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Antimicrobial susceptibility of *Streptococcus pneumoniae* isolated from patients in the northeastern macroregion of São Paulo state, Brazil, 1998-2013

Suscetibilidade antimicrobiana de Streptococcus pneumoniae *isolados de pacientes na macrorregião nordeste do estado de São Paulo, Brasil, entre 1998 e 2013*

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ABSTRACT

Introduction: There are reports worldwide about the increase in infections caused by *Streptococcus pneumoniae* resistant to antimicrobials. **Objective:** Evaluate the susceptibility profile of serotypes of *Streptococcus pneumoniae* associating them with pneumococcal invasive diseases (PID), as well as antimicrobial therapies. **Method:** This is a retrospective cross-sectional research involving secondary data from 1998 to 2013, in the northeastern macroregion of São Paulo state, Brazil, composed of Araraquara, Barretos, Franca and Ribeirão Preto regions, with 90 municipalities. At Instituto Adolfo Lutz (IAL), isolated strains from patients with PID were subjected to identification, serotyping and antimicrobial susceptibility testing. **Results:** From 796 strains analyzed, 14.8% ($n = 118$) were resistant to penicillin, being 3% ($n = 24$) with intermediate resistance and 11.8% ($n = 94$) with full resistance, especially in patients with meningitis. Moreover, resistance to ceftriaxone was 5.3%: 34 (4.3%) with intermediate resistance and 8 (1%) with full resistance. We point out that the greatest level of resistance profiles was observed against sulfamethoxazole/trimethoprim (SMT): 350 (49.4%). On the other hand, antimicrobial susceptibility was described above 90% to chloramphenicol: 99.6% ($n = 696$), erythromycin: 94.7% ($n = 664$), ceftriaxone: 94.7% ($n = 754$) and fully susceptible to vancomycin. Among the 18 most common serotypes, 9V and 14 showed less susceptibility to SMT, to penicillin and ceftriaxone; 19A to SMT and penicillin; 1 to SMT; 12F and 3 to chloramphenicol; 6A to SMT; 6B 23F to erythromycin and penicillin. **Conclusion:** Monitoring of *Streptococcus pneumoniae* antimicrobial resistance is essential to guide the appropriate empirical treatment of pneumococcal disease.

Key words: *Streptococcus pneumoniae*; serotyping; antibacterial agents.

INTRODUCTION

Infections by *Streptococcus pneumoniae* persist as an important health problem worldwide[1], despite the extensive investment in vaccines and the availability of appropriate antibiotic therapy. We must highlight that pneumococcus is part of human nasopharyngeal microbiota and can be isolated including in healthy adults and children who attend institutions of early childhood education. In Brazil, the prevalence of pneumococcus carriers ranges from 13% to 72%, depending on age and presence of associated diseases[2].

In the decade of 1940s, the advent of penicillin apparently controlled pneumococcal diseases. However, as years went by, an increase in resistant strains was observed, both to classical and to the latest-generations treatments[3-10]. In Brazil the first report of resistance to pneumococcus was delivered in 1988[11].

The indiscriminate use of antibiotic drugs is considered a risk factor for the increase in the resistance profile of *S. pneumoniae*, favoring colonization of nasopharynx and the occurrence of pneumococcal invasive diseases (PID) by resistant strains[1, 6]. Researches about PID exhibit regional and seasonal specificities, what determines the need of periodic monitoring for the

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establishment of interventions and control policies. Additionally, surveillance of the antimicrobial susceptibility pattern of strains is enormously valuable in the choice of the initial empirical treatment, as well as for the rational use of antimicrobials[12].

This study was aimed at evaluating the susceptibility profile of different serotypes of *S. pneumoniae* isolated from individuals with PID in the northeastern macroregion of São Paulo state, Brazil, during a period of 16 years.

METHOD

This is a retrospective cross-sectional research focusing secondary data on the antimicrobial susceptibility profile of *S. pneumoniae* isolated from patients with PID in a period of 16 years. Those patients were from the northeastern region of the state of São Paulo, Brazil, registered at the Regional Healthcare Network 13 (RRAS 13), which is part of the Regional Health Department (DRS) of Araraquara, Barretos, Franca, and Ribeirão Preto, with 90 municipalities[13].

Information about serotypes and antimicrobial susceptibility profile were collected from 1998 to 2013 at the Center of Regional Laboratory (CLR) of Instituto Adolfo Lutz in Ribeirão Preto (IAL-RP) and Central IAL/São Paulo. It is appropriate to stress that the Bacteriology Center of IAL acts as a reference laboratory at state and national level for meningitis and pneumococcal infections.

The IAL laboratory uses Gram stain, optochin test and bile solubility test[14], serotyping by the *quellung* reaction[15] and antimicrobial susceptibility profile according to the Clinical and Laboratory Standards Institute (CLSI)[16-18].

Data were analyzed by the Statistical Package for the Social Sciences (SPSS), version 19.0, for the chi-square association test between distribution of cases according to period, clinical diagnosis, serotype, or susceptibility of each antimicrobial drug.

The project was approved by the Human Research Ethics Committee (report no. 26759714.80000.5393).

RESULTS

During a 16-year period, the results were analyzed of 796 cultures of *S. pneumoniae* from patients with PID, with ages ranging from 1 month to 94 years, and meningitis (45.7%) and pneumonia (45%) being the most common PID. Serotypes 14, 3, 19F, 1, 6A, 6B, 23F, 9V, 18C, 19A, 12F, 4, 7F, 5, 11A, 22F, 8 and 9N were the most frequently isolated in the northeastern macroregion of the state of São Paulo, Brazil.

A total of 69.2% of *S. pneumoniae* were susceptible to penicillin and ceftriaxone according to the oxacillin disk screening test. For 30.8% of oxacillin-resistant strains, the minimum inhibitory concentration (MIC) was determined.

For chloramphenicol erythromycin, and sulfamethoxazole/trimethoprim (SMT), the disk-diffusion test defined the profile of susceptibility of *S. pneumoniae*. There was an increase in the pneumococcus susceptibility to SMT after vaccination in 2010 (**Table 1**).

TABLE 1 – Susceptibility profile of *S. pneumoniae* to antimicrobials in isolates of patients with PID treated at RRAS 13, according to year of isolation, 1998-2013

Antimicrobial	Susceptibility profile	Period						Total		*p*-value
		1998/2002		2003/2010		2011/2013				
		n	%*	*n*	%*	*n*	%*	*n*	%*	
Penicillin	Susceptible	200	90.1	397	82.9	81	85.3	678	85.2	0.044
	Intermediate	4	1.8	18	3.7	2	2.1	24	3	
	Resistant	18	8.1	64	13.4	12	12.6	94	11.8	
	Total	222	100	479	100	95	100	796	100	
Ceftriaxone	Susceptible	213	98.6	445	93.5	87	91.6	745	94.7	0.012
	Intermediate	3	1.4	26	5.5	5	5.3	34	4.3	
	Resistant	0	0	5	1.1	3	3.6	8	1	
	Total	216	100	476	100	95	100	787	100	
Chloramphenicol	Susceptible	143	99.3	460	99.8	93	98.9	696	99.6	-
	Intermediate	0	0	0	0	0	0	0	0	
	Resistant	1	0.7	1	0.2	1	1.1	3	0.4	
	Total	144	100	461	100	94	100	699	100	
Erythromycin	Susceptible	137	94.5	440	95.2	87	92.6	664	94.7	0.564
	Intermediate	0	0	1	0.2	0	0	1	0.1	
	Resistant	8	5.5	21	4.6	7	7.4	36	5.1	
	Total	145	100	462	100	94	100	701	100	
SMT	Susceptible	64	44.1	197	42	68	72.3	329	46.5	< 0.001
	Intermediate	9	6.2	19	4.1	1	1.1	29	4.1	
	Resistant	72	49.7	253	53.9	25	26.6	350	49.4	
	Total	145	100	469	100	94	100	708	100	

%: refers to the total of strains tested in each period.*
PID: pneumococcal invasive disease; RRAS 13: Regional Healthcare Network 13; SMT: sulfamethoxazole/trimethoprim.

Among the non-susceptible *S. pneumoniae* (intermediate and resistant), rates of 53.5% for SMT, 14.8% for penicillin, 5.2% for erythromycin, and 0.4% for chloramphenicol occurred. A decrease was evident in susceptibility of pneumococcus to penicillin from 1998-2002 to 2003-2010. Susceptibility to ceftriaxone remained above 90%; however there was a progressive reduction of these rates during the studied period (Table 1).

Penicillin resistance was restricted to serotypes 14, 23F, 19F, 9V, 19A, 6B and 6A (**Table 2**).

TABLE 2 – Serotypes of *S. pneumoniae* more frequently isolated in patients with PID treated at RRAS 13, according to the profile of susceptibility to penicillin, 1998-2013

Serotype	Susceptible		Intermediate		Resistant		Total	
	n	%*	*n*	%*	*n*	%*	*n*	%*
14	90	11.3	19	2.4	36	4.5	145	18.2
3	73	9.2	0	0	0	0	73	9.2
19F	35	4.4	1	0.1	10	1.3	46	5.8
1	43	5.4	0	0	0	0	43	5.4
6A	33	4.4	0	0	6	0.8	39	4.9
6B	29	3.6	2	0.3	7	0.9	38	4.8
23F	24	3	2	0.3	11	1.4	37	4.6
9V	24	3	0	0	10	1.3	34	4.3
18C	33	4.4	0	0	0	0	33	4.1
19A	24	3	0	0	9	1.1	33	4.1
12F	28	3.5	0	0	0	0	28	3.5
4	24	3	0	0	0	0	24	3
7F	21	2.6	0	0	0	0	21	2.6
5	17	2.1	0	0	0	0	17	2.1
11A	15	1.9	0	0	0	0	15	1.9
22F	15	1.9	0	0	0	0	15	1.9
8	12	1.5	0	0	0	0	12	1.5
9N	10	1.3	0	0	0	0	10	1.3
Others**	128	16.1	0	0	5	0.6	133	16.7
Total	678	85.2	24	3	94	11.8	796	100

%: refers to the total of cases; **: 29, 10F, 11A, 11C, 12A, 13, 15A, 15B, 15C, 16F, 17A, 17F, 18A, 18B, 18F, 20, 21, 23A, 23B, 24F, 25A, 28A, 31, 34, 35B, 35F, 37, 38, 42, 6B/D, 6C, 7C, Pool G.*

PID: pneumococcal invasive disease; RRAS 13: Regional Healthcare Network 13.

Regarding the 364 meningitis cases, 25.5% (n = 93) of pneumococci presented penicillin resistance, with MIC between 0.125 and 4 µg/ml. For the other non-meningeal pneumococcal infections, 3.1% of the strains were not susceptible to penicillin (3% with intermediate resistance, and 0.1% with full resistance). Among the 358 *S. pneumoniae* associated with pneumonia, 93.9% (n = 336) were susceptible to penicillin; 5.9% presented intermediate resistance (MIC = 4 µg/ml); and 0.3% (n = 1), full resistance (**Table 3**).

Out of the 796 pneumococcus strains evaluated, 94 (11.8%) were totally resistant to penicillin, with 11.7% isolated from meningitis and just 0.1% from pneumonia. Only 3% of the *S. pneumoniae* isolated from non-meningeal infections presented intermediate resistance to penicillin (Table 3).

Out of the total of 787 strains tested for susceptibility to ceftriaxone, 1% (n = 8) presented full resistance and was associated with meningitis cases. In the evaluation of 361 *S. pneumoniae* isolated from meningitis, 8.6% (n = 31) were not susceptible to ceftriaxone, with 6.4% (n = 23) of intermediate resistance (MIC = 1 µg/ml) and 2.2% (n = 8) of full resistance (MIC = 2 µg/ml) (Table 3).

TABLE 3 – Main PID in patients at the RRAS 13, according to the profile of susceptibility to penicillin and ceftriaxone, 1998-2013

Antimicrobial	PID	Susceptible		Intermediate		Resistant		Total	
		n	%*	*n*	%*	*n*	%*	*n*	%*
Penicillin	Meningitis	271	34	-	-	93	11.7	364	45.7
	Pneumonia	336	42.2	21	2.6	1	0.1	358	45
	Bacterium/sepsis	47	5.9	2	0.3	0	0	49	6.2
	Others**	24	3	1	0.1	0	0	25	3.1
	Total	678	85.2	24	3	94	11.8	796	100
Ceftriaxone	Meningitis	330	41.9	23	2.9	8	1	361	45.8
	Pneumonia	343	43.6	11	1.4	0	0	354	45
	Bacterium/sepsis	48	6.1	0	0	0	0	48	6.1
	Others**	24	3	0	0	0	0	24	3
	Total	745	94.7	34	4.3	8	1	787	100

%: refers to the total of strains tested for each antimicrobial; **: abscess, arthritis, peritonitis, pancreatitis, cirrhosis, surgical site infection, and appendicitis.*

PID: pneumococcal invasive disease; RRAS 13: Regional Healthcare Network 13.

Seven cases (0.9%) of multi-resistant *S. pneumoniae* occurred (resistance to three classes of antimicrobials), with four being isolated from meningitis, two from pneumonia, and one from sepsis. In all of them, simultaneous resistance to penicillin, erythromycin, and SMT was observed, with 14, 19F, 6A, and 6B being the most involved serotypes.

Concerning the most frequent serotypes, the antimicrobial susceptibility evaluation demonstrated that 9V (p = 0.014), 14 ($p \leq 0.001$), 19A ($p = 0.04$) and 23F ($p \leq 0.001$) were less sensitive to penicillin; 9V ($p = 0.003$), 14 ($p < 0.001$), 1 ($p < 0.001$), 19A (p = 0.001) and 6A (p = 0.024) to SMT; 12F (p = 0,009) e 3 ($p = 0{,}001$) to chloramphenicol; 6B ($p < 0.001$) to erythromycin; 9V ($p = 0.001$) and 14 ($p < 0.001$) to ceftriaxone.

Compared with the other serotypes, 1 ($p = 0.005$), 3 ($p < 0.001$), 18C ($p = 0.014$), 7F ($p = 0.053$), 12F ($p = 0.025$) and 4 ($p = 0.038$) were more sensitive to penicillin; and serotypes 3 (p < 0.001), 8 ($p < 0.001$), 7F (p = 0.001), 12F ($p < 0.001$), 22F (p = 0.001), 4 ($p < 0.001$) and 3 ($p = 0.033$) to ceftriaxone.

DISCUSSION

Monitoring antimicrobial resistance of *S. pneumoniae* is fundamental to guide the empirical treatment of PID, as well as to encourage reflections to support public immunization policies.

Lineages of penicillin-resistant *S. pneumoniae* are not limited to infectious pictures. In Brazil, there are reports of this profile in asymptomatic carriers, mainly in children attending day-care centers, a fact that can be associated with a greater use of antimicrobials[6]. In Portugal, evaluation of invasive and non-invasive respiratory pneumococcal infections in all age groups revealed that 18.4% of the strains were not susceptible

to penicillin[19], a percentage higher than the one found in the current research (14.8%).

Regarding *S. pneumoniae* susceptibility to chloramphenicol, erythromycin, and SMT, Santos *et al*. (2013)[20], evaluating the periods before and after introduction of the 10-valent pneumococcal conjugate vaccine (PCV10), in São Paulo, found a similar result to that of the region in this study. In that research, *S. pneumoniae* were less resistant to erythromycin than those presented in Germany (19.9%)[8] and United States (35.3%)[21].

In the present research pneumococcus demonstrated higher level of resistance to SMT, data compatible with the evidences of other national researches[12, 20, 22]. Soeters *et al*. (2011)[12], in South Africa, showed evidence that non-susceptibility of pneumococcus to SMT is generally associated with resistance to multiple drugs, a fact observed in patients with the human immunodeficiency virus (HIV) that use SMT as a prophylactic drug for prevention of opportunistic infections.

In Porto Alegre, the susceptibility values of *S. pneumoniae* were higher than those of our study for SMT (68%), penicillin (28%), erythromycin (15%), and chloramphenicol (3%). However, for ceftriaxone just 1% of the isolated *S. pneumoniae* were not susceptible[9], while in our research 5.3% presented that profile. In both researches all strains were sensitive to vancomycin, a therapeutic option that can be associated with other antimicrobials for the treatment of pneumococcal meningitis[23].

The reduction of susceptibility of pneumococcus to penicillin from 1998-2002 to 2003-2010, which was evidenced in this study, is compatible with what was reported in Rio de Janeiro in 2000-2002 (8%), 2003-2005 (12%), and 2006-2008 (20%)[4].

Penicillin resistance restricted to serotypes 14, 23F, 19F, 9V, 19A, 6B e 6A coincides with serotypes traditionally described as penicillin-resistant in other researches[4, 7, 22, 24, 25]. Serotypes 19A and 6A are not part of PCV10, available in public health care centers, but there is cross-reactivity between serotypes 6B/6A and 19F/19A[26]. These serotypes are related to nasopharyngeal colonization in children[27], thus being more prone to develop reduced susceptibility to penicillin and to macrolides because these are antimicrobials routinely used in the community[21].

In the period before the introduction of conjugated vaccines, the emergency and dissemination of international clones Spain^{9V}-ST156 and Tennessee^{14}-ST67 increased resistance to antimicrobials[25] both here and in other Latin American countries[7]. In Brazil, those clones express the capsule of serotype 14[25]. In Rio de Janeiro, Barroso *et al*. (2012)[4] isolated, from patients with meningitis, penicillin-resistant *S. pneumoniae* (clone Spain^{9V}-ST156) linked to serotype 14.

Several authors reported rates of penicillin resistance of *S. pneumoniae*, isolated from patients with meningitis, ranging from 21.4% to 27.1%[3, 7, 22, 28], compatible with the 25.5% rate found here. On the other hand, lower values were observed in the state of Paraná (15%)[23] and in Salvador (13%-19%)[29], and higher than 50% in Cuba, El Salvador, Honduras and Mexico[7].

For the other non-meningeal pneumococcal infections, our research detected 3% of strains with intermediate resistance and 0.1% with full resistance to penicillin. According to Negrini (2010)[28], in the municipality of Ribeirão Preto, children younger than 5 years presented 3.5% of *S. pneumoniae* with intermediate resistance, and none presented full resistance to penicillin. In 2012, in Brazil, full resistance was not observed to penicillin either, and intermediate resistance was 7.5% and 3.9% for children younger and older than 5 years, respectively. In Argentina, for children younger than 5 years, 100% of the strains were susceptible to penicillin[7].

In this study, among the pneumococci isolated from patients with pneumonia, just 0.1% was totally resistant to penicillin, and 3% of the isolates from non-meningeal infections presented intermediate resistance to penicillin. This piece of data reinforces the consensus of some researches that concluded that patients with pneumonia treated with penicillin presented similar clinical evolution, regardless of whether the *in vitro* susceptibility test result was resistant or sensitive to penicillin[28]. Therefore, for non-meningeal infections, penicillin continues to be the treatment of choice for pneumococcal diseases[30].

In order to treat intermediate resistance infections, habitual doses of penicillin and derivatives are efficient in the treatment of community-acquired pneumonia. However, for the treatment of acute community-acquired bacterial meningitis, third-generation cephalosporin is the empirical initial treatment[23].

With the introduction of conjugated pneumococcal vaccines, besides the expressive reduction in PID, the decline of infections by strains non-susceptible to penicillin was documented, due to decreased serotypes associated with resistance present in the composition of vaccines[1, 7].

In the city of Uberlândia (MG), 27.8% strains with diminished susceptibility to oxacillin were detected, a result similar to the 30.8% of this study. However, for ceftriaxone, the study in Uberlândia detected 12.5% resistance, a rate much higher than the one found in the current study[3]. In Guatemala and Mexico, a superior proportion of *S. pneumoniae* resistant to ceftriaxone (16.7% and 16.5%, respectively)[7] for non-meningeal infections was verified.

In many countries of Latin America, full resistance to ceftriaxone in pneumococcal meningitis isolates is low, with the highest percentage observed in Mexico (32.3%). In Brazil, in non-meningeal infections, a rate of 3% of intermediate resistance to ceftriaxone was reported, with no isolation of the pneumococcus with full resistance[7], a value similar to the one of the region researched in this work.

In general, the resistance profile of *S. pneumoniae* to ceftriaxone is low, yet, the importance of monitoring resistance levels is stressed due to the excellence of this antimicrobial for treatment of bacterial meningitis[29].

Strains of *S. pneumoniae* resistant to penicillin are frequently associated with resistance to other classes of antimicrobials, especially SMT[12]. In Porto Alegre, among the 18 penicillin-resistant pneumococcus strains, seven were resistant to at least two other drugs[9]. In this research, 0.9% of multi-resistant *S. pneumoniae* was reported, with simultaneous resistance to penicillin, erythromycin, and SMT, confirming the most frequent profile of *S. pneumoniae* with multi-resistance. The isolation of multi-resistant lineages represents a world threat; in the USA it commonly relates to serotype 19A after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7)[30]. Our results indicate that serotypes 14, 19F, 6A and 6B were involved in this multi-resistance profile. Besides, *S. pneumonia* with full and simultaneous resistance to penicillin and ceftriaxone were observed in eight (1%) of the patients with meningitis, a value lower than the 13% detected in Rio de Janeiro in isolates of patients with meningitis[4].

According to Hausdorff *et al*. (2005)[24], serotype 1 is considered sensitive to antibiotics, as well as serotypes 3, 18C, 15 and 35. In the present research, compared with other serotypes, 1, 3, 18C, 7F, 12F and 4 were verified to be more sensitive to penicillin; 3, 8, 7F, 12F, 22F, 4 and 3, to ceftriaxone.

Additionally, the relationship of serotype 1 with PID and with colonization of nasopharynx just in short periods is stressed. It is less exposed to the selective antimicrobial pressure, and consequently, it has a lower level of resistance to penicillin[24].

CONCLUSION

S. pneumoniae lineages presented susceptibility above 90% to chloramphenicol, erythromycin and ceftriaxone during the whole studied period, with total susceptibility to vancomycin. Non-susceptibility to penicillin stands out, detected in 14.8% of the strains, with 11.8% with full resistance, mainly in patients with meningitis. Resistance to penicillin was restricted to serotypes 14, 23F, 19F, 9V, 19A, 6B and 6A. The highest level of resistance was detected for SMT.

Serotypes 9V, 14, 19A and 23F were less susceptible to penicillin than the other serotypes, while 7F, 1, 12F, 18C, 3, 4 and 5 were more susceptible to penicillin than the most frequent serotypes in the region.

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RESUMO

Introdução: *Em todo o mundo existem relatos de aumento das infecções causadas por* Streptococcus pneumoniae *resistentes aos antimicrobianos.* ***Objetivo:*** *Avaliar o perfil de suscetibilidade dos sorotipos de* Streptococcus pneumoniae*, associando-os com as doenças invasivas pneumocócicas (DIP), bem como com as terapias antimicrobianas.* ***Método:*** *Trata-se de um seguimento retrospectivo com enfoque em dados secundários de 1998 a 2013, na macrorregião nordeste do estado de São Paulo, Brasil, composta pelas regiões de Araraquara, Barretos, Franca e Ribeirão Preto, com 90 municípios. No Instituto Adolfo Lutz (IAL), as cepas isoladas de pacientes com DIP foram submetidas a identificação, sorotipagem e teste de suscetibilidade aos antimicrobianos.* ***Resultados:*** *Das 796 cepas analisadas, 14,8% (*n = *118) apresentaram resistência a penicilina, sendo 3% (*n = *24) com resistência intermediária e 11,8% (*n = *94) com resistência plena, principalmente em pacientes com meningite. Para ceftriaxona, a resistência foi de 5,3%: 34 (4,3%) com resistência intermediária e 8 (1%) com resistência plena. Há de salientar que o maior nível de resistência das cepas foi observado para sulfametoxazol/trimetoprima (SMT): 350 (49,4%). Por outro lado, a suscetibilidade foi descrita acima de 90% para cloranfenicol: 99,6% (*n = *696); eritromicina: 94,7% (*n = *664); ceftriaxona: 94,7% (*n = *754) e total para vancomicina. Entre os 18 sorotipos mais frequentes, 9V e 14 apresentaram menor suscetibilidade a SMT, penicilina e ceftriaxona; 19A a SMT e penicilina; 1 a SMT; 12F e 3 a cloranfenicol; 6A a SMT; 6B a eritromicina e 23F a penicilina.* ***Conclusão:*** *O monitoramento da resistência antimicrobiana do* Streptococcus pneumoniae *é fundamental para direcionar o tratamento empírico das doenças pneumocócicas.*

Unitermos: Streptococcus pneumoniae*; sorotipagem; antibacterianos.*

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