))

For pubmed

"India"[All Fields] AND "Children"[All Fields] OR "Pediatrics"[All Fields] OR "Neonates"[All Fields] OR "Infants"[All Fields] AND "Antimicrobial resistance"[All Fields] OR "Antibiotic Resistance"[All Fields] OR "Antibiotic Susceptibility"[All Fields] OR "Antibiotic sensitivity"[All Fields] AND "Blood Culture"[All Fields] AND ("2000/01/01"[PDAT] : "2015/07/01"[PDAT])

eAppendix 2

Included studies

1. Agarwal, A. and S.Bhat, (2015) Clinico-microbiological study of neonatal sepsis. *Journal of International Medicine and Dentistry*, 2(1), pp.22–29.
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Author's Response to Decision Letter for (JPIDS-2016-098.R1)

Extremely high rates of antimicrobial resistance in Indian neonates and children are now a major threat to public health.

Grateful for your input.

1. The abstract has been structured as suggested.
2. The phrasing of the results changed as advised.
3. Screening and statistical methods updated.
4. Suggested minor edits carried out.
5. Discussion curtailed by removing the repetitions and focusing on trends.
6. Figure 2 deleted as advised