

CURRENT STATE OF ANTIMICROBIAL RESISTANCE OF *S. PNEUMONIAE* ISOLATED FROM CHILDREN IN RUSSIA: RESULTS OF PROSPECTIVE MULTICENTER STUDY (PEHASus)

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OBJECTIVE

S. pneumoniae is one of the common bacterial pathogens causing respiratory tract infections in children. Therefore it is significant to determine the antimicrobial resistance of that microorganism for empirical therapy of pneumococcal infections.

METHODS

This study was conducted in 23 cities of different regions of Russia in 1999-2005. Identification of the strains was done on the basis of colony morphology, Gram stain, optochin susceptibility and bile solubility tests. Susceptibility to 15 antimicrobials was performed using cation-adjusted Mueller-Hinton broth (BBL, USA) with 2-5% lysed horse blood, inoculum 0,5 MacFarland. Microtiter plates were incubated for 24 h at 35°C. Breakpoints were those of (NCCLS-2004) except for MID - ≤ 1; > 4 mg/L (CFM-1996).

RESULTS

A total of 840 non-duplicate clinical strains of *S. pneumoniae* isolated from children of 1-18 years old were included in this study. Majority of pneumococci (89.8%) were obtained from respiratory samples (sputum - 39.8%, sinus aspirate - 26.5%, BAL - 15.1%, middle ear fluid - 7.5%, pleural fluid - 0.7%), less frequently the strains were isolated from eye discharge (6.7%), invasive samples (2.4%) and others (1.3%). The susceptibility testing results are presented in the Table.

Antimicrobials	I, %	R, %	MIC50/MIC90, (g/ml)
Penicillin G	7.7	0.6	0.015/0.06
Amoxicillin	0	0.2	0.03/0.125
Amoxicillin/clavulanate	0	0.2	0.03/0.06
Cefotaxime	0.2	0.6	0.015/0.06
Erythromycin	0.1	6.0	0.03/0.06
Azithromycin	0.2	5.8	0.03/0.125
Clarithromycin	0.6	5.4	0.015/0.06
Midecamycin acetate	0.2	2.2	0.25/0.5
Clindamycin	0	2.8	0.03/0.06
Telithromycin	0	0	0.008/0.03
Levofloxacin	0	0	0.5/1
Tetracycline	4.9	25.7	0.25/16
Co-trimoxazole	32.8	11.3	0.5/4
Chloramphenicol	2.1	0.2	2/2
Vancomycin	0	0	0.25/0.5

CONCLUSIONS

All β-lactams and macrolides retained high *in vitro* activity against *S. pneumoniae*. No resistance were detected to levofloxacin, telithromycin and vancomycin. Tetracycline and co-trimoxazole should not be recommended for empirical therapy pneumococcal infections because of high resistance.

INTRODUCTION

S. pneumoniae is one of the most common bacterial pathogens in children causing community-acquired respiratory tract infections (e.g. acute otitis media, sinusitis, pneumonia, etc.) which are among the most frequent reasons for seeking of medical advice. One of the highest risk groups for development of pneumococcal infections are children under 2 years old. Currently β-lactams, macrolides are recommended as drugs of choice for treatment of those infections. Taking into account the substantial increase of resistance in different countries of the world, it is of extreme importance to have reliable national, regional and local data.

PURPOSE

To determine the antimicrobial resistance of clinical strains *S. pneumoniae* isolated in children in different parts of Russia.

METHODS

This study was conducted in 23 cities (Chabarovsk, Chelyabinsk, Ekaterinburg, Irkutsk, Yakutsk, Yaroslavl, Kazan, Kovrov, Krasnodar, Moscow, N-Novgorod, Novosibirsk, Novokuznetsk, Penza, Saint Petersburg, Smolensk, Stavropol, Tyumen, Tomsk, Ryazan, Ufa, Vologda, Voronezh) in Russia (Fig. 1).



Fig. 1. Distribution of centers participated in the study

Identification of the strains was done on the basis of colony morphology, Gram stain, optochin susceptibility and bile solubility tests. Susceptibility testing was performed using cation-adjusted Mueller-Hinton broth (BBL, USA) with 2-5% lysed horse blood. Microtiter plates were incubated for 24 h at 35°C at ambient air. *S. pneumoniae* ATCC 49619 was used for quality control. Interpretation of results was done according to CLSI/NCCLS guidelines (2005). χ^2 criterion and Fisher's exact test were used for compare of resistance in 1999-2003 and 2004-2005 years in different age's groups.

RESULTS

A total of 840 non-duplicate clinical strains of *S. pneumoniae* isolated from children of 1-18 years old were included in this study. Majority of pneumococci (89.8%) were obtained from respiratory samples (sputum - 39.8%, sinus aspirate - 26.5%, BAL - 15.1%, middle ear fluid - 7.5%, pleural fluid - 0.7%), less frequent the strains were isolated from invasive samples 2.4% (cerebro-spinal fluid - 1.7%, blood - 0.7%), from eye discharge 6.7% and others 1.3%. The majority of strains were isolated from respiratory sources (89%) and 4% - from sterile sources. The percentages of non-susceptible (intermediately resistant plus resistant) strains are presented in Table 1.

The total of 70 strains were non-susceptible to penicillin G, 45.7% (32) from them were obtained in children less than 3 years old. The high *in vitro* activity possessed aminopenicillins (both amoxicillin

Table 2. Resistance of *S. pneumoniae* in children in Russia in 1999-2003 vs. 2004-2005.

Antimicrobials	Age																			
	<1 month		1 month - 3 years				3 - 7 years				7 - 12 years				12 - 18 years					
	1999-2003, n=6	2004-2005, n=7	1999-2003, n=61	2004-2005, n=167	1999-2003, n=74	2004-2005, n=149	1999-2003, n=71	2004-2005, n=123	1999-2003, n=72	2004-2005, n=110										
	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)				
Penicillin G	0	0	28.6	0	23.0	1.6	7.2	1.8	5.4	0	2.7	0	5.6	0	4.9	0	9.7	0	10.9	0.9
Amoxicillin	0	0	0	0	0	0	0	1.2	0	0	0	0	0	0	0	0	0	0	0	0
Amoxicillin/clavulanate	0	0	0	0	0	0	0	1.2	0	0	0	0	0	0	0	0	0	0	0	0
Cefotaxime	0	0	0	0	0	0	0	1.2	0	0	6.7	0	0	0	0	0	1.4	0	0	0.9
Erythromycin	0	0	0	14.0	0	8.2	0	6.0	0	5.4	0	4.0	0	1.4	0.8	4.9	0	9.7	0	10.0
Azithromycin	0	0	0	14.0	0	8.2	0	6.0	0	5.4	0	3.3	0	1.4	1.6	4	0	9.7	0	10.0
Clarithromycin	0	0	0	14.0	1.6	6.6	0	6.0	0	5.4	0.7	3.3	1.4	1.4	0.8	4	0	8.3	0.9	9.1
Midecamycin acetate	0	0	0	14.3	0	0	0	5.4	0	0	0	2.7	0	0	0	0.8	0	0	0	5.4
Clindamycin	0	0	0	14.0	0	6.6	0	3.6	0	1.3	0	2.0	0	1.4	0	0.8	0	1.4	0	5.4
Telithromycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Levofloxacin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vancomycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tetracycline	0	50.0	0	57.0	1.6	41.0	8.4	29.9	0	20.0	4.0	28.1	2.8	19.7	8.1	20.3	5.6	19.4	3.6	21.8
Co-trimoxazole	33.3	0	14.0	28.5	44.3	8.2	39.5	16.2	35.1	6.7	31.5	16.8	26.8	8.4	30.0	10.6	29.2	2.8	27.3	9.1
Chloramphenicol	0	0	0	14.0	0	8.2	0	4.8	0	2.7	0	6.7	0	1.4	0	2.4	0	4.2	0	7.3

Table 1. Resistance *S. pneumoniae* in children in Russia

Antimicrobials	Age									
	<1 month n=13		1 month-3 years n=228		3-7 years n=223		7-12 years n=194		12-18 years n=182	
	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)	I, (%)	R, (%)
Penicillin G	15.3	0	11.4	1.8	3.4	0	5.1	0	10.4	0.5
Amoxicillin	0	0	0	0.9	0	0	0	0	0	0
Amoxicillin/clavulanate	0	0	0	0.9	0	0	0	0	0	0
Cefotaxime	0	0	0	0.9	0.4	0	0	0	0.5	0.5
Erythromycin	0	8	0	6.6	0	4.5	0.5	3.6	0	9.9
Azithromycin	0	8	0	6.6	0	4.0	1.0	3.1	0	9.9
Clarithromycin	0	8	0.4	6.1	0.5	4.0	1.0	3.1	0.5	8.8
Midecamycin acetate	0	7.7	0	3.9	0	1.7	0	0.5	0	3.3
Clindamycin	0	8	0	4.4	0	1.8	0	1.0	0	3.8
Levofloxacin	0	0	0	0	0	0	0	0	0	0
Telithromycin	0	0	0	0	0	0	0	0	0	0
Vancomycin	0	0	0	0	0	0	0	0	0	0
Tetracycline	1.4	53.8	6.6	32.9	2.7	25.6	6.2	20.1	4.4	20.9
Co-trimoxazole	23.0	15.3	40.8	14.0	32.7	13.4	28.9	9.8	28.0	6.6
Chloramphenicol	0	8	0	5.7	0	5.4	0	2.0	0	6.0

and amoxicillin/clavulanate) and cefotaxime. Macrolides also retained very good *in vitro* activity with 16-membered macrolides being more active indicating presence of strains with possible *mef*-mediated resistance. No resistance was found to levofloxacin, telithromycin and vancomycin. The lowest *in vitro* activity showed tetracycline and co-trimoxazole that significantly compromise potential of their usage for treatment of infections caused by *S. pneumoniae*.

Comparison of resistance rates in children of different age groups is presented in Table 3. It should be noticed that the non-susceptibility to penicillin in age group of 1 month-3 years has statistically significantly decreased ($p=0.002$).

CONCLUSIONS

- All β-lactams and macrolides retained high *in vitro* activity against tested *S. pneumoniae*. These antimicrobials still might be considered as drugs of choice for empirical treatment of pneumococcal infections.
- High non-susceptibility to tetracycline and co-trimoxazole limits their usage for the empirical therapy of infections caused by *S. pneumoniae* in children in Russia.
- There was no resistance detected to levofloxacin, telithromycin and vancomycin.