# CURBING PNEUMOCOCCAL RESISTANCE IN ORPHANAGES: INTERVENTIONS ON THE BASIS OF PROSPECTIVE SURVEILLANCE OF NASOPHARYNGEAL ISOLATES

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## ABSTRACT

**Objectives.** To study the dynamics of antibiotic usage in children from different orphanages located in geographically distinct Russian cities as the result of interventions with the increased use of the most active antimicrobials and restrictions on use of the least active.

**Methods.** This survey was performed as a part of the prospective study CORPUS in 12 orphanages (##1-12) from 5 cities (Moscow, Saint-Petersburg, Smolensk, Karachev, Bryansk) located in European part of Russia. Use of antimicrobials during the previous 12 months was analyzed based upon reviews of medical records of 743 children < 7 years in 2003. Appropriate recommendations on predominant use of selected beta-lactams (e.g. amoxicillin/clavulanate - AMC) with restriction of antimicrobials of other classes (e.g. co-trimoxazole - SXT) were made where applicable on the basis of the expert analysis of antibiotic usage and pneumococcal nasopharyngeal resistance rates. Repeat antibiotic usage analysis was performed 7 months later in 2004 upon reviews of medical records of 752 children < 7 years.

**Results.** Total usage of antimicrobials increased 1.4 times in 2004 (1,065 courses per 752 children in 7 months equivalent to 2.44 courses per child per year) in comparison with 1,301 courses per 743 children in 2003 (1.75 courses per child per year). Beta-lactams were the most frequently prescribed antibiotics (70.6% and 72.1% of all prescriptions in 2003 and 2004 respectively). Among these the predominant ones (in order of frequency) in 2003: ampicillin/oxacillin - AM/OX (17.9%), AMC (16.1%), cefazolin (14.1%), cefotaxime (13.0%) and ampicillin (11.2%); in 2004: AMC (25.5%), AM/OX (18.4%), cefazolin (10.4%), penicillin (PEN) (8.8%) and cefotaxime (7.7%). Usage of AMC increased from 19 to 45 courses/100 children/year, cephalosporins from 42 to 67 courses/100 children/year. Usage of macrolides decreased 2 times: from 20 to 10 courses/100 children/year; at the same time usage of aminogycosides and SXT increased almost twice: from 10 to 19 and from 10 to 18 courses/100 children/year in 2004 vs 2003.

**Conclusion.** The recommended intervention resulted in 2.4 times increase of AMC usage in 2004 vs 2003 with no detectable increase of resistance to PEN and aminopenicillins. Enhanced use of cephalosporins led to increase of resistance to these drugs. In spite of recommendations to restrict usage of AM/OX, aminoglycosides and SXT, the analysis showed that these antimicrobials still accounted for 13.2%, 7.8% and 7.5% of all prescriptions, respectively, thus dictating the need for further enforcement measures.

## INTRODUCTION AND PURPOSE

Antibiotic resistance is a growing problem worldwide requiring national and international approaches and respective interventions. Not only nosocomial but also community-acquired bacteria can harbor various resistance mechanisms that results in problems of choosing of effective empirical antibiotic treatment and leads to clinical failures, complications, prolongation of disability and increase of treatment costs. Inappropriate and excessive antibiotic use is one of the main reasons for the observed increase in antimicrobial resistance. Pattern of use of antimicrobials has been shown to be an independent risk factor for emergence and spread of resistant microorganisms. However there were some positive examples of the possibility to curb antimicrobial resistance or even to decrease prevalence of the resistant strains with the appropriate interventions including changes in the antibiotic usage in hospitals and in community.

Antimicrobial resistance surveillance studies demonstrate that various long-term care facilities in general, and orphanages in particular, are reservoirs of resistant strains, which can spread into community and into clinical settings. For example the rates of resistance of nasopharyngeal isolates of *S.pneumoniae* (SPN) in orphanages to the majority of respective antimicrobials are the highest ever reported in Russia. It was hypothesized that excessive and inappropriate use of antimicrobials in children living in orphanages is one of the causes of the high rates of SPN resistance and that interventions with the appropriate changes of antibiotic use can improve the situation. Our previous study has shown that there was a vast need to restrict usage of some inappropriate agents with inappropriate PK/PD, safety profiles and high rates of antibiotic resistance of potential pathogens. The aim of the current study was to investigate the dynamics of the antibiotic usage in children from different orphanages located in geographically distinct Russian cities as the result of the one-year intervention with the increased use of the most active antimicrobials and restrictions on use of the least active.

## METHODS

This survey was performed as a part of the prospective study CORPUS in 12 orphanages (##1-12) from 5 cities (Moscow, Saint-Petersburg, Smolensk, Karachev, Bryansk) located in European part of Russia. Use of antimicrobials during the previous 12 months was analyzed based upon reviews of medical records of 743 children < 7 years in 2003.

Microbiological part of the study included collection of nasopharyngeal swabs from these children that yielded 399 nasopharyngeal strains of SPN in 2003. Susceptibility to penicillin G (PEN), amoxicillin (AMO), amoxicillin/clavulanate (AMC), cefuroxime (CEF), cefotaxime (CTX), erythromycin (ERY), clindamycin (CLI), chloramphenicol (CHL), tetracycline (TET) and co-trimoxazole (SXT) was performed by broth microdilution (NCCLS/CLSI method).

Appropriate recommendations on predominant use of selected beta-lactams (e.g. AMC) with restriction of antimicrobials of other classes (e.g. SXT) were made where applicable on the basis of the expert analysis of antibiotic usage and pneumococcal nasopharyngeal resistance rates in 2003. Repeated antibiotic usage analysis was performed 7 months later in 2004 upon reviews of medical records of 752 children < 7 years.

Repeated collection of nasopharyngeal swabs from these children yielded 397 SPN isolates and susceptibility testing to the above antimicrobials was performed in 2004 (CLSI broth microdilution method).

Data were recorded in special case report forms, which were later entered using double-entry approaches into a custom designed computer database.

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 1,000 resident-days) for the total studied population and separately for each orphanage.

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.

## RESULTS

Total usage of antimicrobials increased 1.4 times in 2004 (1,065 courses per 752 children in 7 months equivalent to 2.44 courses per child per year) in comparison with 1,301 courses per 743 children in 2003 (1.75 courses per child per year) (Table 1). Therefore, despite recommendations for the judicious use of antimicrobials in the studied population, antibiotic usage has increased. There were only 3 orphanages, all located in Smolensk where antibiotic usage decreased (## 8 and 10) or remained stable (# 9). The most frequently used antimicrobials in different orphanages are presented in Figure 1.

It is worth noting that patterns of usage of different classes of antimicrobials were rather inert. For example despite recommendations for restriction of aminoglycosides the use of these agents increased in half of the studied orphanages (## 1, 2, 4, 5, 7, 11) and at total from 10 to 19 courses/100 children/year in 2004 vs 2003. SXT use also increased (e.g. orphanages ## 3 and 7), and the total use of this agent increased almost twice from 10 to 18 courses/100 children/year in 2004 vs 2003 placing this agent on the third place of the most frequently used antimicrobials in 2004.

Respectively use of macrolides decreased 2 times: from 20 to 10 courses/100 children/year; and lincosamides - >3 times: from 10 to 3 courses/100 children/year.

In all orphanages beta-lactams were the most frequently prescribed antibiotics (70.6% and 72.1% of all prescriptions in 2003 and 2004 respectively). Among these the predominant ones (in order of frequency) in 2003: ampicillin/oxacillin - AM/OX (17.9%), AMC (16.1%), III generation cephalosporins (16.9%) and I generation cephalosporins (14.8%); in 2004: AMC (25.5%), III generation cephalosporins (20.3%), AM/OX (18.4%), I generation cephalosporins (14.7%) (Table 2). Proportions of use of penicillin G and amoxicillin among other beta-lactams remain quite stable, the same is noted for ampicillin/oxacillin and I generation cephalosporins (despite recommendations to substitute these agents with amoxicillin/clavulanate), ampicillin use has somewhat decreased. Usage of amoxicillin/clavulanate increased from 19 to 45 courses/100 children/year, however this increase is far less than the possible target. Use of cephalosporins also increased from 42 to 67 courses/100 children/year predominantly due to the increase of use of III generation (orphanages ## 2, 3, 5, 6, 7, 8) and II generation cephalosporins (in orphanage # 11).

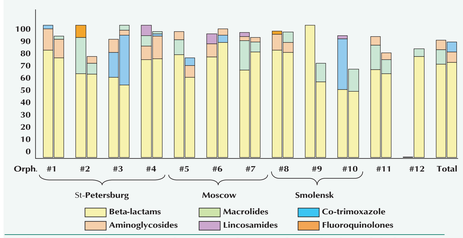


Figure 1. The most frequently used antimicrobials in orphanages 2003 (left bars) vs 2004 (right bars)

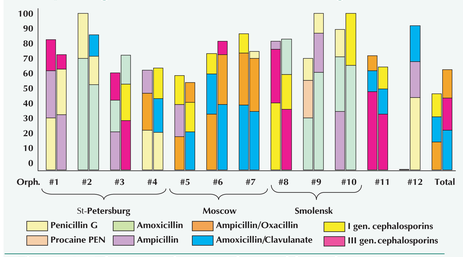


Figure 2. The most frequently used beta-lactams in orphanages 2003 (left bars) vs 2004 (right bars)

Analysis of the antibiotic resistance patters of nasopharyngeal SPN and the dynamics of resistance in 2004 vs 2003 showed no increase in SPN non-susceptibility (NS) or resistance to PEN, AMO and AMC (Figure 3). However our data revealed the statistically significant increase of I and R SPN isolates to I and III generation cephalosporins (CEF and CTX) - 1.3 / 39.4 vs 17.9 / 31.2 and 3.8 / 2.5 vs 9.3 / 8.3 in 2003 vs 2004 respectively. It is noteworthy that NS SPN population to CEF increased due to the higher frequency of I isolates with the stable rate of R strains, while in case of CTX NS - it was due to simultaneous (~2.4 fold and ~3.3 fold) increase of I and R isolates, respectively. At the same time no statistically significant changes occurred in ERY, CLI and SXT susceptibility and there was a statistically significant decrease in CHL R rates (15.0 vs 8.1%).

On the base of these data we conclude that increased use of amoxicillin/clavulanate have no negative impact on the resistance of SPN nasopharyngeal isolates to amoxicillin and its combination with clavulanic acid. At the same time we hypothesize that increased use of cephalosporins may lead to emergence of strains intermediately resistant or highly resistant to these drugs. On the other hand statistically significant decrease of SPN resistance to chloramphenicol can be a positive example of the possibility to diminish resistance rates following the restricted use of antimicrobials.

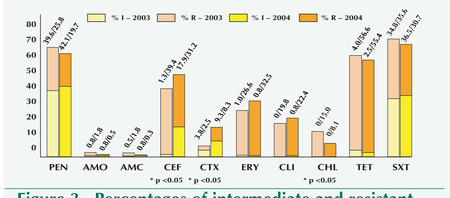


Figure 3. Percentages of intermediate and resistant nasopharyngeal SPN isolated from children in orphanages

Table 1. Summary data on antibiotic use in different orphanages

| Orphanage | #1 | | #2 | | #3 | | #4 | | #5 | | #6 | | #7 | | #8 | | #9 | | #10 | | #11 | | #12 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Survey | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* |
| N of children | 119 | 118 | 24 | 22 | 38 | 32 | 60 | 58 | 70 | 91 | 85 | 91 | 86 | 75 | 114 | 119 | 28 | 28 | 49 | 8 | 70 | 72 | - | 39 | 743 | 752 |
| Courses of Beta-lactams | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N | 30 | 65 | 7 | 24 | 74 | 60 | 94 | 129 | 131 | 132 | 109 | 132 | 147 | 174 | 96 | 31 | 21 | 8 | 40 | 3 | 169 | 216 | - | 13 | 918 | 768 |
| (%) | 81.1 | 75.6 | 63.6 | 63.2 | 60.7 | 55.0 | 74.0 | 74.6 | 78.0 | 60.8 | 76.2 | 60.8 | 66.2 | 79.8 | 81.4 | 79.5 | 100 | 57.1 | 51.3 | 50.0 | 66.5 | 63.3 | - | 76.5 | 70.6 | 72.1 |
| Per child / per year | 0.3 | 0.9 | 0.3 | 1.9 | 1.9 | 3.2 | 1.6 | 3.8 | 1.9 | 2.5 | 1.3 | 2.5 | 1.7 | 3.8 | 0.8 | 0.4 | 0.8 | 0.5 | 0.8 | 0.64 | 2.4 | 5.1 | - | 0.6 | 1.2 | 1.8 |
| Courses of Aminoglycosides | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N | 6 | 12 | - | 2 | 13 | 4 | 10 | 30 | 10 | 19 | 14 | 19 | 7 | 7 | 14 | 3 | - | - | 1 | - | 17 | 18 | - | - | 92 | 84 |
| (%) | 16.2 | 14.0 | - | 5.3 | 10.1 | 3.7 | 7.9 | 17.3 | 6.0 | 8.8 | 9.8 | 8.8 | 3.2 | 3.2 | 11.9 | 7.7 | | | 1.3 | | 6.7 | 5.3 | | | 7.1 | 7.9 |
| Per child / per year | 0.1 | 0.2 | | 0.2 | 0.3 | 0.2 | 0.2 | 0.9 | 0.1 | 0.4 | 0.2 | 0.4 | 0.1 | 0.2 | 0.1 | 0.04 | - | - | 0.02 | - | 0.2 | 0.4 | - | - | 0.1 | 0.2 |
| Courses of Co-trimoxazole | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N | 1 | - | - | 1 | 23 | 41 | - | 3 | 5 | 13 | - | 13 | 5 | 12 | - | - | - | - | 30 | - | 6 | 6 | - | - | 70 | 80 |
| (%) | 2.7 | | | 2.6 | 18.8 | 37.6 | | 1.7 | 3.0 | 5.9 | | 5.9 | 2.3 | 2.5 | | | | | 38.5 | | 2.4 | 1.8 | | | 5.4 | 7.5 |
| Per child / per year | 0.01 | - | - | 0.1 | 0.6 | 2.2 | - | 0.09 | 0.1 | 0.2 | - | 0.2 | 0.1 | 0.3 | - | - | - | - | 0.6 | - | 0.1 | 0.1 | - | - | 0.1 | 0.2 |
| Courses of Macrolides | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N | - | 2 | 3 | 3 | 8 | 4 | 10 | 3 | 19 | 6 | 4 | 6 | 49 | 17 | 2 | 3 | - | 2 | 1 | 1 | 47 | 36 | - | 1 | 143 | 44 |
| (%) | - | 2.3 | 27.3 | 8.0 | 6.6 | 3.7 | 7.9 | 1.7 | 11.3 | 2.8 | 2.8 | 2.8 | 22.1 | 7.8 | 1.7 | 7.7 | | 14.3 | 1.3 | 16.7 | 18.5 | 10.6 | | 5.9 | 11.0 | 4.1 |
| Per child / per year | | 0.03 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.09 | 0.3 | 0.1 | 0.05 | 0.1 | 0.6 | 0.4 | 0.02 | 0.04 | - | 0.1 | 0.02 | 0.2 | 0.7 | 1.6 | - | 0.04 | 0.2 | 0.1 |
| Courses of Lincosamides | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N | - | - | - | 1 | 3 | - | 13 | - | 3 | 5 | 11 | 5 | 7 | 4 | 1 | 1 | - | - | 2 | - | - | - | - | - | 40 | 12 |
| (%) | | | | 2.6 | 2.5 | | 10.2 | | 1.8 | 2.3 | 7.7 | 2.3 | 3.2 | 1.8 | 0.9 | 2.6 | | | 2.6 | | | | | | 3.1 | 1.1 |
| Per child / per year | - | - | - | 0.1 | 0.1 | - | 0.2 | - | 0.04 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.01 | 0.01 | - | - | 0.04 | - | - | - | - | - | 0.1 | 0.03 |
| Total ABx List | 7 | 18 | 5 | 16 | 17 | 17 | 12 | 22 | 14 | 31 | 18 | 31 | 18 | 23 | 18 | 16 | 7 | 8 | 12 | 4 | 21 | 25 | - | 6 | 14** | 17** |
| Total Q-ty of courses | 37 | 86 | 11 | 38 | 122 | 109 | 127 | 173 | 168 | 217 | 143 | 217 | 222 | 218 | 118 | 39 | 21 | 14 | 78 | 6 | 254 | 341 | - | 17 | 1301 | 1065 |
| Per child / per year | 0.3 | 1.2 | 0.5 | 3.0 | 3.2 | 5.8 | 2.1 | 5.1 | 2.4 | 4.1 | 1.7 | 4.1 | 2.6 | 4.5 | 1.0 | 0.6 | 0.8 | 0.9 | 1.6 | 1.3 | 3.6 | 8.1 | - | 0.7 | 1.8 | 2.4 |

* Survey II - N of ABx courses are indicated for 7-months period
** Average number

Table 2. Summary data on beta-lactams use in different orphanages

| Orphanage | #1 | | #2 | | #3 | | #4 | | #5 | | #6 | | #7 | | #8 | | #9 | | #10 | | #11 | | #12 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Survey | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* | I | II* |
| N of children | 119 | 118 | 24 | 22 | 38 | 32 | 60 | 58 | 70 | 91 | 85 | 90 | 86 | 75 | 114 | 119 | 28 | 28 | 49 | 8 | 70 | 72 | - | 39 | 743 | 752 |
| Total courses of Beta-lactams | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N (100%) | 30 | 65 | 7 | 24 | 74 | 60 | 94 | 129 | 131 | 132 | 109 | 129 | 147 | 174 | 96 | 31 | 21 | 8 | 40 | 3 | 169 | 216 | - | 13 | 918 | 768 |
| Per child / per year | 0.3 | 0.9 | 0.3 | 1.9 | 1.9 | 3.2 | 1.6 | 3.8 | 1.9 | 2.5 | 1.3 | 2.5 | 1.7 | 3.8 | 0.8 | 0.4 | 0.8 | 0.5 | 0.8 | 0.64 | 2.4 | 5.1 | - | 0.6 | 1.2 | 1.8 |
| Courses of different Beta-lactams, N / % | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Penicillin G | 10 | 19 | 2 | 4 | 7 | - | 24 | 31 | 14 | 16 | 9 | 9 | 4 | 8 | 1 | - | 3 | 1 | 7 | - | 20 | 16 | - | 6 | 101 | 94 |
| □ | 33.3 | 29.2 | 28.6 | 18.2 | 9.5 | | 25.5 | 24.0 | 10.7 | 12.1 | 8.3 | 7.0 | 2.7 | 4.6 | 1.0 | | 14.3 | 12.5 | 17.5 | | 11.8 | 7.4 | | 46.2 | 11.0 | 12.2 |
| Procaine-Penicillin | - | - | - | - | - | - | - | - | - | 1 | - | - | - | - | - | - | 5 | - | - | - | - | - | - | - | 5 | 1 |
| | | | | | | | | | | 0.8 | | | | | | | 23.8 | | | | | | | | 0.5 | 0.1 |
| Oxacillin | - | 1 | - | 1 | 2 | - | - | - | 1 | 2 | - | - | 1 | - | 2 | - | - | - | 1 | - | - | - | - | - | 7 | 4 |
| | | 1.5 | | 4.5 | 2.7 | | | | 0.8 | 1.5 | | | 0.7 | | 2.1 | | | | 2.6 | | | | | | 0.8 | 0.5 |
| Ampicillin | 9 | 23 | - | - | 18 | 2 | 14 | 6 | 27 | 15 | 3 | 2 | 6 | 5 | 5 | - | 2 | 2 | 15 | - | 4 | 8 | - | 3 | 103 | 58 |
| | 30.0 | 35.4 | | | 24.3 | 3.3 | 14.9 | 4.7 | 20.6 | 11.4 | 2.8 | 1.6 | 4.1 | 2.9 | 5.2 | | 9.5 | 25.0 | 37.5 | | 2.4 | 3.7 | | 23.1 | 11.2 | 7.6 |
| Amoxicillin | - | 1 | 5 | 12 | 15 | 11 | 1 | 5 | 2 | 2 | 4 | 1 | - | 2 | - | 7 | 7 | 5 | 14 | 2 | - | 2 | - | 1 | 48 | 49 |
| | | 1.5 | 71.4 | 54.5 | 20.3 | 18.3 | 1.1 | 3.9 | 1.5 | 1.5 | 3.7 | 0.8 | | 1.2 | | 22.6 | 33.3 | 62.5 | 35.0 | 66.7 | | 0.9 | | 7.7 | 5.2 | 6.4 |
| Carbenicillin | - | - | - | - | - | - | - | - | 2 | 5 | 1 | - | 3 | - | - | - | - | - | - | - | 5 | 6 | - | - | 11 | 6 |
| | | | | | | | | | 1.5 | 3.8 | 0.9 | | 2.0 | | | | | | | | 3.0 | 2.8 | | | 1.2 | 0.8 |
| Amicillin/ Oxacillin | 2 | 2 | - | - | 9 | 4 | 22 | 18 | 28 | 17 | 39 | 41 | 49 | 59 | - | - | - | - | - | - | 15 | 22 | | | 164 | 141 |
| | 6.7 | 3.1 | | | 12.2 | 6.7 | 23.4 | 14.0 | 21.4 | 12.9 | 35.8 | 31.8 | 33.3 | 33.9 | | | | | | | 8.9 | 10.2 | - | - | 17.9 | 18.4 |
| Amoxicillin/ Clavulanate | - | - | - | 3 | - | 10 | 12 | 28 | 20 | 32 | 28 | 54 | 61 | 65 | 3 | 1 | 1 | - | - | - | 23 | 35 | | 3 | 148 | 196 |
| | | | | 13.6 | | 16.7 | 12.8 | 21.7 | 15.3 | 24.2 | 25.7 | 41.9 | 41.5 | 37.4 | 3.1 | 3.2 | 4.8 | | | | 13.6 | 16.2 | - | 23.1 | 16.1 | 25.5 |
| Cefazolin / Cephalexin | 3 | - | - | 2 | 8 | 14 | 8 | 25 | 24 | 25 | 13 | 8 | 18 | - | 41 | 7 | 2 | - | 1 | 1 | 16 | 30 | - | - | 135 | 113 |
| | 10.0 | | | 9.1 | 10.8 | 23.3 | 8.5 | 19.4 | 18.3 | 18.9 | 12.9 | 6.2 | 12.2 | | 42.7 | 22.6 | 9.5 | | 2.5 | 33.3 | 9.5 | 13.9 | | | 14.8 | 14.7 |
| Cefaclor/ Cefuroxime | - | - | - | - | - | - | - | 1 | 8 | - | - | 1 | - | 1 | 4 | 2 | - | - | - | - | 1 | 16 | - | - | 13 | 21 |
| | | | | | | | 0.8 | 6.1 | | | 0.8 | | 0.6 | 4.2 | 6.5 | | | | | | 0.6 | 7.4 | | | 1.4 | 2.7 |
| Cefotaxime/ Ceftriaxone | 6 | 6 | - | 2 | 13 | 19 | 13 | 14 | 5 | 9 | 7 | 11 | 2 | 6 | 33 | 12 | - | - | 1 | - | 75 | 77 | - | - | 155 | 156 |
| | 20.0 | 9.2 | | 9.1 | 17.6 | 31.7 | 13.9 | 10.9 | 3.8 | 6.8 | 6.5 | 8.5 | 1.4 | 3.4 | 34.4 | 38.7 | | | 2.5 | | 44.3 | 35.6 | | | 16.9 | 20.3 |
| Others | - | - | - | - | 2 | - | - | 1 | - | 8 | 2 | 2 | 1 | 5 | 7 | 2 | 1 | - | 1 | - | 10 | 4 | - | - | 24 | 22 |
| | | | | | 2.8 | | | 0.8 | | 6.1 | 1.8 | 1.6 | 0.7 | 2.9 | 7.2 | 6.5 | 4.8 | | 2.5 | | 5.9 | 1.8 | | | 2.7 | 2.9 |

## CONCLUSIONS

The recommended intervention resulted in 2.4 times increase of AMC usage in 2004 vs 2003 with no detectable increase of resistance to PEN and aminopenicillins. Enhanced use of cephalosporins led to increase of resistance to these drugs. In spite of recommendations to restrict usage of AM/OX, aminoglycosides and SXT, the analysis showed that these antimicrobials still accounted for 13.2%, 7.9% and 7.5% of all prescriptions, respectively, thus dictating the need for further enforcement measures.

ACKNOWLEDGEMENT

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