

# RELATIONSHIP BETWEEN USE OF ANTIMICROBIALS IN ORPHANAGES AND PNEUMOCOCCAL RESISTANCE: IS A STORY SO SIMPLE?

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## ABSTRACT

**Objectives:** *S. pneumoniae* from children from orphanages are more resistant in comparison with clinical strains and those from day-care centers. A study was designed to evaluate possible influence of antimicrobials on resistance in strains from orphanages in geographically distinct Russian cities.

**Methods:** Nasopharyngeal swabs were collected from 743 children <7 years in 11 orphanages in 4 cities (Moscow, Saint-Petersburg, Smolensk, Karachev). Susceptibility to penicillin G (PEN), amoxicillin (AMO), amoxicillin/clavulanate (AMC), cefuroxime (CEF), cefotaxime (CTX), erythromycin (ERY), azithromycin (AZI), clindamycin (CLI), chloramphenicol (CHL), levofloxacin (LEV), tetracycline (TET), co-trimoxazole (SXT) was performed by microdilution (NCCLS). Profile of use of antimicrobials in previous 12 months was taken from case histories.

**Results:** A total of 399 *S. pneumoniae* were isolated with carriage rate from 36.1% to 75.9%. The prescription of antimicrobials varied from 31 courses/100 children/year to 363 courses/100 children/year. Predominant use of the following antimicrobials seems to correlate with the non-susceptibility: PEN in orphanage No. 4 (18.9% of prescriptions vs. 78.9% of non-susceptible isolates), AZI in orphanage No. 7 and 11 (19.8% vs. 58.8% and 15.4% vs. 44.4%), SXT in orphanage No. 3 (18.9% and 34.6%). Frequent use of AMO and AMC does not seem to be associated with resistance to these compounds: e.g. 27.1% of use of AMC in orphanage No. 7 vs. 0% of resistance, 19.6% of use of AMC in orphanage No. 6 vs. 0% of resistance. Also use of parenteral beta-lactams (with the exception of PEN) did not lead to any significant changes in resistance of *S. pneumoniae*.

**Conclusions:** Frequent use of PEN, AZI and SXT has been associated with resistance of nasopharyngeal *S. pneumoniae* in orphanages. In contrast, in this study, use (of up to 27% of all agents used) of AMO, AMC does not seem to influence resistance of *S. pneumoniae*.

## INTRODUCTION

*Streptococcus pneumoniae* is one of the leading bacterial pathogens causing a variety of different community-acquired infections among different populations. Children under 7 years old, especially those residing in orphanages or visiting day-care centers, are at high risk for colonization by *S. pneumoniae* and, sometimes, of subsequent development of diseases.

Surveillance of pneumococcal nasopharyngeal colonization and resistance of these strains from children attending day-care centers or orphanages has been found to be a practical and useful way to estimate the prevalence of the resistant isolates in a community and to be a good predictor of the development of pneumococcal resistance in clinical infections [Klugman K.P., e.a., 1995; Yagupsky P., e.a., 1998; Sirogiannopoulos G.A., e.a., 2000]. In addition the carriage of resistant isolates of potential respiratory pathogens (*S.pneumoniae*, *H.influenzae* and others) was found to be an independent risk factor for the development of infections (Principi N., e.a., 1999).

Previously published data from Russian orphanages showed substantial variation in carriage rates, with the highest reaching 76.5%. *S. pneumoniae* from children from orphanages are more resistant in comparison with clinical strains and those from day-care centers, and these resistant strains can spread to day-care centers and into clinical settings.

Pattern of the use of antimicrobials has been shown to be an independent risk factor for emergence and spread of resistant microorganisms. However use of different antibiotics has unequal impact on development of resistance to corresponding classes of antimicrobials, and restriction of antibiotic usage has variable influence on the dynamics of antimicrobial resistance in *S.pneumoniae* [Baquero F., e.a., 1991, 2000; Bronzwaer S., e.a., 2002; Granizo J.J., e.a., 2000; Chen D.K., e.a., 1999; Nsuech P.-R., 2005]

## OBJECTIVE

To evaluate influence of antimicrobials on resistance in strains from orphanages in geographically distinct Russian cities.

## METHODS

Nasopharyngeal swabs were collected from 743 children < 7 years in 11 orphanages in four cities of the Central and North-Western regions of Russian Federation: Saint-Petersburg (Orph. 1, Orph. 2, Orph. 3, Orph. 4), Moscow (Orph. 5, Orph. 6, Orph. 7), Smolensk (Orph. 8, Orph. 9, Orph. 10), Karachev (Orph. 11). Immediately after collection, swabs were plated onto 5% Columbia blood agar (bioMerieux, Marcy l'Etoile, France) with 5 g/mL gentamicin (Sigma, St Louis, MO, USA). Plates were then transported to the laboratory, with minimal temperature variations, where they were incubated at 35°C and 3-5% CO<sub>2</sub> atmosphere for 24 h. *S. pneumoniae* was identified on the basis of colony morphology, susceptibility to optochin (bioMerieux) and a tube bile solubility test using 10% sodium desoxycholate (Sigma).

Susceptibility to penicillin G (PEN), amoxicillin (AMO), amoxicillin/clavulanate (AMC), cefuroxime (CEF), cefotaxime (CTX), erythromycin (ERY), azithromycin (AZI), clindamycin (CLI), chloramphenicol (CHL), levofloxacin (LEV), tetracycline (TET), co-trimoxazole (SXT) was performed by microdilution (NCCLS). Breakpoints were those of NCCLS except for CIP (<2; 4; >8 mg/L).

Medical records of 743 children <7 years were reviewed for the use of antimicrobials during the previous 12 months. Data were recorded in special case report forms, which were later entered using double-entry approaches into a custom designed computer database.

The study was approved by the Independent Ethics Committee of the State Medical Academy (Smolensk, Russia). All information collected from the children's medical records was processed in strict confidentiality.

Statistical analysis was performed for all variables using SAS System. Use of antibiotics was calculated as the quantity of courses per child per year (and per 1000 resident-days) for the total studied population and separately for each orphanage.

## RESULTS

A total of 399 *S. pneumoniae* were isolated with carriage rate varying from 36.1% to 75.9% between orphanages.

Average resistance rates in *S. pneumoniae* isolated in orphanages is presented in Table 1.

Table 1. Rates of resistance of nasopharyngeal isolates of *S.pneumoniae*, isolated in orphanages

ABX	PEN	AMX	AMX/CA	CEF	CTX	ERY	AZI	CLA	CLI	CHL	CIP	TET	SXT
I,	39.6	0.8	0.5	1.3	3.8	1.0	0.5	1.0	0	0	0	4.0	34.8
%(N)	(158)	(3)	(2)	(5)	(15)	(4)	(2)	(4)				(16)	(139)
R,	25.8	1.8	1.8	39.4	2.5	26.6	27.3	26.6	19.8	15.0	0	56.6	35.6
%(N)	(103)	(7)	(7)	(157)	(10)	(106)	(109)	(106)	(79)	(60)		(226)	(142)

In general, prescription of antimicrobials varied from 0.31 courses per child/per year in infant Orph. 2 to 3.63 courses per child/per year in Orph. 11. In all orphanages, beta-lactams were the most frequently prescribed (55.3 to 100% of all antimicrobials). See Table 2, Figures 1 and 2.

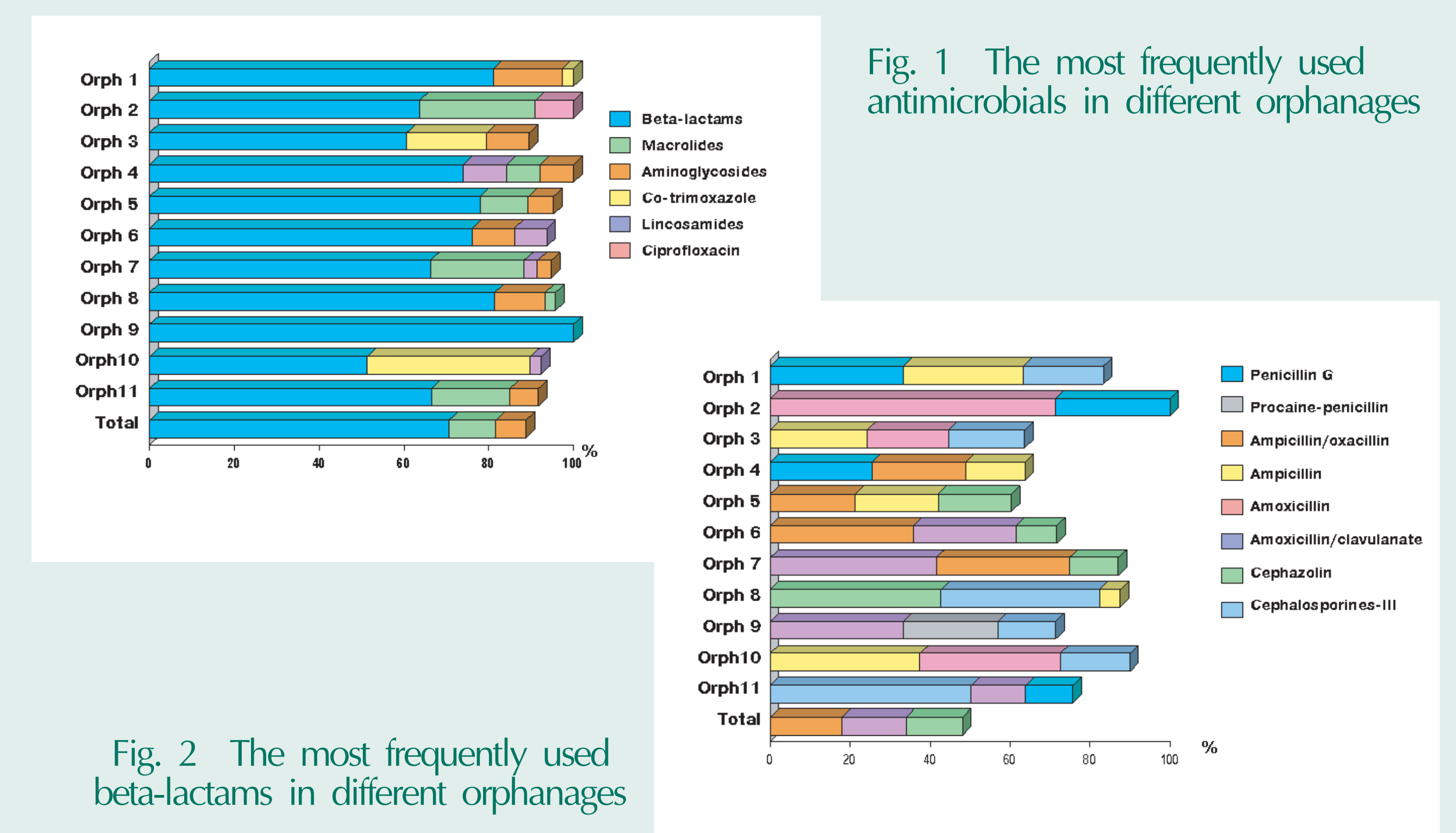


Table 2. Summary data on antibiotic use in different orphanages (Courses of ABx Per child / per year)

	Orph. 1	Orph. 2	Orph. 3	Orph. 4	Orph. 5	Orph. 6	Orph. 7	Orph. 8	Orph. 9	Orph. 10	Orph. 11	Total
N of children	119	24	38	60	70	85	86	114	28	49	70	743
Beta-lactams	0.3	0.3	1.9	1.6	1.9	1.3	1.7	0.8	0.8	0.8	2.4	1.2
Aminoglycosides	0.1		0.3	0.2	0.1	0.2	0.1	0.1		0.02	0.2	0.1
Co-trimoxazole	0.01		0.6		0.1		0.1			0.6	0.1	0.1
Macrolides		0.1	0.2	0.2	0.3	0.05	0.6	0.02		0.02	0.7	0.2
Lincosamides			0.1	0.2	0.04	0.2	0.1	0.01		0.04		0.1
Quinolones		0.04				0.05	0.01	0.03				0.01
Nitrofuranes			0.03				0.07	0.02				0.01
Total Q-ty of courses Per child / per year	0.3	0.5	3.2	2.1	2.4	1.7	2.6	1.0	0.8	1.6	3.6	1.8
Total Q-ty of courses	37	11	122	127	168	143	222	118	21	78	254	1301

Predominant use of the following antimicrobials seems to correlate with the resistance: PEN in Orph. 4 in Saint-Petersburg (18.9% of prescriptions vs. 42.3% of resistance), AZI in Moscow Orph. 7 and Orph. 11 (19.6% vs. 54.8% and 15.1% vs. 40.0%), SXT in Orph. 3 in Saint-Petersburg (18.9% and 15.4%).

Frequent use of AMO and AMC does not seem to be associated with resistance to these compounds: e.g. in Moscow 27.1% of use of AMC in Orph. 7 vs. 0% of resistance, 19.6% of use of AMC in Orph. 6 vs. 0% of resistance, 11.9% of use of AMC in Orph. 5 vs. 0% of resistance.

Also in general (with the exception of PEN) use of parenteral compounds (e.g. I or III generation cephalosporins) did not lead to any changes in susceptibility of studied pneumococci.

## CONCLUSIONS

The rates of resistance found in pneumococci in orphanages were the highest ever reported in Russia. Of special importance is the alarmingly high non-susceptibility to SXT (70.4%), PEN (65.4%), TET (60.6%), ERY (27.6%) and CLI (19.8%), substantially compromising the possibility of their usage for therapy of pneumococcal infections in studied communities.

Among the tested antimicrobials, quinolones and aminopenicillins (AMX and AMX/CA) were the most active, but only the latter could be used for empiric therapy of pneumococcal infections in studied orphanages.

Predominant use of PEN, AZI and SXT has been associated with resistance of nasopharyngeal pneumococci in orphanages. In contrast, use of AMO, AMC and parenteral cephalosporins does not seem to influence resistance of circulating strains.