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CHANGES IN SUSCEPTIBILITY PATTERN OF STREPTOCOCCUS PNEUMONIA AT TAWAM HOSPITAL IN AL AIN , UNITED ARAB EMIRATES DURING (2004-2011)

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ABSTRACT

Objective: Objective of the study was to find out the prevalence and antimicrobial susceptibility pattern of Streptococcus *pneumoniae* isolates at local hospital.

Study Design: Retrospective study.

Place and Duration of Study: Microbiology department of Tawam hospital isolates from 2004-2011.

Material and Methods: A total of 1066 isolates of Streptococcus *pneumoniae* were obtained from various clinical specimens at Microbiology section of Department of Laboratory Medicine, Tawam hospital, Al Ain, United Arab Emirates, from the period stretching over eight calendar years; 2004- 2011. We examined the data of all the *S. pneumoniae* isolates from the different body sites since 2004 until 2011, there were changes in the antibiotic susceptibility interpretation of *S. pneumoniae* to some antibiotics especially penicillin and ceftriaxone. For this study purpose, the 2011 CLSI guidelines is used retrospectively to interpret the antibiotics susceptibility for all the isolates (2004-2011).

Results: The total number of isolates per year remained stable (p = 0.957). The number of isolates from blood showed a significant increase (p<0.05). During the period (2009-2011), most of the isolates were from the pediatric patients (<1–15 years of age) and the elderly (51-95 years old). The isolates were fully sensitive to levofloxacin and vancomycin. There was no significant change in sensitivity to tetracycline, and trimethoprim/ sulphamethaxazole. Until 2010, there was a significant drop in sensitivity to erythromycin (p=0.001, OR= 0.8). In 2011, though insignificant, susceptibility dropped to 47.4%. There was a significant drop in sensitivity to chloramphenicol (p<0.05, OR 1.2) and clindamycin (p<0.05, OR =0.7). Only 41.3% isolates were sensitive to penicillin G (meningitis) in 2004, which remained fairly the same until 2011, when it was 40.2%. In case of other body sites, the isolates sensitive to penicillin G (non- meningitis) were 98.4% in 2004 and 98.3% in 2011. The sensitivity to ceftriaxone (meningitis) dropped significantly from 93.3% to 81.2%. (p<.001 and OR=0.7). The isolates sensitivity to ceftriaxone (non-meningitis) dropped significantly as well from 99.2% in 2004 and 96.6 % in 2011 (p=.014, OR=0.6). There was no significant change in reduced sensitivity to penicillin G for meningitis and non-meningitis. There was a significant increase in the intermediate sensitivity of S. *pneumoniae* isolates to ceftriaxone (meningitis) from 5.8% in 2004 to 15.4 % in 2011 (p<.001 and OR= 1.3) and ceftriaxone (non- meningitis) from 0.8% to 3.4 %.(p<.001 andOR=1.4).

Conclusions: The resistance of *S. pneumoniae* to ceftriaxone, erythromycin, chloamphenicol and clindamycin is increasing.

Keywords: Antibiotic susceptibility, Serotypes, Streptococcus pneumonia.

INTRODUCTION

Streptococcus *pneumoniae* (*S. pneumoniae*) remains a common pathogen and leading cause of morbidity and mortality[1]. Transmission of S. *pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract[2]. This organism continues to be common cause of mild to severe and life threatening diseases including pneumonia, bacteremia and meningitis, and it is also a frequent causes of upper respiratory tract infections like otitis media and sinusitis[3].

S. *pneumoniae* was known to be completely susceptible to penicillin and other beta-lactam antibiotics. However, since 1980s, a dramatic increase in antibiotic resistance among

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S. pneumoniae has been observed in many parts of the world. Streptococcus *pneumoniae*, colonizes the nose and pharynx. The nasopharyngeal carriage rates are higher in children. The carriage rates show geographic diversity and seasonal fluctuation[1-3]. *S. pneumoniae* spreads from person to person by the inhalation of respiratory droplets (e.g. coughing, sneezing) from an infected person. Many people carry this organisma symptomatically. Carriers may have more than one serotype of the organism. The bacterium can sometimes cause severe illness in children, the elderly and other people with weakened immune systems. *S. pneumoniae* is the most common cause of ear infections (otitis media) bacteremia, meningitis, *pneumonia*, and sinusitis, conjunctivitis, sepsis (blood infection) in children (4,5) as well as *pneumonia* in immunocompromised individuals and the elderly. S. *pneumoniae* is considered "invasive" when it is found in the blood, spinal fluid or other normally sterile sites. Invasive disease occurs when a person acquires a serotype other than the onecarried.

The emergence of resistance of *S. spneumoniae* to antibiotics is of major global concern. The aim of this study was to highlight the significance of S. *pneumoniae* isolates and their pattern of antibiotic susceptibility, over a period of eight years.

Table-1: Monthly Distribution of Streptococcus pneumoniae isolates (2004-2011).

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2004	10	4	17	10	9	7	9	8	8	7	15	14
2005	17	17	11	9	13	7	3	6	17	10	12	16
2006	13	13	14	3	6	5	4	3	11	13	13	10
2007	11	10	16	15	10	15	14	7	9	11	20	12
2008	6	13	14	8	14	12	15	6		24	16	15
2009	11	10	14	14	12	13	5	11	7	8	5	11
2010	18	15	11	10	11	4	7	8	6	6	11	9
2011	9	14	18	11	17	7	6	4	5	14	13	10
Total	95	96	115	80	92	70	63	53	63	93	105	87

Table-2: Susceptibility of S. *pneumoniae* isolates to the antibiotics tested.

		Chloramphenicol	Clindamycin	Erythromycin	Levofloxacin	Trimethoprim/Sulfamethoxazole	Tetracycline	Vancomycin
2004	%S	95.0	84.0	71.0	100	43.0	69.0	100
	n	95	84	103	79	7	91	67
2005	%S	97.0	79.0	69.0	100	49.0	76.0	100
	n	65	103	134	118	39	119	123
2006	%S	92.0	68.0	59.0	100	41.0	70.0	100
	n	39	93	93	90	56	80	93
2007	%S	95.0	76.0	57.0	100	38.0	63.0	100
	n	64	143	150	138	73	147	156
2008	%S	87.9	97.0	61.4	100	54.0	73.4	100
	n	33	125	136	136	100	139	139
2009	%S	100.0	94.1	69.0	100	53.2	68.7	100
	n	11	17	84	83	79	83	83
2010	%S	98.9	85.7	52.7	100	50.0	62.0	100
	n	88	21	110	100	98	108	105
2011	%S	94.2	61.3	47.4	100	54.5	63.8	100
	n	104	31	116	104	101	116	116
p-value		.002	.000	.290	1.000	.236	.063	1.000

%S: Percentage of isolates susceptible.

MATERIAL AND METHODS

Total 1066 isloates were selected by non-probability purposive sampling. The identification was made by the conventional microbiology methods: optochin sensitivity, the API Strep (Analytic Profile Index) strips from BioMerieux and Vitek 2 GP identification cards. This was carried out at microbiology section of department of laboratory medicine,Tawam hospital, Al Ain, United Arab Emirates, to cover the period stretching over eight calendar years; 2004- 2011.

Based on the available saved data of Microbiology Laboratory results, from 2004 until April 2008 (Laboratory information system Epicenter, version 4.0), a retrospective study was done. Further data for three more years (2009-2011) was added; from newly acquired Cerner based Laboratory information System. The data regarding *S. pneumoniae* isolates from clinical specimens was evaluated, retrospectively.

Table-3: Susceptibility of S. *pneumoniae* isolates to penicillin and ceftriaxone.

		Ceftriaxone (meningitis)	Ceftriaxone (non-meningitis)	Penicillin (meningitis)	Penicillin (non-meningitis)
2004	%S	93.3	99.2	41.3	98.4
	%I	5.8%	0.8%	0.0%	0.80%
	n	121	121	121	121
2005	%S	99.3	100	46.8	99.3
	%I	0.7%	0.0%	0.0%	0.70%
	n	141	141	141	141
2006	%S	95.7	100	44.1	100
	%I	4.3%	0.0%	0.0%	0.0%
	n	93	93	93	93
2007	%S	94.8	99.4	36.6	100
	%I	4.6%	0.6%	0.0%	0.0%
	n	154	154	154	154
2008	%S	85.8	98.5	40.6	100
	%I	13.5%	1.5%	0.0%	0.0%
	n	138	138	138	138
2009	%S	86.9	100	46.4	100
	%I	13.1%	0.0%	0.0%	0.0%
	n	84	84	84	84
2010	%S	82.3	97.2	40.7	98.1
	%I	14.8%	1.9%	0.0%	1/9%
	n	108	108	108	108
2011	%S	81.2	96.6	40.2	98.3
	%I	15.4	3.4%	0.0%	1.7%
	n	117	117	117	117

%S: Percentage of isolates susceptible
%I; Percentage of isolates Intermediate n: Number of isolates tested
n: Number of isolates tested

Antibiotic susceptibility testing was done by the disc diffusion method during the period January 2004 and June 2006. For the *S. pneumoniae* penicillin and ceftriaxone susceptibility is tested initially with the oxacillin disc and in case of its resistance, Etest was performed. With effect from July 2006, Vitek 2 was used for the antibiotic susceptibility after being validated, while the disc diffusion method continued to be used for testing S. *pneumoniae* at occasions where the Vitek 2 failed or recommended to retest the organism's susceptibility. Although the antibiotic panel is standardized, at times when antibiotic is not available due to shortage of supply, the isolate will not be tested for that antibiotic.

The Etests (AB Biodisk Solna, Sweden) measured minimum inhibitory concentrations (MIC) of penicillin and ceftriaxone for S. *pneumoniae*. The 2011 CLSI guidelines were followed for the interpretation of the antibiotic disc diffusion and Etests results retrospectively because some breakpoints for interpretation of MICs and disc zones have changed[11].

The data of S. *pneumoniae* from the epicenter and Cerner was transcribed to the WHONET and analyzed by WHONET version 5.3, a software program for the management of microbiology laboratory data. The algorithm used for handling repeat isolates was patient based and only the first isolate per patient was included in the analysis. Repeat isolates of the patient from the same body site are considered as duplicate and are excluded from analysis. For the same patient, isolates from different

body sites are considered separate isolates and are included in the analysis.

Cumulative antibiogram reports of the different isolates and antimicrobials for the eight calendar years (2004-2011) were compared. Kirby-Bauer disc diffusion was the method of testing antibiotic susceptibility during the years 2004-2006. Isolates of pneumococci were tested initially with oxacillin disc (1 microgram). Isolates with oxacillin zone sizes ≥ 20 mm are susceptible to penicillin (MIC ≤ 0.06µg/ml) and ceftriaxone[6]. The isolates with oxacillin zone diameters of ≤ 19 mm are tested by etest for penicillin and ceftriaxone. Penicillin was tested by etest since vitek 2 does not report MIC below 1.

Statistical Analysis

Data had been analyzed by SPSS Statistics version 17.0. The percentage of sensitive isolates to the different antibiotics tested, the number of isolates andtheir distribution during each month of the year and the number of isolates for the different age groups were recorded.

Logistic regression was used to assess the association between the year of sampling and the antimicrobial resistance of S. *pneumoniae* to observe any change in the percentage of resistance. The odds ratio (OR) and 95% confidence interval (CI) were calculated

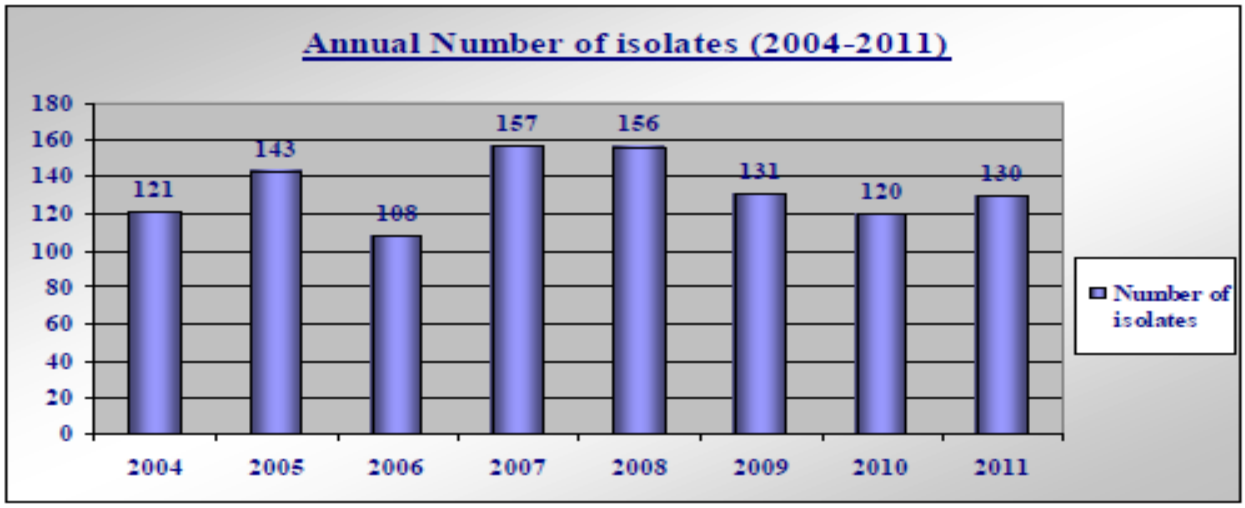

Figure-1: Annual Number of S. *pneumonia* isolates (2004 – 2011).

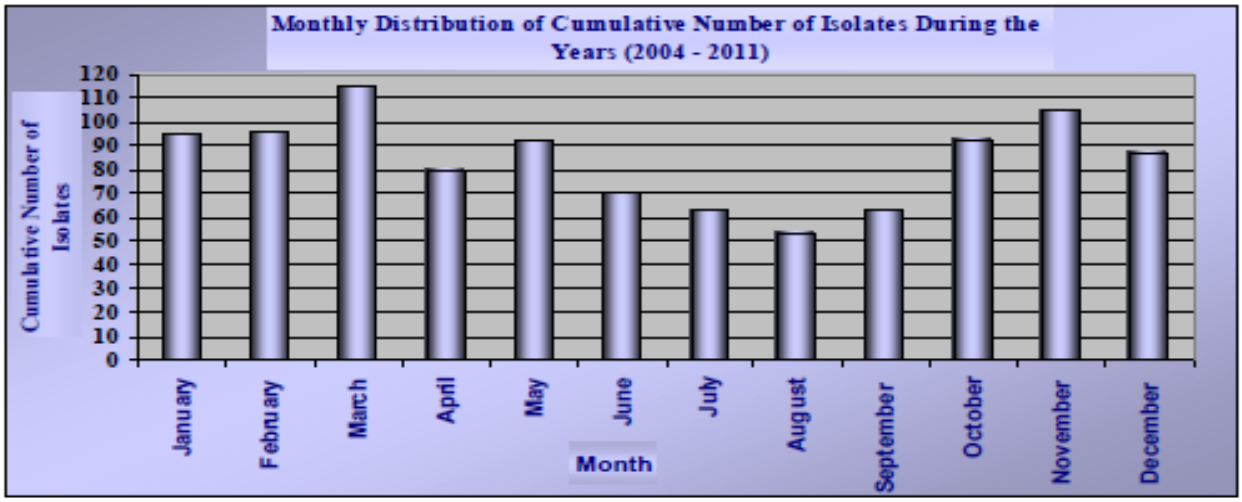

Figure-2: Cumulative monthly distribution of S. *pneumoniae* isolates.

RESULTS

During the period 2004-2011 total number of isolates were 1066 (fig-1), there was no significant change in the number of isolates per

year (p=0.957). The mean of isolates was133. The range was (108 to157).

The isolates were universally sensitive to levofloxacin and vancomycin. There was no significant change in sensitivity to tetracycline, and trimethoprim/ sulphamethaxazole. Until 2010 there was a significant drop in sensitivity to erythromycin (p= 0.001, OR= 0.8). In 2011, though insignificant, susceptibility dropped to 47.4%. There was a significant drop in sensitivity to chloramphenicol (p<0.05, OR 1.2) and clindamycin (p<0.05, OR =0.7).

For the β-lactam antibiotics, the definition of susceptibility has been changed, as from 2003 onwards; it is concentration dependent based on the body site. It might be resistant to achievable antibiotic level in the CSF. On the other hand, it might be susceptible for the heavily vascular sites of infection, where it reaches by blood i.e. otitis media, sinusitis or *pneumoniae*. The CLSI guidelines set different breakpoints for the antibiotics depending on whether the S. *pneumonie* infection is meningeal or non-meningeal. CLSI set breakpoints initially for ceftriaxone alone until the year 2010 when breakpoints for penicillin was set as well. For this study purpose, the2010 CLSI guidelines are used retrospectively for all the isolates (2004-2010).

Only 41.3% isolates were sensitive to penicillin G (meningitis) in 2004, which remained fairly the same until 2011, when it was 40.2%. In case of other body sites, the isolates sensitive to penicillin G (non-meningitis) were 98.4% in 2004 and 98.3% in 2011. The sensitivity to ceftriaxone (meningitis) dropped significantly from 93.3% to 81.2%. (p<.001 and OR=0.7). The isolates sensitivity to Ceftriaxone (non-meningitis) dropped significantly as well from 99.2% in2004 and 96.6 % in 2011(p=.014, OR=0.6).

Reduced or intermediates susceptibility to beta-lactam antibiotics was also assessed. There was no significant change in reduced sensitivity to penicillin G for meningitis and non-meningitis. There was a significant increase in the intermediate sensitivity of streptococcus S. *pneumoniae* isolates to ceftriaxone (meningitis) from 5.8% in 2004 to 15.4 % in 2011 (p<.001 and OR= 1.3) and ceftriaxone (non- meningitis) from 0.8% to 3.4 %.(p<.001 and OR=1.4).

DISCUSSION

During this study the annual number of *S. pneumoniae* isolates did not change during the last 8 years. The number of isolates could be greater as it is well known that *S. pneumoniae* is the major cause of community acquired *pneumoniae* where the organism is isolated only in 5 to 18 percent. Better recovery of the organism requires more invasive techniques to obtain the specimen to be tested[7].

S. pneumoniae was isolated in a similar percentage from the eye, ear and sputum during the study.The isolates were more significantly increased in the blood. This could be of clinical significance as bacteremia is serious. In a study of 100 veterans, 19% of patients with pneumococcal bacteremia died during the first week of infection as compared to 4% of patients with no bacteremia[8].

The majority of the isolates were from the children and the elderly as it is observed in other studies. Isolates were mainly from patients in the ≥ 65 and < 2 year old age groups[9].

The *S. pneumoniae* isolates in our study were fully sensitive to levofloxacin which is the only quinolone tested. Despite the fact that levofloxacin and ciprofloxacin exhibit different bactericidal effect on strains of *S. pneumonia*[10], our levofloxacin results are comparable to studies using both of those quinolones. In other parts of the world, there is emergence of quinolone resistant isolates. In Saudi Arabia, in a study of patients in 4 hospitals (1996-1998)[11]. A total of 1.1% of isolates were resistant to levofloxacin. In USA, the resistance to levofloxacin was 1% and 2% to ciprofloxacin[12,13]. In Canada resistance was 1.5% in (1993-1994) and became 2.9 in (1997-1998)[14]. In Vietnam, resistance to ciprofloxacin was 28% (2007)[15]. Quinolones are highly effective in treating community acquired *pneumonia*. Resistance can be acquired by prior exposure to quinolones, nursing home residence, nosocomial disease and chronic pulmonary disease[16].

In Tawam hospital, 37% of isolates were resistant to tetracyclines, a finding similar to a study conducted in Saudi Arabia, with 38.5% tetracycline resistance[17]isolates. Resistance to tetracyclines in USA was 20%, in Canada 6% in other countries 25% to 40 % (18-20) and in Vietnam, 75%[16].

There was no significant change in higher than the figure (33.3%) seen in one study in Saudi Arabia[17]. In USA macrolides resistance was 17-35% (2000-2003)[22]. Resistance to Erythromycin ranged 55% in Asia, 92% inVietnam, 70% in Japan[23,24].

While clindamycin, in USA 5-10 percentage are resistant[18], 38% are resistant in our study. A similar figure 33% was seen in the study done

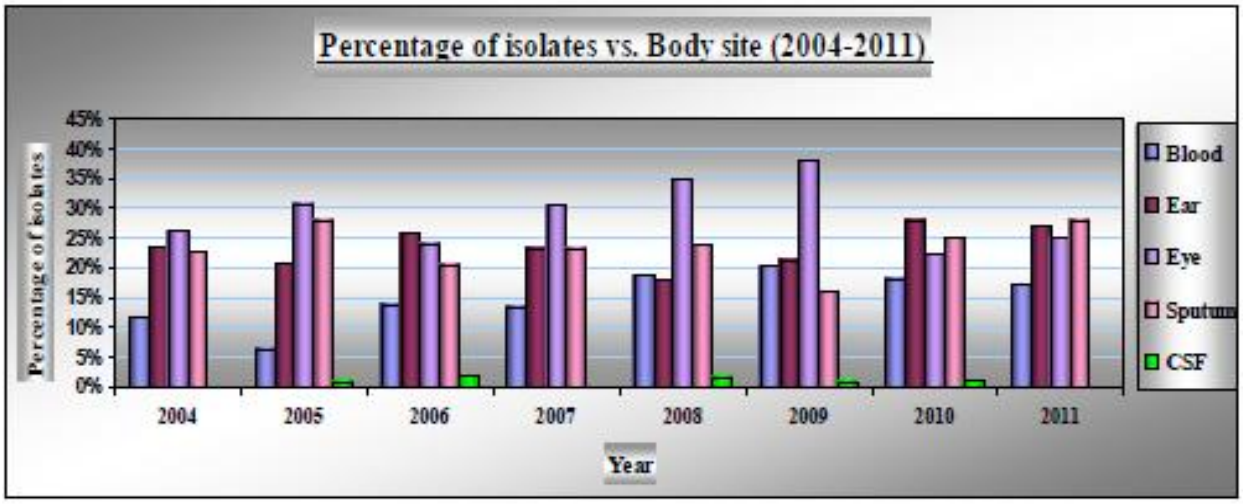

Figure-3: S. *pneumoniae* isolates from different body sites.

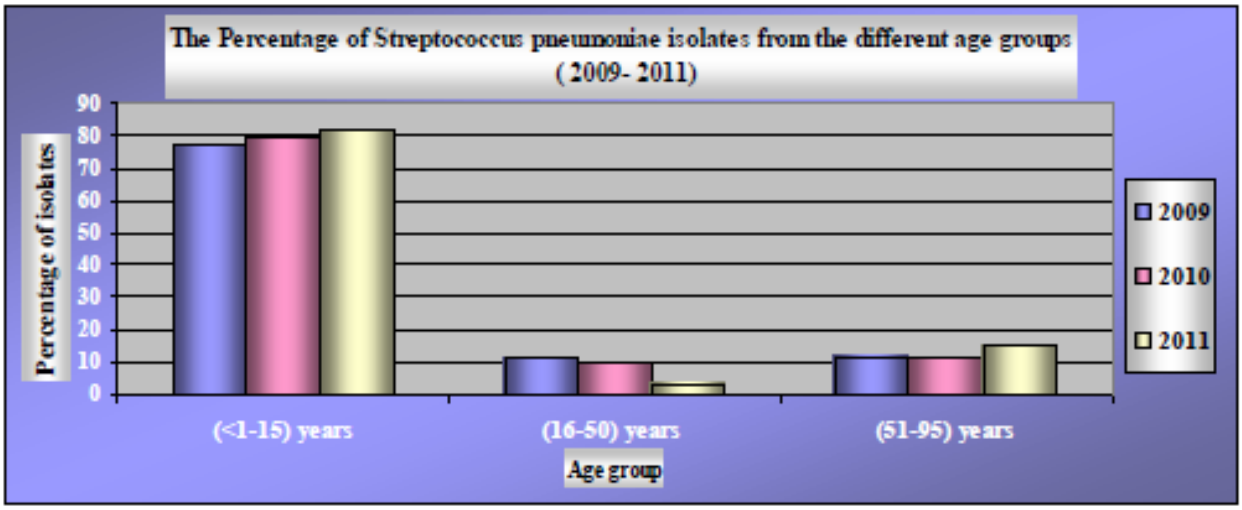

Figure-4:The percentage ofS. *pneumoniae isolates* from the different age groups3.

Trimethoprim/Sulfamethoxazole susceptibility from 43.0% to 54.5 %. The percentage of resistance is 45.5% which is similar to the figure 41% in Kuwait (one year study in 3 major hospitals)[21] in USA , in (1999-2000) , 29.3 % were resistant[22] and in Vietnam (2007) 78%[16].

Erythromycin showed significant drop in sensitivity. There is a significant variation in the figures from the different countries. In this study 52.6% of isolates were resistant which is in the United Arab Emirates[25].

Penicillin resistance was the same during the study 59.8%. The figure is similar to that in the Gulf area. In Kuwait, one year study in 3 major hospitals, penicillin was 46% resistant and 9% intermediate[21].In Saudi Arabia, King Faisal Specialist Hospital 172 isolates (1995-1999), in a 5 years study 51% were resistant to penicillin[26]. In Saudi Arabia, in a 7-years retrospective review of invasive pediatric

pnemococcal diseases in military hospital in the Southern region. Penicillin intermediate was found in 48.5%, 2.4 % resistant[24]. In the 2 years study, 2004-2005, penicillin resistance in Kuwait was 60%[27] . In Spain, published in 1998, 49% resistant to penicillin[28] and in Vietnam 75%[15].

Ceftriaxone non-meningitis resistance ranged from 0.8 to 3.4 while the meningitis resistance ranged from 6.7 to 18.8. In USA resistance to ceftraixone ranges from 1.2% to 6.9%[29]. In Saudi Arabia, King Faisal Specialist Hospital (1995-1999), in a 5 years study, ceftiaxone resistance was 7%[26]. In Kuwait, one year study in a 3 major hospitals, 9% were resistant to ceftriaxone[21]. Cetriaxone resistance rate was lower than the isolates from the neighboring area.

Pneumococcal isolates showed higher in vitro resistance to penicillin and ceftriaxone. This leads to question in the use of those antimicrobial agents that have been used extensively for treatment in the past. The first penicillin resistant S. *pneumoniae* were isolated in Australia in1967[30]. The emergence of penicillin resistance continued to increase worldwide. The empirical use of penicillin for treatment became inadequate thereafter. Studies were conducted to evaluate the in vitro resistance paralleled with increase in mortality or morbidity to use penicillin for treatment. Many studies showed that penicillin is still effective in treating cases with resistant or intermediate susceptibility[30-32]. In a 10 years study in Spain, there was no significant difference in mortality between cephalosporin sensitive and cephalosporin resistant groups. Regarding penicillin, mortality was higher (38%) with the penicillin resistant than penicillin sensitive (22%)[32]. But after correcting for factors that cause poor prognosis, which were more present in the penicillin resistant group, there was no significant difference in mortality. In study carried out in South Africa and in Spain, there was no difference in mortality rate between penicillin sensitive and penicillin intermediate groups who received penicillin treatment[32]. It is advisable to assess the risk factors of penicillin resistance, if the patient is severely ill, has meningitis or underlying disease[30-32]. Pallars et al suggested using high dose of Penicillin yield good response in treating intermediate resistant infections[32].

CONCLUSION

The antibiotic susceptibility of *S. pneumoniae* to levofloxacin, vancomycin, trimethoprim/sulfamethoxazole, penicillin and tetracycline did not change significantly during the last 8 years. There was a significant change in sensitivity to chloramphenicol, clindamycin and ceftriaxone.

The number of invasive pneumococcal disease in the children <5 years who are the target group to be vaccinated should be monitored in the country to check the effect of the pneumococcal vaccine. After 7- valent pneumococcal conjugate vaccine (PCV7) was administered in 2001-2002, there was a significant drop in the number of invasive pneumococcal disease in the children <5 years in the year 2003in USA[23].

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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