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Multidrug Resistance in Infants and Children

*Gian Maria Pacifici[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Bacterial infections may cause disease and death. Infants and children are often subject to bacterial infections. Antimicrobials kill bacteria protecting the infected patients and reducing the risk of morbidity and mortality caused by bacteria. The antibiotics may lose their antibacterial activity when they become resistant to bacteria. The resistance to different antibiotics in bacteria is named multidrug-resistance. Gram-negative bacilli, especially Escherichia coli, Klebsiella, Enterobacter, Salmonella, Shigella, Pseudomonas, Streptococcus, and Haemophilus influenzae type b, may become resistant. Amikacin ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone tetracycline, chloramphenicol, ciprofloxacin, and gentamicin may cause bacterial-resistance. Resistance to bacteria for several pathogens makes complications in the treatment of infections caused by them. Salmonella strains may become resistant to ampicillin, cephalotin, ceftriaxone, gentamicin, amikacin, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracycline. Shigella strains may become resistant to ampicillin, cotrimoxazole, chloramphenicol, and streptomycin. Multidrug-resistance of Streptococcus pneumoniae may be due to β-lactams, macrolides, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole.

Multidrug-resistance of Pseudomonas aeruginosa may become resistant to β-lactams, chloramphenicol, trimethoprim-sulfamethoxazole, and tetracycline. The antibacterial activity against Haemophilus strains may occur with ampicillin, sulbactam-ampicillin, trimethoprim-sulfamethoxazole, gentamicin, chloramphenicol, and ciprofloxacin. Multidrug-resistance of the Klebsiella species may be due with ampicillin, cefotaxime, cefuroxime, co-amxilav, mezlocillin, chloramphenicol, gentamicin, and ceftazidime. Multidrug-resistance of Escherichia coli may be caused by ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, and ceftazidime. Vibrio cholera may become resistant to cotrimoxazole, chloramphenicol, ampicillin, with least resistance to erythromicin, tetracycline, and ciprofloxacin. The aim of this study is to review the published data on the resistance of different antimicrobials in infants and children.

Key Words: Bacteria, Children, Infants, Infections, Multidrug-Resistance.

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Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

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1- INTRODUCTION

Antibiotic-resistant bacteria include the enteric gram-negative bacilli, especially Escherichia coli, Klebsiella, Enterobacter, Salmonella, Shigella, Pseudomonas, Streptococcus, and Haemophilus influenzae type b, which may become multidrug-resistant (1). Among these bacteria there is now high-level resistance to standard antibiotics, including amikacin ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone tetracycline, chloramphenicol, ciprofloxacin, and gentamicin. Reasons behind the increase in antibiotic-resistant bacterial infections are the widespread unregulated use of antibiotics and the very large burden of bacterial infections. Risk factors for development of resistant enteric gram-negative infections include village births, prolonged hospital stay, kwashiorkor in adopted children and previous treatment with broad-spectrum antibiotics.

Cost-effective strategies to combat these pathogens will need to be broad and must focus on reducing the use of antibiotics for trivial illnesses, reducing the need to use antibiotics and reducing the risk factors for resistant bacteria sepsis. There must be stricter regulation of commercial pharmacies, education of health workers on how to avoid inappropriate antibiotic prescribing, a focus on the prevention of pneumonia by immunization with new vaccines, improvement in the quality and uptake of formal maternal care services and public health measures within villages. In addition, there is a need for better surveillance for antibiotic-resistant bacteria within hospitals; this will require substantial improvements in laboratory facilities and carefully planned research collaboration. A national committee should be established to advise on these matters and coordinate interventions. Among 58 isolates, 22 strains were found to harbor one Beta -lactamase (β-lactamase) gene, and the proportions of resistance to ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, chloramphenicol, ceftriaxone, and ceftazidime, were 81.8%, 63.6%, 40.9%, 18.2%, and 9.1%, respectively (2). A further 30 strains carrying multiple Beta -lactamase genes had increased resistance to the above antimicrobial agents (100%, 83.3%, 70.0%, and 30.0%, respectively). In contrast, antibiotic resistance in the last 6 strains without a detectable β-lactamase gene was substantially reduced. Drug resistance may be associated with the β-lactamase gene number, with a greater number of β-lactamase genes resulting in higher antibiotic resistance. Overall, antimicrobial susceptibility testing showed a high level of resistance to ampicillin (81.8%), chloramphenicol (72.7%), tetracycline (96.9%), and cotrimoxazole (87.9%). Ampicillin resistance was related to an integron-borne OXA-1-type β-lactamase in 85.1% of the cases and to a TEM-1-type β-lactamase in the remaining 14.8%. Resistance to cotrimoxazole was due to the presence of a Dihydrofolate reductase (DHFR) gene in all groups except one of Salmonella flexneri, where a DHFR VII gene was found within an integron. Chloramphenicol resistance was associated in every case with positive chloramphenicol acetyltransferase activity. All strains were susceptible to nalidixic acid, ciprofloxacin, ceftazidime, cefotaxime, and cefoxitin (3).

Gram-negative bacteria identified were Pseudomonas species (20.5%), Pseudomonas aeruginosa (1.86%), Salmonella species (1.09%), Acinetobacter naumannii (8.13%), Escherichia coli (4.06%), and Klebsiella species (5.16%) (4). Gram-negative pathogens were more than gram-positive in bloodstream. Antimicrobial susceptibility was performed against: amikacin, ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone,

tetracycline, chloramphenicol, ciprofloxacin, and gentamicin. Resistance to different antibiotics in the most important isolated bacteria were: 32.1%, 10.8%, 87.8%, 96.0%, 39.1%, 35.2%, 49.4%, 69.0%, 80.02%, 22.0%, 59.0%, 30.1%, respectively, for Pseudomonas species, and 32.0%, 3.7%, 84.2%, 83.2%, 80.1%, 75.4%, 44.8%, 45.2%, 33.3%, 19.0%, 34.1%, 11.5%, respectively, for Acinetobacter species. Resistance to majority of the antimicrobial agents for several pathogens implicated in bloodstream infections, particularly in gram-negative bacteria, can give rise to complications in the treatment of infection cause by them.

2- MATERIALS AND METHODS

2-1. Literature Search

The bibliographic search was performed electronically using Web of Science (via PubMed) database as search engine; November 2017 was the cutoff point.

2-2. Search Terms

The following key words "Neonates", "Infants", "Bacteria", and "Bacteria resistance neonates " were used.

3- RESULTS

3-1. Multidrug-resistance of Salmonella species in infants and children

Commons et al. (5) have determined the incidence and trends in antibiotic resistance in Australian Salmonella enterica subspecies, Salmonella enterica, Salmonella serovar, Salmonella typhi, and Salmonella paratyphi isolates over the past 26 years. These authors analyzed 2,551 isolates, which originated from 74 countries or regions, mainly India (33%) and Indonesia (22%). The incidence of resistance, among Australian residents, increased from 4 to 5 before 2003 to 7 cases per million person-years after 2003. Multidrug-resistance (chloramphenicol, ampicillin, trimethoprim) and nalidixic acid resistance emerged rapidly from the early 1990s, with nalidixic acid resistance increasing to 70% in 2009 to 2010, while multidrug-resistance was relatively stable at between 4% and 11%. Nalidixic acid and multidrug-resistance rates are highest in isolates from the Indian subcontinent. Some countries in South-East Asia, such as Indonesia, had very low rates of resistance; however, this varied across the region. Nalidixic acid resistance has become widespread in enterica fever isolates from the Indian subcontinent and some parts of South-East Asia, justifying the use of ceftriaxone or azithromycin rather than ciprofloxacin as first-line treatment. However, resistance in some countries remains rare, potentially allowing treatment to be adjusted according to the country of origin.

From May 2003 to December 2007, 2,223 Salmonella cases were identified in the New York State FoodNet catchment area (6). Antimicrobial susceptibility testing was completed on the isolates of 98.5% of the cases (n = 2,189). The most common serotypes included Typhimurium (n = 444), Enteritis (n = 392), Newport (n = 175), Heidelberg (n = 170), and Tennessee (n = 77). Overall, almost 80% (n = 1,742) of the Salmonella isolates were pansusceptible, 7% (n = 151) were multidrug-resistant isolates and were resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline and these were named (R-type ACSSuT). Substantial declines in resistance to almost all antimicrobial agents were observed, most declining from levels 15% to 20% in 2003 and 6% to 12% in 2007.

Table.1 shows nontyphoidal Salmonella isolate resistant by antibacterial resistance pattern and agent within the New York State foodborne diseases active

surveillance network in 2003 to 2007 (*please see the table in the end of paper*). R-type ACSSuT varied by serotype with the highest proportions occurring in Typhimurium 17.8% (79/444), Newport 29.1% (51/175), Dublin 75% (6/8), L (+) tartrate 40% (4/10), and Choleraeus 66.7% (2/3). Antimicrobial susceptibility for 2,189 FoodNet cases (98.5% of total cases) showed 79.6% pansusceptible, 6.9% R-type ACSSuT, and 13.5% resistant to at least one antimicrobial agent but not R-type ACSSuT. Four (0.2%) isolates were resistant to ciprofloxacin. From 2004 to 2007, cases with R-type ACSSuT significantly decreased from 8.7% (37/424) to 4.8% (24/499) ($p < 0.01$). Serotypes with the highest proportion of R-type ACSSuT included Salmonella Typhimurium 17.9% (79/444), and Salmonella Newport 29.1% (51/175).

Among Salmonella Typhimurium isolates, over 40% of the African-American cases (19/46) had R-type ACSSuT isolates, compared with 15.7% of the Caucasian cases (58/369) ($p < 0.01$). R-type ACSSuT Salmonella Typhimurium cases were hospitalized (41.8%) more frequently than pansusceptible Salmonella Typhimurium cases (24.9%), after controlling for age (p-< 0.05). Length of hospitalization was not significantly different. Although R-type ACSSuT not Salmonella Typhimurium has decreased since 2003 within the New York State FoodNet catchment area, monitoring resistance patterns remains important in identifying emerging resistant strains, vulnerable populations, and determining appropriate presumptive treatment regimens. The higher rate of R-type ACSSuT among the African-American cases requires further study. Six Salmonella Agona strains from an outbreak of 15 days duration which occurred in a public hospital in Rio de Janeiro, Brazil, were analyzed. The outbreak involved six infants (mean age, 24 days; mean body weight, 1,612 grams); all of them had severe clinical signs and symptoms (7). Two of them had surgical implications, two were preterm and two had respiratory distress at birth. The salmonella strains were resistant to nine antimicrobial agents (ampicillin, cefaclidine, ceftriaxone, gentamicin, amikacin, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracycline). Analysis of the plasmid pattern of the wild strains and of the transconjugants confirmed that these were identical strains.

A total of 508 Salmonella strains isolated during 1983 and 1986 in Tehran, Iran, from cases of diarrhea in children were tested for sensitivity to 10 antimicrobial drugs and their ability to transfer the resistance determinants (8). Salmonella typhimurium and Salmonella Havana were most common (45.7% and 30.9%, respectively) followed by Salmonella typhi (2.9%), and Salmonella Iarochelle (2.4%). The antimicrobial agents used were chloramphenicol, gentamicin, tetracycline, ampicillin, cephalotin, trimethoprim-sulfamethoxazole, kanamycin, nalidixic acid, streptomycin, and furoxone.

A percentage of 91 of the Salmonellae isolates contained resistance determinants, of which 89.6% were resistant to more than one agent. Strains resistant to 4-7 antibiotics comprised 85.6% of the total isolates. Ampicillin resistance was found in 85.4% and nalidixic acid in 2.7%. A total of different patterns of resistance to the antimicrobial agents used were observed, of which chloramphenicol, tetracycline, ampicillin, trimethoprim-sulfamethoxazole, kanamycin, streptomycin and chloramphenicol, cephalotin were the most frequently encountered. A percentage of 71.9 of the resistant strains contained transferable resistance factors and Salmonella typhimurium had the highest rate of transfer (90.8%). Resistance to chloramphenicol had the highest rate of transfer among the agents used (77.4%)

and streptomycin the lowest (20.0%). The pattern most frequently transferred was chloramphenicol, tetracycline, ampicillin, trimethoprim-sulfamethoxazole, and kanamycin (41.9%).

3-2. Multidrug-resistance of Shigella species in infants and children

Antimicrobial susceptibility of Shigella species and Escherichia coli, isolated from diarrheal patients in Lagos, was studied from March 1999 to February 2000 by Iwalokun et al. (9). Four hundred fifty-nine isolates were identified as Shigella (n = 62), and Escherichia coli (n = 397). Shigella flexneri, Shigella dysenteriae, Shigella sonnei accounted for 51.6%, 17.7%, 17.7%, and 13%, respectively (**Table.2**), of the total number of Shigella isolated (*please see the table in the end of paper*). Eleven cases of shigellosis occurred in the age group of 0 to 9 years, 22 cases in the age group 10 to 19 years, and 29 cases in the age group of ≥ 20 years. Of the 397 Escherichia coli isolates, 11 were enteropathogenic, and 7 of these strains were isolated with Shigella from stool samples of patients aged 0 to 9 years (71.4%) and 10 to 19 years (28.6%). Over 70% of the Shigella isolates were resistant to two or more drugs, including ampicillin and tetracycline. Twenty-one distinct multidrug-resistance patterns were observed in these isolates.

During 1990 to 2000, resistance to ampicillin increased from 70% to 90%, cotrimoxazole from 77% to 85%, chloramphenicol from 71% to 77%, streptomycin from 71% to 79% but with MIC_{50} and MIC_{90} (minimal inhibitory concentration [MIC]) values outside the susceptible range. While the resistance to ciprofloxacin and ofloxacin remained with MIC_{50} and MIC_{90} values of 0.008 and 0.0016 µg/ml, respectively. The present findings reveal the endemic pattern of shigellosis with Shigella flexneri as the predominant serogroup in Lagos. Children and young adults were at a higher risk of severe shigellosis. These results also suggest that ampicillin, tetracycline, cotrimoxazole, and streptomycin should not be used as first-line drugs in the treatment of shigellosis. Nalidixic acid should still be selectively used for treatment, while ciprofloxacin and ofloxacin can be ideal alternatives. One hundred and twenty-eight Shigella strains isolated from newborn and infant faecal specimens at Kaohsiung Medical College Hospital in Taiwan were serogrouped, serotyped and examined for multidrug-resistance patterns and for the presence of plasmids (10).

Forty-seven per cent of the isolates were found to belong to the Shigella sonnei serogroup, 41% to the Shigella flexneri serogroup, 9% to the Shigella boydii serogroup, and 3% to the Shigella dysenteriae serogroup. The serotype with the greater number of strains was Shigella sonnei I (29%) followed by Shigella flexneri 1 (27%). Each strain was tested for resistance to 11 antimicrobial agents. Eighty-eight per cent of the strains were resistant to tetracycline, 87% to chloramphenicol, 84% to streptomycin, 52% to ampicillin, 25% to nalidixic acid, 29% to kanamycin, 11% to cephalotin and neomycin, 10% to cotrimoxazole, 1% to amikacin and none to gentamicin (**Table.3**) (*please see the table in the end of paper*).

Clinical isolates demonstrating multidrug-resistance were found to harbor a large transmissible plasmid of 45-75 megadaltons (MDa) while isolates without multiple resistances did not. Two large virulence plasmids of 123 and 110 MDa were found in 12 strains of Shigella flexneri and in 4 strains of Shigella sonnei phase I. Small plasmids of 4.5, 4.2, 3.5, 2.8, 2.5 and 1.5 MDa were also present in all strains. These small plasmids were species specific and can be used as marker plasmids to identify species.

Shigella species belong to the family Enterobacteriacae and are responsible for shigellosis or bacillary dysentery, an important cause of worldwide morbidity and mortality. Bastos and Loureiro (11) studied the multidrug-resistance profiles of 122 Shigella species strains (81 Shigella flexneri, 41 Shigella sonnei, 1 Shigella boydii) isolated from patients (female and males from 0 to 80 years of age) presenting diarrhea in different districts of the State of Pàra, in the North of Brazil. The antibiotic resistance of the strains, isolated from human fecal samples, was determined by the diffusion disk method and by using the VITEK-2 system.

The highest resistance rate found was the resistance rate to tetracycline (93.8%), followed by the resistance rate to chloramphenicol (63.9%) and to trimethoprim-sulfamethoxazole (63.1%). Resistance to at least three drugs was more common among Shigella flexneri than Shigella sonnei (39.5% versus 10%). Six (4.9%) strains were susceptible to all the antibiotics tested. All strains were susceptible to cefotaxime, ceftazidime, ciprofloxacin, nalidixic acid and nitrofurantoin. High rates of multidrug-resistance in Shigella species are a serious public health concern in Brazil. It is extremely important to continuously monitor the antimicrobial resistance of Shigella species for effective therapy and control measures against shigellosis. Eighty-six strains of Shigella species were isolated during the dry season from stool samples of children under 5 years of age in Ifakara, Tanzania (3). The epidemiological relationship as well as the antimicrobial susceptibly and mechanisms of resistance to ampicillin, chloramphenicol, and cotrimoxazole were investigated. Four different epidemiological tools, pulsed-field gel electrophoresis, repetitive estrogenic palindromic- polymerase chain reaction (PCR), plasma analysis, and antibiogram, were compared for typing Shigella strains. Seventy-eight (90%) strains were Shigella flexneri and were distributed into four groups, by either pulsed-field gel electrophoresis or repetitive estrogenic palindromic, with 51, 17, 7 and 3 strains. The four strains of Shigella dysenteries belonged to the same serogroup, and the four strains of Shigella were distributed in two serogroups with three and one strain each. Plasmid analysis showed a high level of heterogeneity among strains belonging to the same pulsed-field gel electrophoresis serogroup, while the antibiogram was less discriminative.

Repetitive estrogenic palindromic-PCR provided an alternative, rapid, powerful genotyping for Shigella species. Overall, antimicrobial susceptibility testing showed a high level of resistance to ampicillin (81.8%), chloramphenicol (72.7%), tetracycline (96.9%), and cotrimoxazole (87.9%). Ampicillin resistance was related to an integron-borne OXA-1-type β-lactamase in 85.1% of the cases and to a TEM-1-type β-lactamase in the remaining 14.8%. Resistance to cotrimoxazole was due to the presence of a DHFR gene in all groups except one of Shigella flexneri, where a DHFR gene VII gene was found within an integron. Chloramphenicol resistance was associated in every case with positive acetyltransferase activity. All strains were susceptible to nalidixic acid, ciprofloxacin, ceftazidime, cefotaxime, and cefoxitin. Therefore, these antimicrobial agents may be a good alternative for the treatment of diarrhea caused by Shigella in Tanzania. Diversity within Shigella dysenteriae (n = 40) and Shigella boydii (n = 30) isolates from children living in Egypt aged < 5 years was investigated by El-Gendy et al. (12). Shigella-associated diarrhea occurred mainly in summer months and in children aged < 3 years, it commonly presented with vomiting and fever. Serotypes 7 (30%), 2 (28%), and 3 (23%) accounted

for most of Shigella dysenteriae isolates; 50% of Shigella boydii isolates were serotype 2. Shigella dysenteriae and Shigella boydii isolates were often resistant to ampicillin, chloramphenicol, and tetracycline (42% to 17%), although resistance varied among serotypes. Pulsed-field gel electrophoresis separated the isolates into distinct clusters correlating with species and serotype. Genetic differences in trimethoprim-sulfamethoxazole and β-lactam-encoding resistance genes were also evident. Shigella dysenteriae and Shigella boydii are genetically diverse pathogens in Egypt; the high level of multidrug-resistance associated with both pathogens and resistance to the most available inexpensive antibiotics underlines the importance of continuing surveillance.

Mandomando et al. (13) assessed the antimicrobial and mechanisms of resistance of 109 Shigella and 40 Salmonella isolates from children with diarrhea in southern Mozambique. The susceptibility to 7 antimicrobial agents was tested by disk diffusion, and mechanisms of resistance were searched by PCR or colorimetric method. A high proportion of Shigella isolates were resistant to chloramphenicol (52%), ampicillin (56%), tetracycline (66%), and trimethoprim-sulfamethoxazole (84%).

Table.4 shows the MIC_{50}, MIC_{90} and the percent of resistance of 3 species of Shigella and salmonella in children aged less than 5 years (*please see the table in the end of paper*). Sixty-five percent of the isolates were multidrug-resistant. Shigella flexneri isolates were more resistant than those of Shigella sonnei to ampicillin (66% versus 0.0%, $p < 0.001$), and to chloramphenicol (61% versus 0.0%, $p < 0.001$), whereas Shigella sonnei isolates presented higher resistance to tetracycline than Shigella flexneri isolates (93% versus 64%, $p = 0.02$). Resistance among Salmonella isolates was as follows: tetracycline and chloramphenicol, 15% each; trimethoprim-sulfamethoxazole (18%), and ampicillin 25%. Only 3% of Salmonella isolates were resistant to nalidixic, ampicillin, ciprofloxacin or ceftriaxone. Among Salmonella isolates, multidrug-resistance was found in 23% of patients. Among Shigella isolates, antibiotic resistance was related mainly to the presence of OXA-1-like β-lactamases for ampicillin, dfrA1 genes for trimethoprim-sulfamethoxazole, tetB genes for tetracycline, and chloramphenicol acetyltransferase activity for chloramphenicol. The present data show that Shigella isolates are resistant mostly to the most available, inexpensive antibiotics by various molecular mechanisms but remain susceptible to ciprofloxacin, which is the first line for empirical treatment of shigellosis.

Egah et al. (14) studied the alarming rise in antimicrobial resistance among Shigella species in Jos, Plateau State. Stool samples of eight hundred and ten patients who presented at the Jos University Teaching Hospital with diarrhea/dysentery were analyzed using standard bacteriological techniques. The antimicrobial susceptibility of the isolates was determined. Twenty-five Shigella species were isolated representing 3.1% isolation rate. The male to female ratio was 1.3:1, children age 0 to 10 years old constituted 16 (64%) of cases. Shigella flexneri (48%) was the most common serogroup. This was followed by Shigella boydii (24%), Shigella sonnei (20%), and Shigella dysenteriae (8%). Most strains of Shigella species were resistant to ampicillin (96.0%), chloramphenicol (96.0%), cotrimoxazole (88%), nalidixic acid (84%), and tetracycline (t5%). All strains were found to be sensitive to ciprofloxacin. The drugs of choice in the treatment of Shigella infection in this environment should be ciprofloxacin and ofloxacin. Gentamicin was the third drug

of choice but its use is limited since the infection is not systematic. To avoid continuous abuse of antibiotics in Nigeria there should be an effective legislation by the government to control the indiscriminate purchase of antibiotics. Twenty-one Shigella isolates were obtained from bloody faecal specimens of diarrheal patients at Rajbari District Hospital from January 1994 to June 1995, and serogrouped (15). Fourteen (67%) isolates belonged to the Shigella dysenteriae serogroup and 7 (33%) to Shigella flexneri serogroup. Shigella dysenteriae strains were further serotyped; all were Shigella dysenteriae type 1. Each strain was tested for resistance to 6 common antimicrobial agents. The two strains had different antibiotic susceptibility patterns.

The 7 Shigella flexneri showed 6 different resistant patterns and the 14 Shigella dysenteriae type 1 isolates had 4 resistance patterns. One of the Shigella dysenteriae type 1 isolates was resistant to all 6 antimicrobial agents tested and twice to a different combination of 4 antimicrobials. The 14 (100%) Shigella dysenteriae 1 strains were resistant to 3 major antimicrobial agents: ampicillin, tetracycline, and chloramphenicol; 13 (93%) were resistant to 5 agents: ampicillin, tetracycline, chloramphenicol, trimethoprim-sulfamethoxazole, and nalidixic acid. Ciprofloxacin was the only drug active against all 7 Shigella flexneri and 13 of the 14 (93%) Shigella dysenteriae type 1 strains.

Antimicrobial susceptibility assay demonstrated that Shigella was more resistant to ampicillin, ceftriaxone, and sulfamethoxazole than Salmonella (16). The enteric pathogens causing diarrhea impair children's health severely. This study retrospectively analyzed 1,577 pathogens isolated from inpatients and outpatients in six hospitals located in Northern (Inner Mongolia), Northeastern (Hebei), Eastern (Shanghai and Jiangsu), Southern (Hainan), and Central (Hubei) China between 2008 and 2013; Of the 1,577 enteric pathogens, Salmonella presented with the highest frequency (36.0%), followed by diarrhoegenic Escherichia coli (23.7%), Staphylococcus aureus (15.0%), Shigella (13.1%), and Aeromonas (4.6%). The predominant pathogens varied in different regions of China, with Salmonella most prevalent in Shanghai and Hainan, diarrhoegenic Escherichia coli most prevalent in Inner Mongolia, Jiangsu and Hubei, and Shigella most prevalent in Hebei. Enteric pathogens were more frequently isolated in males (56.9%) than in females (43.1%).

The highest proportion of all enteric pathogens was found in infants (67.6%) with a peak in summer and autumn (68.5%). Of the top two serotypes in Salmonella, Typhimurium was more resistant to ciprofloxacin, sulfamethoxazole and chloramphenicol than Enteritidis ($p < 0.001$). Meanwhile, the resistance rates of Shigella flexneri against ampicillin/sulbactam, ciprofloxacin, and chloramphenicol were significantly higher than those of Shigella sonnei ($p < 0.001$). Multidrug-resistance was apparent in 58.2% of Shigella and 45.9% of Salmonella, and this phenomenon was more pronounced in Shigella flexneri.

3-3. Multidrug-resistance of Streptococcus pneumoniae in infants and children

Streptococcus pneumoniae is a frequent cause of respiratory tract infections. In the United States and worldwide, antimicrobial resistance of Streptococcus pneumoniae has complicated the management of infections caused by this organism (17). In the United States, antimicrobial resistance of Streptococcus evolved almost entirely during the 1990s. Resistance currently exists at high rates

with β-lactams, macrolides, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole. Multiresistant strains that are resistant to penicillin plus at least 2 other antimicrobial classes are also increasing in prevalence. Fluoro-quinolone resistance remains at low levels in the United States. Control of the problem of antimicrobial resistance will require more judicious and appropriate use of antimicrobials, the development of new agents with novel targets of action, and strategies for preventing disease from occurring in the first place. In addition, the pursuit of an understanding of resistance mechanisms and pharmacodynamics as they relate to clinical outcome must be an ongoing effort, and that knowledge must be applied to the development of more effective approaches for the treatment of infections caused by Streptococcus pneumoniae.

Table.5 shows the in vitro activity of selected β-lactam antimicrobials versus Streptococcus pneumoniae sorted by penicillin susceptible category and **Table.6** summarizes the current resistance rates of non-β-lactam antimicrobials versus Streptococcus pneumoniae, by penicillin susceptible category. Ninety Cambodian children were hospitalized with invasive pneumococcus pneumoniae, with a median age of 2.3 years (range, 0.9 to 6.2 years) (18) (*please see the tables in the end of paper*).

The case fatality was 15.6%. Of 50 Streptococcus pneumoniae isolates available for further testing, 46% were penicillin non-susceptible and 8% were ceftriaxone non-susceptible, 78% were cotrimoxazole resistant, and 30% chloramphenicol resistant. There were no significant changes in resistance levels over the five-year period. The most common serotypes were 1 (11/50; 22%), 23F (8/50; 16%), 14 (6/50; 12%), 5 (5/50; 10%), and 19A (3/50; 6%). Coverage by Seven-valent pneumococcal conjugate vaccine (PCV7), Pneumococcal conjugate vaccine 10 (PCV10), and Pneumococcal vaccine 13 (PCV13) was 44%, 76%, and 92%, respectively. Moore et al. (18) identified novel multilocus sequence types and resist types using whole genome sequencing. Invasive pneumococcus sequence is an important disease in Cambodian children and can have a significant mortality. PCV13 coverage of the serotypes determined in studied strains was high and consistent with another recent study. The phenotypic resistance patterns observed was similar to other regional studies. The use of whole genome sequencing in the present study provides additional typing and resists types.

Fifty-nine Streptococcus pneumoniae strains were isolates from infection (n=31) and colonization (n = 28) sites of patients (children and adults) (19). The majority (66.1%) of the isolates belonged to 5 serotypes all included in pneumococcal conjugate vaccines (PCVs): 6B, 9V, 14, 19F, and 23F. The potential coverage of 10-valent and 13-valent PCV was 71.2% and 76.3%, respectively. Resistance rates were very high and 69.5% of isolates were multidrug-resistant: non-susceptibility rates to penicillin, amoxicillin, and cefotaxime were 66.1%, 40.7%, and 76.3%, respectively; resistance rates to erythromycin, clindamycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole were 69.5%, 61.0%, 37.3%, 22.0%, and 67.8%, respectively.

The most frequent serotypes had STs characteristic of multidrug-resistant international clones known to be highly successful and important causes of pneumococcal infection: Spain 23F-ST81, Franc 9V/14-ST156, Spain 6B-ST90, 19-ST320, and Portugal 19F-ST177. The majority of Streptococcus pneumoniae strains recovered from immunocompromised patients in Tunisia is representative of multidrug-resistant pandemic clones that express serotypes

targeted by PVCs. To contain the burden of pneumococcal disease and improve treatment choice among Tunisian immunocompromised patients PVCs should be offered to all of them.

3-4. Multidrug-resistance of Salmonella in infants and children

Solghan et al. (6) described the prevalence and trends of nontyphoidal Salmonella antimicrobial susceptibility within the New York State Foodborne Diseases Active Surveillance Network. The New York State Department of Health, Wadsworth Center Public Health Laboratory tested all Salmonella isolates from the New York State FoodNet catchment area between May 2003 and December 2007 for antimicrobial susceptibility to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, nalidixic acid, and ciprofloxacin. Isolate susceptibility results were linked to their corresponding demographic and clinical data and analyzed. Multidrug-resistant isolates were defined as resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline and this multidrug-resistant was defined "R-type ACSSuT".

Antimicrobial susceptibility for 2,189 FooNet cases (98.5% of total cases) showed 79.6% pansusceptible, 6.9% R-type ACSSuT, and 13% resistant to at least one antimicrobial agent but not R-type ACSSuT. Four (0.2%) isolates were resistant to ciprofloxacin. From 2004 to 2007, cases with R-type ACSSuT significantly decreased from 8.7% (37/424) to 4.8% (24/499) (p-level < 0.01). Serotypes with the highest proportion of R-type ACSSuT included Salmonella Typhimurium 17.9% (79/444), and Salmonella Newport 29.1% (51/175). Among Salmonella Typhimurium isolates, over 40% of the African-American cases (19/46) had R-type ACSSuT isolates, compared with 15.7% of the Caucasian cases (58/369) (p-level < 0.01). R-type ACSSuT nontyphoidal Salmonella has decreased since 2003 within the New York State FoodNet catchment area. Monitoring resistance patterns remains important in identifying emerging resistant strains, the vulnerable population, and determining appropriate presumptive treatment regimens. In Africa, multidrug-resistant non-typhoidal salmonella are one of the leading causes of morbidity and the high rate of mortality in children under 5 years of age, second in importance only to pneumococcal disease. Kariuki et al. (20) studied the non-typhoidal Salmonella isolates from pediatric patients admitted at two hospital in Nairobi, Kenya, and followed the index cases to their homes, where rectal swabs and stools from parents and siblings, and animals in close contact, were obtained.

The majority of non-typhoidal salmonella from cases were Salmonella enterica serotype Typhimurium (106 out of 193; 54.9%) and Salmonella enterica serotype Enteritidis (64; 33.2%), a significant proportion (34.2%) of which were multiply resistant to 3 or more antibiotics, including ampicillin, tetracycline, cotrimoxazole and chloramphenicol. Only 23.4% of non-typhoidal salmonella were fully susceptible to all 10 antibiotic tested. Of the 32 non-typhoidal salmonella obtained from contacts (9 adults and 23 children) at the times of index cases, 21 (65.6%) isolates were similar by antibiotic-susceptibility profiles and plasmid content, and their Xbal- and Spel-digestion chromosomal DNA patterns were indistinguishable from those of the corresponding index cases.

Only 3 out of 180 (1.7%) samples from environmental sources, including animals, soil, sewers and food, contained non-typhoidal salmonella matching those from corresponding index cases. The carriage of non-typhoidal salmonella in an asymptomatic population was represented

by 6.9% of human contacts from 27 out of 127 homes sampled. This population of carriers may represent an important reservoir of non-typhoidal salmonella that would play a significant role in the epidemiology of community-acquired non-typhoidal salmonella bacteremia in children. Mwangi et al. (21) retrospectively reviewed data from children admitted with acute bacterial meningitis to a Kenyan district hospital from 1994 through 2000. These authors also examined the antibiotic susceptibility patterns. A total of 390 cases (1.3% of all admissions) of whom 88% were less than 5 years old. The apparent minimum annual incidence in children younger than 5 years of age increased from 120 to 202 per 100,000 children between 1995 and 2000 ($p < 0.001$). Increasing the lumbar punctures performed by including prostrated or convulsing children significantly increased the number of cases detected ($p < 0.005$).

The most common organisms in infants with age less than 3 months were streptococci and Enterobacteriacae. Streptococcus pneumoniae (43.1%) and Haemophilus influenzae (41.9%) were predominant in the postneonatal period. The overall mortality rate was 30.1%, and 23.5% of survivors developed neurologic sequelae. Chloramphenicol resistance of Haemophilus influenzae rose from 8% in 1994 to 80% in 2000 ($p < 0.0001$) accompanied by an apparent increase in mortality rate. Acute bacterial meningitis in rural Kenya is a severe illness with substantial mortality and morbidity. Prognosis could be improved by broadening the criteria for lumbar puncture and use of appropriate antibiotics.

3-5. Multidrug-resistance of Pseudomonas aeruginosa in infants and children

Thirty-two neonates with a mean age of 12.5 days hospitalized in a neonatal intensive care unit of a public maternity hospital in Rio de Janeiro, Brazil, were seized by Pseudomonas aeruginosa during the period from July 1997 to July 1999 (22). Twenty (62.5%) patients received antimicrobials before positive blood cultures presentation. A total of 87.5% neonates were premature, 62.5% presented very-low-birth weight and 40.6% had asphyxia. High multidrug-resistance percentage to β-lactams, chloramphenicol, trimethoprim-sulfamethoxazole and tetracycline was detected among the isolated strains. All isolated strains were classified multidrug-resistant. Most strains presented serotype O11 while pulsed field gel electrophoresis analysis revealed seven distinct clones with isolation predominance of a single clone (75%) isolated from July 1997 to June 1988. Etiologic agents of meningitis were prospectively investigated among patients admitted to Usman Danfondio, University Teaching Hospital, Sokoto (23).

Of 1,097 cerebrospinal fluid samples submitted to the microbiology laboratory from various wards of the hospital, 289 (26%) were microscopically, culturally and/or serologically proven to be affected by bacterial meningitis. The etiologic spectrum was as follows: Neisseria meningitis (61%), Streptococcus pneumoniae (18%), Haemophilus influenzae (10%), Staphylococcus aureus (6%), Coliform bacilli (3%), Escherichia coli (0.7%), Mycobacterium tuberculosis (0.7%), Listeria monocytogenes (0.4%), Flavobacterium meningosepticum (0.4%), and Pseudomonas putrifaciens (0.4%). Bacterial meningitis was most prevalent (195; 68%) among children aged 1 to 9 years, while adults and neonates were least affected. Coliform bacilli caused 5 of 8 neonatal cases. Males were more frequently affected than females ($p < 0.05$). Culture and microscopy were comparatively less efficient than the search for bacterial antigens, specifically in the

diagnosis of Haemophilus meningitis. Antimicrobial susceptibility of Neisseria meningitides to ampicillin and benzyl penicillin reduced progressively over the years ($F = 406.98$; $p < 0.001$). Nineteen (11%) of the isolates (5 Meningococci, 7 Staphylococcus aureus, 1 Haemophilus influenzae and 6 others) showed simultaneous resistance to chloramphenicol, ampicillin and benzyl penicillin.

3-6. Multidrug-resistance of Haemophilus strains in infants and children

Haemophilus bacteria are normally present in the upper respiratory tract of healthy individuals. However, these bacteria could be opportunistic pathogens especially in children (24). A total of 154 Haemophilus strains were isolated from throat swabs of 208 children who had upper respiratory tract infections (24). Among the 154 Haemophilus strains isolated, n= 117 Haemophilus influenzae (76%), n= 35 Haemophilus parainfluenzae (22.7), and n= 2 Haemophilus aphrophilus (13%) were identified by API of New Hampshire (NH). β-lactamase activity was positive in 42 isolates of 117 Haemophilus influenzae isolates, while it was negative in 75 isolates. β-Lactamase activity was positive in 20 Haemophilus parainfluenzae isolates, and negative in 15.

All the Haemophilus aphrophilus isolates were β-lactamase negative. It is known that β-lactamase positive Haemophilus bacteria are resistant to some antibiotics. Therefore, the antibiotic resistance of Haemophilus was further investigated in relation to β-lactamase activity. The in vitro antibacterial susceptibilities of Haemophilus strains for ampicillin, sulbactam-ampicillin, trimethoprim-sulfamethoxazole, gentamicin, chloramphenicol, and ciprofloxacin were tested by disk diffusion method on chocolate agar. In 42 β-lactamase-positive Haemophilus influenzae isolates, 32 isolates were resistant against ampicillin. In 20 β-lactamase-positive Haemophilus parainfluenzae isolates, 16 were resistant to ampicillin. The 2 β-lactamase-negative Haemophilus aphrophilus were sensitive to ampicillin. **Table.7** shows the susceptibility and resistance in β-lactamase-positive Haemophilus isolates against various antibiotics, and **Table.8** shows the susceptibility and resistance in β-lactamase-negative Haemophilus isolates against various antibiotics (*please see the tables in the end of paper*).

3-7. Multidrug-resistance of Staphylococcus aureus in infants and children

Wang et al. (25) correlated the multidrug-resistance (MDR) and sequence type (ST) clones of community-associated (CA) methicillin-resistant Staphylococcus aureus (MRSA) to identify the genes responsible for clindamycin and mupirocin in Staphylococcus aureus from pediatric hospital in mainland China. A total of 435 Staphylococcus aureus isolates were collected. Compared with CA methicillin susceptible Staphylococcus aureus (MSSA), the resistance rates of CA-MRSA to ciprofloxacin, chloramphenicol, gentamicin, and tetracycline were higher (19.0 versus 2.6%, $p < 0.001$; 14.7 versus 3.1%, $p < 0.001$; 14.7 versus 3.1%, $p < 0.01$; and 46.0 versus 13.3%, $p < 0.001$, respectively).

Compared with hospital-associated (HA)-MRSA, the resistance rates of CA-MRSA to ciprofloxacin, gentamicin, rifampicin, tetracycline, and trimethoprim-sulfamethoxazole were lower (19 versus 94.8%, $p < 0.001$; 14.7 versus 84.4%, $p < 0.0001$; 5.5 versus 88.3%, $p < 0.001$; 46 versus 94.8%, $p < 0.001$; 1.8 versus 9.1%. $p < 0.01$, respectively). The resistance rates of CA-MRSA, HA-MRSA and CA-MSSA to clindamycin (92.0, 77.9, and 64.1%, respectively), and erythromycin

(85.9, 77.9, and 63.1%, respectively) were high. The MDR rates (resistance to three or more non-β-lactams) were 49.6, 100, and 14% in the CA-MRSA, HA-MRSA and CA-MSSA isolates, respectively. Five of seven ST clones in the CA-MRSA isolates, namely ST59, ST338, ST45, ST910 and ST965, had MDR rates > 50% (67.9, 87.5, 100, 50, and 83.3%, respectively). The constitutive phenotype of macrolide-lincosamide-streptogramin B (MLSb) resistance (69%) and the ermB gene (38.1%) predominated among the MLSb-resistance CA-Staphylococcus aureus strains.

The resistance rate to mupirocin was 2.3% and plasmids carrying the mupA gene varied in size between 23 and 54.2 kb in six strains with high-level resistance as determined by Southern blot analysis. The present data show that resistance to non-β-lactams, especially to clindamycin, is high in CA-MRSA isolates from Chinese children and that the profile of resistance is related to clonal type. The present findings reveal distinctive patterns of MLSb-resistant genes among CA-Staphylococcus aureus isolates. **Table.9** shows the antimicrobial resistance to non-β-lactam agents of Staphylococcus aureus isolated from pediatric hospitals in mainland China (*please see the table in the end of paper*).

Methicillin-resistant Staphylococcus aureus (MRSA) is a common multidrug-resistant (MDR) pathogen (26). Herein are discussed MRSA and its infections in Krasnoyarsk, Siberian Russia between 2007 and 2011. The incidence of MRSA in 3,662 subjects was 22.0% and 2.9% for healthcare- and community-associated MRSA (HA- and CA-MRSA), respectively. The 15-day mortality rates for MRSA hospital- and community-acquired pneumonia (HAP and CAP) were 6.5% and 50%, respectively. MRSA CAP cases included pediatric deaths; of the MRSA pneumonia episodes available, ≥ 27.3% were associated with bacteremia. Most cases of HA-MRSA examined exhibited ST239/spa3 (t037)/SCCmecIII.1.1.2 (designated as ST239Kras), while all CA-MRSA cases examined were ST8/spa1 (t008)/SCCmecIV.3.1.1 (IVc) (designated as ST8Kras). ST239Kras and ST8Kras strongly expressed cytolytic peptide (phenol-soluble modulin alpha (PSMα); and δ-hemolysin, hld) genes, similar to CA-MRSA. ST239Kras pneumonia may have been attributed to a unique set of multiple virulence factors (MVFs): toxic shock syndrome toxin-1 (TSST-1), elevated PSMα/Hld expression, α-hemolysin, the staphylococcal enterotoxin SEK/SEQ, and the immune evasion factor SCIN/SAK, and collagen adhesion. Regarding ST8Kras, SEA was included in MVFs, some of which were common to ST239Kras.

The ST239Kras (strain OC3) genome contained: a completely unique phage, φSa7-like (W), with no at repetition; Staphylococcus aureus pathogenicity island SaPI2R, the first TSST-1 gene-positive (tst+) SaPI in the ST239 lineage; and a super copy of IS256 (≥22 copies/genome). ST239Kras carried the Brazilian SCCmecIII.1.1.2 and United Kingdom-type test. ST239Kras and ST8Kras were MDR, with the same levofloxacin resistance mutations; small, but transmissible chloramphenicol resistance plasmids spread widely enough not to be ignored. These results suggest that novel MDR and MVF+ HA- and CA-MRSA (ST239Kras and ST8Kras) emerged in Siberian Russia (Krasnoyarsk) associated with fatal pneumonia, and also with ST239Kras, a new (Siberian Russian) clade of the ST239 lineage, which was created through stepwise evolution during its potential transmission route of Brazil-Europe-Russia/Krasnoyarsk, thereby selective advantages from unique MVFs and the MDR.

3-8. Multidrug-resistance of Klebsiella isolates in a neonatal intensive care unit

An outbreak of multiresistant Klebsiella pneumoniae occurring in a neonatal intensive care unit is described by Reish et al. (27). All infections developed at least 5 days after admission to the unit (range, 5 to 40 Days). Four infants had septicemia and one had urinary tract infection. Three of the infected infants died. All Klebsiella isolates were resistant to ampicillin, cefotaxime, cefuroxime, co-amxilav, mezlocillin, chloramphenicol, gentamicin, and ceftazidime (except in two); all were susceptible to imipenem and quinolones. An extensive case-control study identified the following significant risk factors for colonization: prematurity; presence of indwelling catheters; previous antibiotic treatment; and parenteral nutrition. The outbreak was controlled with re-emphasis on strict hand-washing practices, chortling, closure of the unit to outborn admissions, and changing the regimen of empirical antibiotic therapy. Physicians should be aware of multiresistant Klebsiella species and change treatment whenever clinically indicated, even before culture results are available.

3-9. Multidrug-resistance of Enteropathogenic Escherichia coli (EPEC) isolates in infants and children

Huang et al. (28) investigated the drug resistance and β-lactamase genotype distribution of enteropathogenic Escherichia coli isolated from pediatric patients with diarrhea in southern China. The prevalence of enteropathogenic Escherichia coli in children with diarrhea was 3.53%. The commonest serotypes were O55:K59 and O126:K1, and the typical enteropathogenic Escherichia coli were more prevalent than atypical enteropathogenic Escherichia coli (51 versus 7). Isolates from this region were most commonly found to be resistant to ampicillin and cotrimoxazole, followed by chloramphenicol, ceftriaxone, and ceftazidime. More than 96% of the strains were susceptible to cefoperazone/sulbactam and imipenem. The most common β-lactamase genotypes identified in 58 strains were blaCTX-M-1 (60.3%), blaTEM (56.9%), blaCTX-M-0 (27.6%), and blaSHV (15.5%). Among 58 isolates, 22 strains were found to harbor one β-lactamase gene, and the proportions of resistance to ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, and ceftazidime, were 81.8%, 63.6%, 40.9%, 18.2%, and 9.1%, respectively. A further 30 strains carrying multiple β-lactamase genes had increased resistance to the above antimicrobial agents (100%, 83.3%, 70.0%, 60.0% and 30.0%, respectively). In contrast, antibiotic resistance in the last 6 strains without a detectable β-lactamase gene was substantially reduced. Drug resistance may be associated with the β-lactamase gene number, with a greater number of β-lactamase genes resulting in higher antibiotic resistance.

3-10. Multidrug-resistance of Vibrio cholera in infants and children

Various Vibrio cholera serogroups cause cholera, which occurs as a major epidemic disease in most developing countries (29). The study was undertaken during cholera epidemics in North West Ethiopia from August 2006 to September 2008. Diarrheic stool samples were processed per the standard microbiology procedures at Bahir Dar Regional Health Research Laboratory. Antimicrobial susceptibility tests were performed using disc diffusion technique per Kirby-Bauer method. Eighty- one Vibrio cholera 01 serotype Inaba were isolated from stools of cholera cases. Antibiograms of Vibrio cholera 01 Inaba showed that 71.6% of isolates were resistant against two, 18.4% to three and 5% to four antibiotics.

All Vibrio cholera Inaba isolates were resistant to cotrimoxazole n= 81 (100%). High levels of resistance were also shown to chloramphenicol n= 76 (94%), and ampicillin n= 72 (89%) with least resistance to erythromycin n= 12 (15%), tetracycline n= 5 (6.2%), and ciprofloxacin n= 1 (1.2%). However, all isolates remain susceptible to doxycycline n= 81 (100%). In the study area, doxycycline or ciprofloxacin could be used for treatment of adult cholera cases whereas erythromycin is an alternative for young children. Antimicrobial susceptibility tests are strongly recommended for Vibrio cholera strains in treatment intervention during epidemics.

4- DISCUSSION

Pathogenic bacteria may cause disease and death. The major pathogenetic bacteria are the enteric gram-negative bacilli, especially Escherichia coli, Klebsiella, Enterobacter, Haemophilus influenzae type b, Pseudomonas species, Salmonella Species, Shigella species, Streptococcus pneumoniae, Acinetobacter naumannii, and Vibrio cholera. The antibiotics that cause resistance to these organisms are ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, and ceftazidime. When a bacterial becomes resistant to at least two or more, antimicrobials; this effect is named multidrug-resistant. Resistance to chloramphenicol usually is caused by a plasmid-encoded acetyltransferase that inactivate the drug. Acetylated derivatives of chloramphenicol fail to bind to bacterial ribosomes (30). Ampicillin resistance is related to an integron-borne OXA-1-type β-lactamase in 85.2% of the cases and to a TEM-1-type β-lactamase in the remaining 14.8%. Resistance to cotrimoxazole was due to the presence of a DHFR gene in all groups except one of Salmonella flexneri, where a DHFR VII gene was found within an integron. Chloramphenicol resistance was associated in every case with positive chloramphenicol acetyltransferase activity. All strains were susceptible to nalidixic acid, ciprofloxacin, ceftazidime, cefotaxime, and cefoxitin (3). Antimicrobial susceptibility was performed against: amikacin, ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone, tetracycline, chloramphenicol, ciprofloxacin, and gentamicin (4). Gram-negative bacteria identified were Pseudomonas species (20.5%), Pseudomonas aeruginosa (1.86%), Salmonella species (1.09%), Acinetobacter naumannii (8.13%), Escherichia coli (4.06%), and Klebsiella species (5.16%) (4). Gram-negative pathogens were more than gram-positive in the bloodstream. Antimicrobial susceptibility was made against: amikacin, ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone, tetracycline, chloramphenicol, ciprofloxacin, and gentamicin.

Resistance to different antibiotics in the most important isolated bacteria were: 32.1%, 10.8%, 87.8%, 96.0%, 39.1%, 35.2%, 49.4%, 69.0%, 80.02%, 22.0%, 59.0%, 30.1%, respectively, for Pseudomonas species, and 32.0%, 3.7%, 84.2%, 83.2%, 80.1%, 75.4%, 44.8%, 45.2%, 33.3%, 19.0%, 34.1%, 11.5%, respectively, for Acinetobacter species. Resistance to a majority of the antimicrobial agents for several pathogens implicated in bloodstream infections, particularly in gram-negative bacteria, can make complications in treatment of infection caused by them. A multidrug-resistance of Salmonella enterica subspecies: Salmonella enterica, Salmonella serovar, Salmonella typhi, and Salmonella paratyphi is caused by chloramphenicol, ampicillin, trimethoprim and nalidixic acid (5). In neonates, Salmonella strains were resistant to ampicillin, cephalotin, ceftriaxone,

gentamicin, amikacin, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracycline. Analysis of the plasmid pattern of the wild strains and of the transconjugants confirmed that these were identical strains (7). Salmonella typhimurium and Salmonella Havana were the most common (45.7% and 30.9%, respectively) followed by Salmonella typhi (2.9%), and Salmonella Iarochelle (2.4%) (8). The antimicrobials used were chloramphenicol, gentamicin, tetracycline, ampicillin, cephalotin, trimethoprim-sulfamethoxazole, kanamycin, nalidixic acid, streptomycin, and furoxone. Strains resistant to 4-7 antibiotics comprised 85.6% of total isolates. A percentage of 71.9 of resistant strains contained transferable resistance factors and Salmonella Typhimurium had the highest rate of transfer (90.8%). Chloramphenicol had the highest rate of transfer among the agents used (77.4%) and streptomycin the lowest (20.0%). A total of Shigella species (n = 62) were isolated from diarrheal patients (9).

Over 70% of the Shigella was resistant to two or more antibiotics. Twenty-one distinct multidrug-resistance patterns were observed in these isolates. A percentage of 91 of the salmonellae isolated contained resistance determinants, of which 89.6% were resistant to more than one antimicrobial. Strains resistant to 4-7 antibiotics comprised 85.6% of the total isolates. Resistance to chloramphenicol had the highest rate of transfer among the antimicrobial used (77.4%) and streptomycin the lowest (20.0%). The resistance patterns most frequently transferred was chloramphenicol, tetracycline, ampicillin, trimethoprim-sulfamethoxazole, and kanamycin. One hundred and twenty-eight Shigella strains were isolated from newborn and infant faecal specimens (10). Six Shigella strains were observed. Each strain was tested for resistance to 11 antibiotics. The resistance varied from 84% for chloramphenicol to 1% for Kanamycin, while no resistance was observed for gentamicin. Clinical isolates demonstrating multidrug-resistance were found to harbor a large transmissible plasmid of 45-75 MDa while isolates without multiple-resistance did not. Two large virulence plasmids of 123 and 110 MDa were found in 12 strains of Shigella flexneri, and 4 strains of Shigella sonnei. Small plasmids of 4.5, 4.2, 3.5, 2.8, and 1.5 MDa were present in all strains. These plasmids were species-specific and can be used as marker plasmids to identify species. Bastos and Loureiro (11) studied the multidrug-resistance profiles in 122 Shigella strains isolated from patients aged from 0 to 80 years presenting diarrhea. The highest resistance rate rates were found for tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole. esistance to at least three drugs was more common among Shigella sonnei (39.5%) and Shigella sonnei (10%). Six (4.9%) of Shigella strains were susceptible to all antibiotics tested. Resistance to at least three drugs was common among Shigella flexneri and Shigella sonnei.

Navia et al. (3) investigated the epidemiological relationship as well as the antimicrobial susceptibility and the mechanisms of resistance to ampicillin, chloramphenicol, and cotrimoxazole in 86 strains of Shigella species isolated from the stool samples of children less than 5 years of age. Shigella flexneri was the major Shigella strain (90%). Overall, antimicrobial susceptibility testing showed a high level of resistance to ampicillin, chloramphenicol, tetracycline, and cotrimoxazole. Ampicillin resistance was related to an integron-borne OXA-1-type β-lactamase in 85.2% of the cases and to a TEM-1-type β-lactamase in the remaining 14.8%. Resistance to cotrimoxazole was due to the presence of a DHFR gene in all groups except one of Shigella flexneri, where a DHFR VII gene

was found within an integron. Resistance to chloramphenicol is caused by a plasmid by a plasma-encoded acetyltransferase that inactivate the drug. Resistance also can result from decreased permeability and from ribosomal mutation. Acetylated derivatives of chloramphenicol fail to bind to bacterial ribosome (30). All strains were susceptible to nalidixic acid, ciprofloxacin, ceftazidime, cefotaxime, and cefoxitin.

El-Genday et al. (12) investigated the diversity within Shigella dysenteriae and Shigella boydii isolated from stool samples of diarrheic children aged < 5 years. Shigella dysenteriae and Shigella boydii isolates were often resistant to ampicillin, chloramphenicol, and tetracycline. Genetic differences in trimethoprim-sulfamethoxazole and β-lactam-encoding resistance genes were also present. Shigella dysenteriae and Shigella boydii are genetically diverse pathogens and the high level of multidrug-resistance associated with both pathogens and their resistance to the most available inexpensive antibiotics underlines the importance of continuing surveillance. Mandomando et al. (13) assessed the antimicrobial and mechanisms of resistance in 109 Shigella and 40 Salmonella isolates from children with diarrhea aged less than 5 years.

A high proportion of Shigella isolates were resistant to chloramphenicol, ampicillin, tetracycline, and trimethoprim-sulfamethoxazole. Sixty-five percent of the isolates were multidrug-resistant. Shigella flexneri isolates were more resistant than Shigella sonnei to ampicillin, and chloramphenicol, whereas Shigella sonnei isolates were more resistant to tetracycline. Among Shigella isolates, antibiotic resistance was related mainly to the presence of OXA-1-like β-lactamases for ampicillin, dfrA1 genes for trimethoprim-sulfamethoxazole, tetB genes for tetracycline, and acetyltransferase for chloramphenicol. Salmonella isolates were resistant to tetracycline, chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin. Multidrug-resistance of Salmonella isolates was found in 23% of patients. Egah et al. (14) collected stool samples from eight hundred and ten children. The Shigella isolated was flexneri, boydii, sonnei, and dysenteriae. Most strains of Shigella isolated were resistant to ampicillin, chloramphenicol, cotrimoxazole, nalidixic acid, and tetracycline. All strains were found to be sensitive to ciprofloxacin. Jahan and Hossain (15) collected 21 Shigella specimens from diarrheal bloody faecal, 14 (67%) specimens were Shigella dysenteriae 1 and 7 (33%) were Shigella flexneri. The two strains had different antibiotic susceptibility patterns. All Shigella isolates were tested for resistance to 6 common antibiotics. The two strains had different antibiotic susceptibility patterns. The Shigella flexneri isolates showed resistant patterns to all antibiotic tested and the Shigella dysenteriae 1 isolates were resistant to 4 antibiotics.

All Shigella dysenteriae type 1 strains were resistant to 6 antimicrobials tested and twice to a different combination of 4 antibiotics. Resistance of Streptococcus currently exists at high rates with β-lactams, macrolides, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole. Multiresistant strains-strains that are resistant to penicillin plus at least 2 other antimicrobial classes are also increasing in prevalence. Moore et al. [18] studied 90 Cambodian children, with a median age of 2.3 years (range, 0.9 to 6.2 years), hospitalized with invasive pneumococcus pneumoniae infection. Of 50 Streptococcus pneumoniae strains available for further testing, 46% were cotrimoxazole resistant, and 30% were chloramphenicol resistant. The most common serotypes were 1 (22%), 23F (16%), 14 (12%), 5 (12%), and 19A (6%). Coverage by PCV7, PCV10, and PCV13

was 44%, 76%, and 92%, respectively. Invasive pneumococcus sequence is an important disease and can have a significant mortality rate. Raddaoui et al. (19) isolated 31 infections and 28 sites of children and adults. The majority (66.1%) of the isolates belonged to 5 serotypes all included in PCVAs: 6B, 9V, 14, 19F, and 23F. The potential coverage of 10-valent and 13-valent PCV was 71.2% and 76.3%, respectively. Resistance rates were very high and 69.5% of isolates to erythromycin, clindamycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole ranged from 22.0 and 69.5%. The most frequent serotypes had STs characteristic of multidrug-resistant international clones known to be highly successful and important causes of pneumococcal infection.

Solghan et al. (6) described the prevalence and trends of nontyphoidal Salmonella antimicrobial susceptibility within the New York State Fordborne Disease Active Surveillance Network. From May 2003 and December 2007, the New York State Department of Health, Wadsworth Center Public Health Laboratory tested all salmonella isolates from the New York State catchment area. The susceptibility to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, nalidixic acid, and ciprofloxacin was investigated. Multidrug-resistant isolates were defined as resistant to ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline and were referred to as (R-type ACSSut). Antimicrobial susceptibility for 2,189 FoodNet cases (98.5% of total cases) showed 79.6% pansusceptible, 7% R-type were ACSSut, and 13% resistant to at least one antibiotic. From 2004 to 2007, cases with R-type ACSSut decreased from 8.7% to 4.8% (p-level < 0.01). Serotypes with the highest proportion of R-type ACSSut included Salmonella Typhimurium isolates 17.9% and Salmonella Newport 29.1%.

In Africa, multidrug-resistant non-typhoid Salmonella are one of the leading causes of morbidity and high rate of mortality in children under 5 years of age. The majority of non-typhoid Salmonella from cases were Salmonella enterica serotype Typhimurium (54.9%) and Salmonella enterica serotype Enteritidis (33.2%) (20). A significant proportion (34.2%) was multidrug-resistant to 3 or more antibiotics. From 1994 through 2000, Mwangi et al. (21) reviewed data from 390 children, aged less than 5 years of age, 88% were admitted with acute bacterial meningitis to a Kenyan district hospital. From 1995 and 2000, the apparent minimum annual incidence in children younger than 5 years increased from 120 to 202 per 100,000 children ($p < 0.001$).

The most common organisms isolated in infants younger than 3 months were streptococci and Enterobacteriacae. Streptococcus pneumoniae (43.1%) and Haemophilus influenzae (41.9%) were predominant in the postnatal period. The mortality rate was 30.1% and 23.5% of survivors developed neurologic sequelae. Chloramphenicol resistance of Haemophilus influenzae rose from 8% in 1994 to 80% in 2000 ($p < 0.0001$) accompanied by an increase in mortality rate. From July 1997 to July 1999, 32 neonates with a mean age of 12.5 days were hospitalized in an intensive care unit in Rio de Janeiro, Brazil. Pseudomonas aeruginosa was the prevalent pathogen (22). High multidrug-resistance percentage to β-lactams, chloramphenicol, trimethoprim-sulfamethoxazole, and tetracycline was detected among the isolate strains. All isolated strains were classified multidrug-resistant. Emele (23) sampled 1,097 cerebrospinal fluid specimens. A total of 289 (26%) were affected by bacterial meningitis. Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Coliform bacilli, Escherichia coli,

Mycobacterium tuberculosis, Listeria monocytogenes, Flavobacterium meningitis, and Pseudomonas putrefaciens were the isolates observed. Nineteen (11%) of the isolates, (5 Meningococci, 7 Staphylococcus aureus, 1 Haemophilus influenzae, and 6 others) showed resistance to chloramphenicol, ampicillin and benzyl penicillin. A total of 154 Haemophilus strains were isolated from throat swabs of 208 children who had upper respiratory tract infections (24). Among 154 Haemophilus strains isolates, Haemophilus influenzae, Haemophilus parainfluenzae, and Haemophilus aphrophilus were identified by API NH. The antibiotic resistance of Haemophilus was investigated in relation to β-lactamase activity. The in vitro antibacterial susceptibilities of Haemophilus strains for ampicillin, sulbactam-ampicillin, trimethoprim-sulfamethoxazole, gentamicin, chloramphenicol, and ciprofloxacin were tested by disk diffusion method on chocolate agar. Among 42 β-lactamase-positive Haemophilus influenzae isolates, 32 isolates were resistant to ampicillin. In 20 β-lactamase-positive Haemophilus parainfluenzae isolates, 16 were resistant to ampicillin. Two β-lactamase-negative Haemophilus aphrophilus were sensitive to ampicillin.

A total of 435 Staphylococcus aureus isolates were collected in children by Wang et al. (25). These authors correlated the multidrug-resistance (MDR) and sequence type (ST) clones of community-associated (CA) methicillin-resistance Staphylococcus aureus (MRSA) to identify the genes responsible for clindamycin and mupirocin in Staphylococcus aureus in children. Compared with CA methicillin susceptible Staphylococcus aureus (MSSA), the resistance rates of CA-MRSA to ciprofloxacin, chloramphenicol, gentamicin, and tetracycline were higher. Compared with hospital-associated (HA)-MRSA, the resistance rates of CA-MRSA to ciprofloxacin, gentamicin, rifampicin, tetracycline, and trimethoprim-sulfamethoxazole was lower. The MDR rates (resistance to three or more non-β-lactams) were 49.6, 100, and 14 in the CA-MRSA, HA-MRSA and CA-MSSA isolates, respectively. Five of seven ST clones in the CA-MRSA isolates, namely ST59, ST338, ST45, ST910, and ST965, had MDR rates > 50%. The constitutive phenotype of macrolide-lincosamide-streptogramin B (MLSb) resistance (69%) and the ermB gene (38.1%) predominated among the MLSb-resistance CA-Staphylococcus aureus strains. These data show that the resistance to non-β-lactams, especially to clindamycin, is high in CA-MRSA isolates from children and that the profile of resistance is related to clonal type.

Reish et al. (27) described the outbreak of multiresistant Klebsiella pneumoniae in a neonatal intensive care unit. Four infants had septicemia and one had urinary tract infection. All Klebsiella isolates were resistant to ampicillin, cefotaxime, cefuroxime, co-amoxiclav, mezlocillin, chloramphenicol, gentamicin, and ceftazidime. The outbreak was controlled with re-emphasis on strict hand-washing practices, chortling, closure of the unit to outborn admission, and changing the regimen of empirical antibiotic therapy. Huang et al. (28) investigated the drug resistance and β-lactamase genotype distribution of enteropathogenic Escherichia coli isolated from pediatric patients.

The commonest serotypes were O55:K59 and O126:K1. The typical enteropathogenic Escherichia coli were more prevalent than atypical enteropathogenic Escherichia coli (51 versus 7). The isolates of Escherichia coli were most commonly found to be resistant to ampicillin and cotrimoxazole, followed by chloramphenicol, ceftriaxone, and ceftazidime. The most common β-

lactamase genotypes identified in 58 trains were blaCTX-M-1, blaTEM, blaCTX-M-0, and blaSHV. Among 58 isolates, 22 strains were found to harbour one β-lactamase gene and were resistant to ampicillin, cotrimoxazole, chloramphenicol, ceftriaxone, and ceftazidime. A further 30 strains carrying multiple β-lactamase genes had increased resistance to the above antimicrobial agents. Drug resistance may be associated with the β-lactamase gene number, with a greater number of β-lactamase genes resulting in higher antibiotic resistance. Various Vibrio cholerae occurs as a major epidemic disease in most developing countries (29). Diarrheic stool samples were collected during cholera epidemics, and processed per the standard microbiologic procedures. Eighty-one Vibrio cholerae 01 serotype Inaba were isolated from stools of cholera cases. All Vibrio cholera was resistant to cotrimoxazole. High levels of resistance were also shown to chloramphenicol, ampicillin, with least resistance to erythromicin, tetracycline, and ciprofloxacin. However, all isolates remain susceptible to doxycycline. Doxycycline or ciprofloxacin could be used for treatment of adult cholera cases whereas erythromycin is an alternative for young children. Antimicrobial susceptibility tests are strongly recommended for Vibrio cholera strains in treatment intervention during epidemics.

5- CONCLUSIONS

In conclusion, bacterial infections may cause disease and death. Infants and children are often subject to bacterial infections. Antibiotics are essential drugs to combat and win bacterial infections. Antimicrobials kill bacteria protecting the infected patients, and therefore, reducing the risk of morbidity and mortality rate. The administration of antimicrobials may reduce the bacteria susceptibility to antibiotics. When the bacteria become resistant to antimicrobials, the antibiotics lose their protective effects against infected patients. The resistance to two, or more, antibiotics is named multidrug-resistance. Amikacin, ampicillin, amoxicillin, amoxiclav, cefuroxime, cefotaxime, ceftazidime, cefoperazone, tetracycline, chloramphenicol, ciprofloxacin, and gentamicin may cause bacterial-resistance. Gram-negative bacilli, especially Escherichia coli, Klebsiella, Enterobacter, Salmonella, Shigella, Pseudomonas, Streptococcus, and Haemophilus influenzae type b, may become resistant to antimicrobials. Reasons behind the increase in antibiotic-resistant bacterial infections are the widespread unregulated use of antibiotics and the very large burden of bacterial infections. There is a need for better surveillance for antibiotic-resistant bacteria within hospitals; this requires substantial improvements in laboratory facilities and carefully planned research collaboration. A national committee should be established to advise on these matters and coordinate interventions. In literature there is not review on the multidrug-resistance in infants and children.

6- CONFLICT OF INTEREST

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Table-1: Nontyphoidal Salmonella isolate resistance to antimicrobial patterns and agents within the New York State foodborne diseases active surveillance network, 2003-2007 (n = 2,189), by Solghan et al. (6).

Number (%) by diagnosis year						
Antibiotic	2003 (n = 310)	2004 (n = 424)	2005 (n = 477)	2006 (n = 479)	2007 (n = 499)	Total (n = 2,189)
Ampicillin	52 (16.8)	60 (14.2)	45 (9.4)	52 (10.9)	43 (8.6)	252 (11.5)
Chloramphenicol	44 (14.2)	38 (9.0)	29 (6.1)	25 (5.2)	27 (4.4)	163 (7.4)
Streptomycin	59 (19.0)	63 (14.9)	65 (13.6)	54 11.3)	48 (9.6)	289 (13.2)
Sulfisoxazole	59 (19.0)	62 (14.6)	68 (14.3)	49 (10.2)	48 (9.6)	286 (13.1)
Tetracycline	61 (19.7)	67 (15.8)	69 (14.5)	54 (11.3)	61 (12.2)	312 (14.3)
Ciprofloxacin	0	3 (0.7)	0	0	1 (0.2)	4 (0.2)
Nalidixic acid	---	---	7 (1.5)	10 (2.1)	13 (2.6)	30 (2.1)

Nalidixic acid susceptibility testing began in 2005 as a screening test for ciprofloxacin resistance.

Table-2: The comparison and incidence of resistance to 12 antibiotics among 62 Shigella isolates and serogroups from Lagos, Nigeria, by Iwalokun et al. (9).

Antibiotic	Percent of resistant Shigella isolates in 1990	Shigella resistant isolates									
		Resistance of total Shigella isolates		Shigella dysenteriae		Shigella flexneri		Shigella sonnei		Shigella boydii	
		Number	%	Number	%	Number	%	Number	%	Number	%
Ampicillin	70.0	56	90.3	9	81.8	30	93.7	7	87.5	10	90.9
Tetracycline	89.0	49	79.0	9	81.8	25	78.1	6	75.0	9	81.8
Colistin sulphate	91	51	82.3	10	90.9	27	84.4	6	75.0	8	72.7
Cotrimoxazole	74	53	85.5	9	81.8	27	84.4	7	87.5	10	90.9
Chloramphenicol	711	48	77.4	10	90.0	26	81.3	4	50.0	8	72.7
Streptomycin	71	49	79.0	10	90.9	26	81.3	5	62.5	8	72.7
Cefotaxime	---	277	43.5	5	45.5	15	46.9	3	37.5	4	36.1
Nalidixic acid	0.0	2	11.3	1	9.1	5	15.6	1	12.5	1	9.1
Nitrofurantoin	0.0	2	3.2	0	0.0	2	6.3	0	0	0	0.0
Gentamicin	10.0	0	3.2	1	9.1	0	0.0	0	0	0	0.0
Ofloxacin	0.0	9	0.0	0	0.0	0	0.0	0	0	0	0.0
Ciprofloxacin	---		0.0	0	0.0	0	0.0	0	0	0	0.0

Table-3: Percentage of strains showing the drug resistance and geometric mean of minimal inhibitory concentrations (MIC) in Shigella percentage. The percentage shows the drug resistance (geometric mean MIC, µg/ml), by Lin and Chang (10).

Strain (Number isolated)	Ap	Ka	Cr	Cm	Tc	Sm	Nm	Gm	Nx	TMP-SMZ	An
Shigella dysenteriae (4)	25 (11.3)	0 (4.0)	0 (4.8)	75 (128)	75 (64.0)	75 (107)	0 (8.0)	5 (5.7)	0 (4.0)	0 2.8)	0 (8.0)
Shigella flexneri (53)	81 (48.6)	23 (5.6)	11 (4.3)	89 (85.3)	92 (66.6)	92 (68.3)	9 (5.9)	0 (1.5)	17 (7.3)	9 (7.9)	0 (5.9)
Shigella boydii (11)	64 (128)	45 (53.0)	27 (14.1)	100 (225.7)	100 (106)	82 (64.0)	36 (38.7)	0 (2.7)	27 (14.1)	0 (2.5)	0 (5.5)
Shigella sonnei (60)	27 (13.9)	13 (5.5)	8 (4.1)	84 (170.9)	84 (85.4)	78 (57.0)	8 (5.2)	0 (2.1)	33 (9.0)	13 (16.6)	2 (4.3)
Average	52 (37.4)	20 (9.6)	11 (5.1)	87 (117.6)	88 (78.7)	84 (63.9)	11 (8.4)	0 (2.1)	25 (8.6)	10 (11.6)	1 (4.8)

Ap: ampicillin; Tc: tetracycline; NX: nalidixic acid; An: amikacin; Ka: kanamycin; Sm: streptomycin; Cr: cephalotin; Nm: neomycin; Cm: chloramphenicol; Gm: gentamicin; TMP-SMZ: sulfamethoxazole-trimethoprim.

Table-4: Antimicrobial resistance (%) of Shigella and Salmonella isolates from children less than 5 years of age with diarrhea. The figures are the MIC_{50}, MIC_{90}, and the % resistance, by Mandomando et al. (13).

Organism (Nunber isolates)	Ampicillin			Chloramphenicol			Trimethoprim-sulfamethoxazole			Tetracycline		
Shigella species (109)	MIC_{50}	MIC_{90}	% Resistance	MIC_{50}	MIC_{90}	% Resistance	MIC_{50}	MIC_{90}	% Resistance	MIC_{50}	MIC_{90}	% Resistance
Shigella flexneri (94)	64	128	66a	32	32	61a	>128	>128	84	32	64	64
Shigella sonnei (15)	1	32	0	2	32	0	>128	>128	100	32	64	93b
Salmonella species (40)	≤0.5	>128	>128	≤0.5	>128	15	≤0.5	>128	18	≤0.5	1	15
Salmonella infants (10)	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	0	≤0.5	≤0.5	0	≤0.5	≤0.5	0
Salmonella Typhimurium (9)	>128	>128	>128	1	>128	22	1	>128	44	≤0.5	1	0
Salmonella Virchow (5)	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	0	≤0.5	≤0.5	0	≤0.5	≤0.5	0
Other Salmonella isolates	≤0.5	≤0.5	≤0.5	≤0.5	>128	25	≤0.5	>128	19	≤0.5	>128	25

[a]Salmonella flexneri isolates were more frequently resistant to ampicillin and chloramphenicol than S. sonnei isolates (p-level < 0.001; Fisher's exact test). MIC_{50}, 50% of isolates inhibited; MIC_{90}, 90% of isolates inhibited, µg/ml). [b]Salmonella Sonnei isolates were more frequently resistant to tetracycline than S. sonnei isolates (p-level < 0.02; chi-squared test).

Table-5: In vitro activity of selected β-lactam antimicrobials versus Streptococcus pneumoniae, sorted by penicillin category, by Brueggemann and Doern (17).

Variables	Penicillin susceptible		Penicillin intermediate		Penicillin resistant		Total	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Amoxicillin/clavulanic acid	0.015	0.03	0.25	1	2	4	0.015	2
Cefproxil	0.12	0.25	2	8	16	32	0.25	16
Cefuroxime	0.03	0.12	1	4	8	16	0.03	8
Ceftriaxone	0.03	0.06	0.25	1	2	4	0.03	2

MIC_{50}, 50% of isolates inhibited; MIC_{90}, 90% of isolates inhibited (μg/ml).

Table-6: Current resistance rates of non-β-lactam antimicrobials versus Streptococcus pneumoniae, by penicillin susceptible category, by Brueggemann and Doern (17).

Antimicrobial	Penicillin susceptible (n = 1,008)	Penicillin intermediate (n = 194)	Penicillin resistant (n = 329)	Total (n = 1,531)
Erythromycin	5.6	43.3	78.1	25.9
Clindamycin	1.4	19.1	25.2	8.8
Tetracycline	3.1	32.0	48.0	16.4
Chloramphenicol	1.0	13.9	27.7	8.4
Trimethoprim-sulfamethoxazole	7.6	39.2	94.5	30.3

Erythromycin, ≥ 1 μg/ml; clindamycin, ≥ 1 μg/ml; tetracycline, ≥ 8 μg/ml; chloramphenicol, 8 μg/ml; trimethoprim-sulfamethoxazole, ≥ 4 μg/ml.

Table-7: Susceptibility and resistance rates in β-lactamase-positive Haemophilus isolates against various antibiotics, by Brueggemann and Doern (17).

Antibiotics	Haemophilus influenzae (n = 42)		Haemophilus parainfluenzae (n = 20)	
	Susceptible	Resistant	Susceptible	Resistant
Ampicillin	10	32	4	16
Sulbactam-ampicillin	23	19	6	14
Trimethoprim-sulfamethoxazole	13	29	5	15
Gentamicin	11	31	6	14
Chloramphenicol	28	14	10	10
Ciprofloxacin	36	6	18	2

Table-8: Susceptibility and resistance rates in β-lactamase-negative Haemophilus isolates against various antibiotics, by Uraz et al. (24).

Variables	Haemophilus influenzae (n = 75)		Haemophilus parainfluenzae (n = 15)		Haemophilus aphrophilus (n = 2)	
Antibiotic	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
Ampicillin	52	23	15	---	2	---
Sulbactam-ampicillin	58	17	14	1	2	---
Trimethoprim-sulfamethoxazole	17	58	3	12	1	1
Gentamicin	11	64	3	12	2	---
Chloramphenicol	42	33	10	2	1	1
Ciprofloxacin	71	4	15	---	2	---

Table-9: Antimicrobial resistance to non-β-lactam antibiotics of Staphylococcus aureus isolated from pediatric hospitals in mainland China, by Wang et al. (25).

Variables	MRSA						MSSA			*P-value	P-value
	CA-MRSA (n = 163)			HA-MRSA (n = 77)			CA-MSSA (n = 195)				
Antibiotic	Number (%)	MIC_{50}	MIC_{90}	Number (%)	MIC_{50}	MIC_{90}	Number (%)	MIC_{50}	MIC_{90}		
Penicillin	162 (99.4)	16	256	77 (100)	32	256	175 (89.7)	0.5	2	<0.05	<0.05
Cefoxitin	163 (100)	32	256	77 (100)	> 256	>256	0 (0)	0.5	2	<0.05	<0.001
Cefuroxime	145 (90)	64	> 256	77 (100)	> 256	> 256	8 (4.1)	0.5	1	<0.05	<0.001
Erythromycin	140(85.9)	> 256	> 256	60 (77.9)	> 256	> 256	123(63.1)	> 256	> 256	<0.05	<0.001
Clindamycin	150(92.0)	>256	> 256	60(77.9)	>256	256	125(54.1)	32	> 256	<0.01	<0.001
Ciprofloxacin	31 (19.9)	1	64	73(94.8)	128	64	5 (2.6)	1	8	0.001	<0.001
Chloramphenicol	24 (14.7)	16	128	10(13.0)	4	> 256	11(5.6)	8	16	<0.05	<0.01
Gentamicin	24(14.7)	2	64	65 (88.3)	> 256	> 256	2 (1.0)	2	128	<0.001	>0.05
Rifampicin	9 (5.5)	0.008	8	68 (88.3)	> 256	> 256	26(13.3)	0.016	1	<0.001	<0.001
Tetracycline	75 (46.0)	16	32	73(94.8)	32	256	5 (2.6)	0.5	32	<0.001	>0.05
Trimethoprim-sulfamethoxazole	3 (18)	1	32	7(9.1)	0.5	4	0(0)	4	32	<0.01	>0.05
Vancomycin	0 (0)	0.5	1	0 (0)	0.5	1	2(1.0)	0.5	0.5	<0.05	>0.05
Fusidic acid	1 (0.6)	0.064	0.125	1 (1.3)	4	4	0 (0)	0.064	0.125	<0.05	>0.05
Tigecycline	0 (0)	0.5	0.5	0 (0)	0.5	0.5	0 (0)	0.25	0.5	<0.05	>0.05
Mupirocin	9 (5.5)	0.32	0.064	1 (1.3)	0.064	0.064	0 (0)	0.064	0.064	<0.05	>0.05
Linezolid	0 (0)	0.5	2	0(0)	1	2	0 (0)	2	2	<0.05	>0.05

CA-MRSA = community-associated methicillin-resistance Staphylococcus aureus; HA-MRSA = hospital-associated methicillin-resistance Staphylococcus aureus; CA-MRSA = community-associated methicillin-susceptible Staphylococcus aureus; MSSA = methicillin-susceptible Staphylococcus aureus; CA-MSSA = community-associated methicillin-susceptible Staphylococcus aureus; MIC = minimal inhibitory concentration (μg/ml); *P-value = CA-MRSA compared with HA-MRSA; P-value = ca-MRSA compared with CA-MSSA.