

Antibacterial Resistance of Community-Acquired Respiratory Tract Pathogens Recovered from Patients in Latin America: Results from the PROTEKT Surveillance Study (1999–2000)

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PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) is a global surveillance study established in 1999 to monitor antibacterial resistance of respiratory tract organisms. Thirteen centers from Argentina, Brazil and Mexico participated during 1999-2000; they collected 1,806 isolates (*Streptococcus pneumoniae* 518, *Haemophilus influenzae* 520, *Moraxella catarrhalis* 140, *Staphylococcus aureus* 351, *S. pyogenes* 277). Overall, 218 (42.1%) of the *S. pneumoniae* isolates had reduced susceptibility to penicillin, 79 (15.3%) were penicillin-resistant and 79 (15.3%) were erythromycin-resistant. Mexico had the highest prevalence of penicillin (76.5%) and erythromycin (31.2%) resistance. Of 77 erythromycin-resistant *S. pneumoniae* tested for resistance genotype, 43 possessed *mef(A)*, 33 possessed *erm(B)* and 1 possessed both *erm(B)* and *mef(A)* mechanism. All *S. pneumoniae* isolates were fully susceptible to telithromycin, linezolid, teicoplanin and vancomycin. Among *H. influenzae* isolates, 88 (16.9%) produced β -lactamase, ranging from 11% (Brazil) to 24.5% (Mexico). Among *M. catarrhalis* isolates, 138 (98.6%) produced β -lactamase. Twenty-four (8.7%) of the *S. pyogenes* isolates were erythromycin-resistant; resistance being attributable to *mefA* (n=18), *ermTR* (n=5) and *ermB* (n=1). All *H. influenzae*, *M. catarrhalis* and *S. pyogenes* were fully susceptible to telithromycin. Methicillin resistance was found in 26.5% of the *S. aureus* isolates (Argentina 15%; Mexico 20%; Brazil 31.3%). Telithromycin was effective against 97.7% of methicillin-susceptible isolates. PROTEKT confirms that antibacterial resistance is an emerging problem in Latin America. The previously reported high levels of pneumococcal resistance to the β -lactam and macrolides were exceeded. New agents that do not induce resistance or that exert low selective pressure, e.g. telithromycin, are essential to safeguard future antibacterial efficacy.

Key Words: PROTEKT, Latin America, resistance, respiratory tract infections, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Staphylococcus aureus*.

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The prevalence of antibacterial resistance among pathogens commonly involved in community-acquired respiratory tract infections (RTIs), including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, represents a global problem and appears to be increasing in many countries in Latin America. In particular, β -lactam and macrolide resistance among *S. pneumoniae* has reached high

levels in several Latin American countries, including Argentina, Brazil and Mexico. For example, in their analysis of 264 Latin American pneumococcal isolates as part of the SENTRY programme, Odland et al. [1] found that 9.9% were fully resistant to penicillin. Similarly, of the 1,100 *S. pneumoniae* isolates from seven Latin American and Caribbean countries surveyed by the LASER study group in 1997 [2], 6.9% were fully resistant to penicillin. In terms of macrolide resistance, previous studies have reported an overall level of approximately 12% to 13% [2-4].

In addition to the high overall rates of resistance reported previously, the prevalence of lower RTIs caused by these pathogens is known to vary greatly depending on geographic location, and the same is true for the rates of resistance to antibacterial drugs. Important differences exist between the rates of antibacterial resistance in Latin America countries and even between the rates in different cities within each country [2-4]. Furthermore, multiple-resistance to the β -lactams and other antimicrobial agents, such as the cephalosporins and the macrolide-lincosamide-streptogramin (MLS) group of antibiotics, is a common problem.

These issues have driven research towards improving antibiotic usage strategies, and towards the development of new agents that do not induce or cause selection for resistance, as this will be important for safeguarding future antibiotic efficacy. The ketolides are a new family of agents within the MLS class, designed specifically not to induce MLS_B resistance. Telithromycin, the first member of this family to be approved for clinical use, has a well-balanced spectrum of activity covering common RTI bacteria, as well as atypical and intracellular pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* [5,6]. The activity of telithromycin also extends to many RTI bacterial strains that have become resistant to existing agents, in particular penicillin-, erythromycin- and fluoroquinolone-resistant *S. pneumoniae* [5]. The development of newer agents, like the ketolides, needs to be complemented by more rational prescribing of antibiotics in order to help limit the spread of resistance.

With this in mind, continued surveillance of resistance amongst the bacterial species most commonly associated with community-acquired RTIs is essential. PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) is a longitudinal global surveillance programme, established in 1999 to study the antibacterial susceptibility of common community-acquired RTI pathogens in Northern and Latin America, Eastern and Western Europe, and the Asia Pacific region. We report here on the 1999-2000 PROTEKT findings on antibacterial resistance among community-acquired RTI isolates from participating centers in Latin America, and the activity of the ketolide telithromycin against these isolates.

Materials and Methods

Participating Centers

During the 1999-2000 winter season, isolates of common pathogens were collected from patients with community-acquired RTIs at 13 participating centers across Latin America. The 13 centers included two centers in Argentina, seven centers in Brazil and four centers in Mexico.

Each center was requested to collect 165 isolates as follows: 20 *S. aureus*, 25 *S. pyogenes*, 60 *S. pneumoniae*, 40 *H. influenzae* and 20 *M. catarrhalis*. In practice the number of isolates collected ranged from 24 to 294 per center, the variation being attributable to a variety of local factors.

Isolate Collection and Storage

Isolates of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Streptococcus pyogenes* and *Staphylococcus aureus* were collected from patients with one of the following types of community-acquired RTIs: acute/chronic sinusitis, acute/chronic otitis media, acute/chronic tonsillitis/pharyngitis, bacterial exacerbation of chronic bronchitis, acute exacerbation of chronic obstructive airways disease, or community-acquired pneumonia. Isolates collected from hospitalised patients within 48 hours of admission were also

included. The following were reasons for exclusion from the analyses: isolates collected from patients with nosocomial lower RTIs or cystic fibrosis, duplicate strains, strains originating from existing collections, and isolates from sputum samples with a poor Gram stain. Demographic data were collected routinely as part of the study.

The four main sources for isolates of RTI pathogens were blood, sputum, bronchoalveolar lavage cultures and middle ear fluid cultures. In addition, four other infection sources were considered acceptable, namely nasopharyngeal swab or aspirate cultures, sinus aspirate cultures, and throat cultures (*S. pyogenes* only). Following collection, isolates were stored in heavy suspension in horse serum, skimmed milk, Protect™ tubes, or in the microbank system at a temperature at or below -20°C , and subsequently shipped to a central, accredited laboratory (GR Micro Ltd, London, UK) for microbiological investigation. Criteria for isolate identification and re-identification have been described in detail [7,8].

Antibacterial Susceptibility Testing

A range of β -lactam, MLS and fluoroquinolone antibacterial agents were tested. Penicillin, amoxicillin/clavulanate (2:1 ratio), cefuroxime, cefixime, cefaclor, cefpodoxime, clindamycin, erythromycin, clarithromycin, azithromycin, telithromycin, quinupristin-dalfopristin (Synercid, 30:70 ratio), teicoplanin, vancomycin, ciprofloxacin, levofloxacin, moxifloxacin, tetracycline, linezolid and co-trimoxazole (1:19 ratio) were tested against Gram-positive pathogens. All Gram-negative pathogens were tested with the following: ampicillin, amoxicillin, amoxicillin/clavulanate (2:1 ratio), cefditoren, cefprozil, cefuroxime, cefixime, cefdinir, cefaclor, cefpodoxime, erythromycin, clarithromycin, azithromycin, telithromycin, ciprofloxacin, levofloxacin, moxifloxacin, tetracycline, chloramphenicol, linezolid and co-trimoxazole (1:19 ratio).

The central laboratory determined minimum inhibitory concentrations (MICs) using lyophilised microtitre plates (Sensititre system, Trek Diagnostics) with an inoculum of 5×10^4 colony forming units (CFU)

in 100 ml media. Susceptibility tests were conducted according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines for the broth microdilution method [9]. After overnight incubation with the test antibacterial aerobically at 37°C , MIC endpoints were read as the lowest concentration of agent that totally inhibited macroscopically visible growth of the inoculum.

Published NCCLS breakpoints [10] were used to define susceptibility. Since NCCLS breakpoints are not yet available for the new ketolide telithromycin, only MIC₅₀, MIC₉₀ and MIC range were reported.

Determination of Bacterial Resistance Mechanisms

β -lactamase production was determined in *M. catarrhalis* and *H. influenzae*, using the chromogenic cephalosporin (nitrocef) test (Unipath Ltd, Basingstoke, UK). All macrolide-resistant *S. pneumoniae* isolates were processed and tested for the presence of *erm*(A), *erm*(A) subclass *erm*(TR), *erm*(B), *erm*(C), and *mef*(A) genes using a multiplex rapid-cycle polymerase chain reaction (PCR) with microwell-format probe hybridisation, as described previously [11]. A similar methodology was also employed for *S. pyogenes* to test for the presence of *erm*(A), *erm*(A) subclass *erm*(TR), *erm*(B), *erm*(C), and *mef*(A).

Results

A total of 1,806 isolates were collected (Table 1). Of these, 453 (25.1%) were collected from paediatric patients (<14 years of age); this frequency ranged from 30/200 (15%) in Argentina, 123/646 (19.0%) in Mexico to 300/960 (31.3%) in Brazil.

Susceptibility of *S. pneumoniae* Isolates

A total of 518 *S. pneumoniae* isolates were available for microbiological investigation in Latin America (Argentina, n=55; Brazil, n=260; Mexico, n=203) (Table 1). Overall, 218 (42.1%) of the *S. pneumoniae* isolates had reduced susceptibility to

penicillin (MIC >0.06 mg/L), 79 (15.3%) of which were fully resistant (MIC \geq 2 mg/L (Table 2). The highest proportion of fully resistant isolates was observed in Mexico, where resistance reached 76.5% in Mexico City (24.1% overall). While the overall proportion of fully resistant isolates was relatively low in most centers in Brazil (8.1% overall), 30.0% of the isolates from Brasilia were fully resistant to penicillin. As shown in Table 3, the pattern of pneumococcal resistance to penicillin was also seen for the other β -lactam antibacterials tested across Latin America. The notable exception was amoxicillin/clavulanate, which remained active against 98.7% of the isolates.

While the number of *S. pneumoniae* isolates with intermediate and full resistance to erythromycin was lower than that observed for penicillin (15.5% vs. 42.1%), the proportion of isolates with full resistance was identical (15.3%) (Table 2). MIC distributions for azithromycin, clarithromycin, erythromycin and telithromycin are shown in Figure 1; there were no major differences among the participating countries. As with penicillin, the highest rates of erythromycin resistance were observed in Mexico, reaching 23.0% in Mexico City Center 31 and 31.2% in Monterrey (27.6% overall). In all, 77 erythromycin-resistant *S. pneumoniae* were analysed for their underlying mechanism of resistance. Of these, 43 tested positive for *mef(A)* and 33 tested positive for *erm(B)*, while another isolate tested positive for *mefA* and *ermB* (Table 4). Differences in the prevalence of resistance, as well as in the mechanisms of erythromycin resistance, were evident among the different centers participating in the study (Tables 2, 3 and 4).

A trend towards decreasing activity of other β -lactams and the macrolides was observed among *S. pneumoniae* isolates with reduced susceptibility to penicillin (Table 3); almost 100% of penicillin-resistant strains were resistant to the other β -lactams, with the exception of amoxicillin/ clavulanate (3.8%), and 22.8% were resistant to erythromycin (Table 3). Resistance to co-trimoxazole and tetracycline was also high (45.6% and 21.8%, respectively) particularly in those resistant to penicillin (Table 3). Of the other agents

tested, linezolid, teicoplanin and vancomycin were the only ones to which *S. pneumoniae* remained 100% susceptible, irrespective of penicillin or erythromycin resistance (susceptibility breakpoints are shown in Table 3 and Figure 2). Against *S. pneumoniae*, telithromycin had an MIC₉₀ of 0.06 mg/L, with 100% of the isolates being susceptible to this agent at an MIC of 0.5 mg/L.

The overall prevalence of resistance to the fluoroquinolones was low (0.8%), with one isolate (0.4%) in Brazil and three isolates (1.5%) in Mexico being fully resistant to levofloxacin (MIC \geq 8 mg/L) (Table 2). These fluoroquinolone-resistant isolates also had reduced susceptibility to many of the β -lactam and MLS antibacterial agents tested, but retained full susceptibility to clindamycin, linezolid, teicoplanin, vancomycin and the ketolide telithromycin at an MIC of 0.5 mg/L.

Susceptibility of *H. influenzae* and *M. catarrhalis* Isolates

Of the 520 *H. influenzae* isolates collected in Latin America (Table 1), 88 (16.9%) produced β -lactamase, ranging from 11.0% in Brazil, to 19.2% in Argentina, and to 24.6% in Mexico. These isolates were resistant to ampicillin and amoxicillin, although no β -lactamase-negative, ampicillin-resistant *H. influenzae* isolates were detected (Table 5).

β -lactamase-producing *H. influenzae* were also found to be resistant to the following antibacterials: cefaclor (2.3%), cefprozil (4.5%), chloramphenicol (11.4%) and tetracycline (12.5%), although the overall rate of resistance to these agents among *H. influenzae* isolates remained low (<3%, Table 5). In contrast, resistance to co-trimoxazole was high in both β -lactamase-positive and -negative strains; resistance was reported for 34.8% of the *H. influenzae* isolates (β -lactamase-negative, 30.1%; β -lactamase-positive, 58.0%). All other agents retained high activity against *H. influenzae* (Table 5). Importantly, *H. influenzae* remained susceptible to the ketolide telithromycin and the macrolide azithromycin (Figure 3), irrespective of β -lactamase production. The MIC₉₀ and range for telithromycin against *H. influenzae* were 2 and 0.002-4 mg/L, respectively.

Table 1. Number of isolates of respiratory pathogens collected from Latin America during the PROTEKT study, 1999-2000

Countries	No. of isolates				
	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>M. catarrhalis</i>	<i>S. aureus</i>	<i>S. pyogenes</i>
Argentina (n=200)	55	52	40	20	33
Brazil (n=960)	260	273	71	211	145
Mexico (n=646)	203	195	29	120	99
Total (n=1806)	518	520	140	351	277

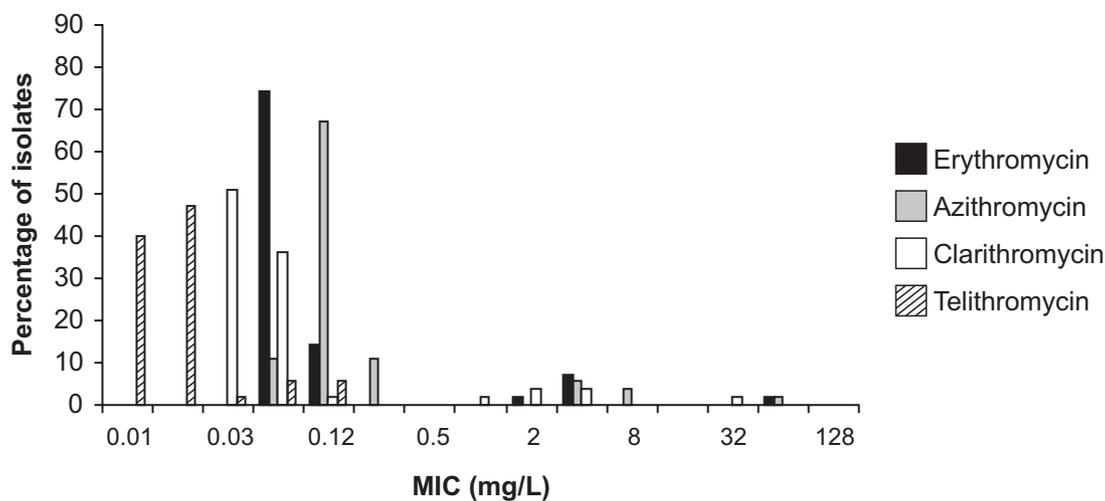
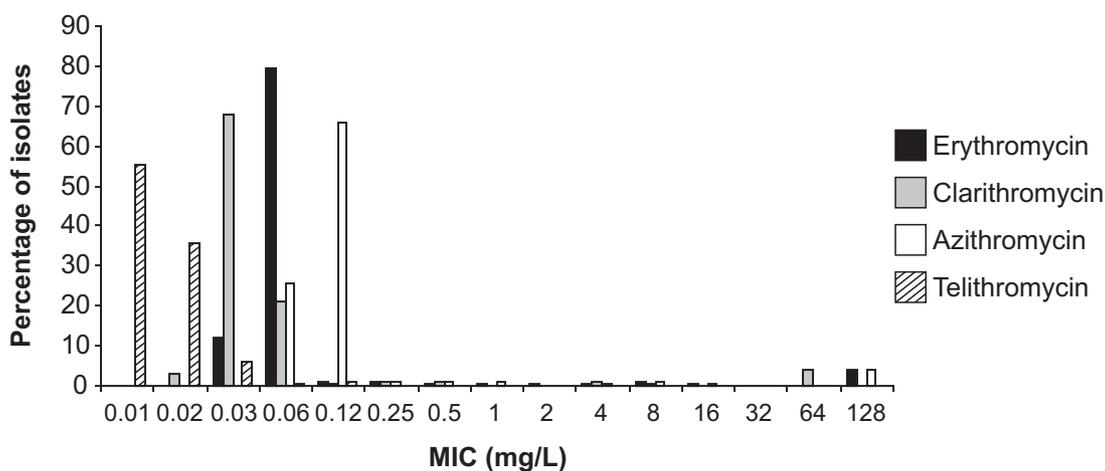
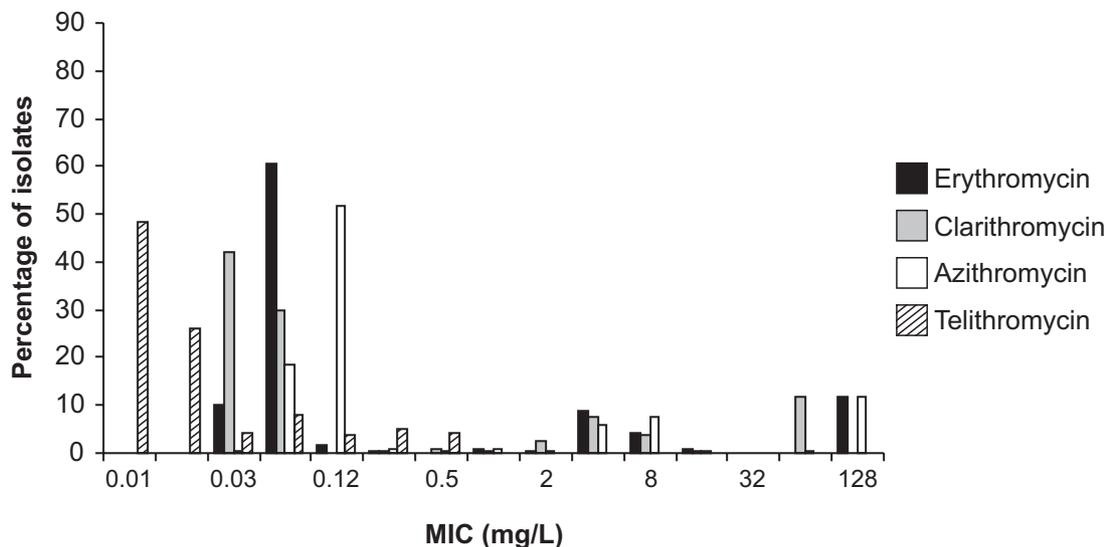
Figure 1a. PROTEKT 1999-2000: MIC distributions for macrolides and telithromycin against *S. pneumoniae* in 1999-2000 from Argentina**Figure 1b.** PROTEKT 1999-2000: MIC distributions for macrolides and telithromycin against *S. pneumoniae* in 1999-2000 from Brazil

Figure 1c. PROTEKT 1999-2000: MIC distributions for macrolides and telithromycin against *S. pneumoniae* in 1999-2000 from Mexico



β -lactamase was produced by almost all of the 140 isolates of *M. catarrhalis* collected in Latin America, including 97.5% of the isolates from Argentina, 98.6% of those from Brazil, and 100% from Mexico (98.6% overall). With the exception of ampicillin and amoxicillin, for which the overall rates of resistance were 82.9% and 87.1%, respectively, almost all of the *M. catarrhalis* isolates collected in Latin America were fully susceptible to the other antibacterials (Table 5). However, a trend towards a decreasing susceptibility to other β -lactams (cefaclor, cefdinir and cefprozil), and also co-trimoxazole, was observed. MIC values for telithromycin against *M. catarrhalis* ranged from 0.008 to 0.25 mg/L (MIC₅₀: 0.06 mg/L, MIC₉₀, 0.12 mg/L).

Susceptibility of *S. pyogenes* Isolates

In total, 277 isolates of *S. pyogenes* were submitted in Latin America and underwent microbiological investigation (Table 1). As expected, *S. pyogenes* remained fully susceptible to penicillin, and hence by NCCLS criteria [10] to other β -lactams.

Twenty-four (8.7%) isolates were found to be resistant to erythromycin and azithromycin and 22 (7.9%) were resistant to clarithromycin, of which 18 tested positive for *mef*(A), 5 for *erm*(TR) and one isolate tested positive for

ermB. The prevalence of macrolide resistance among *S. pyogenes* varied between countries (5.5% in Brazil, 11.1% in Mexico and 12.1% in Argentina). In addition, 18.4% of the isolates were fully resistant to tetracycline (8.1% in Mexico, 21.2% in Argentina and 24.8% in Brazil). Against *S. pyogenes*, telithromycin had an MIC₉₀ of 0.015 mg/L, with 100% of the isolates being susceptible to this agent at an MIC of ≤ 0.5 mg/L).

Susceptibility of *S. aureus* Isolates

Overall, 351 isolates of *S. aureus* were collected from centers in Latin America (Table 1). Methicillin-resistant *S. aureus* (MRSA) isolates from Argentina (15%), Mexico (20%) and Brazil (31.3%) were detected, giving an overall MRSA rate of 26.5% in Latin America. However, all isolates were fully susceptible to vancomycin, linezolid and teicoplanin, irrespective of methicillin susceptibility. Eighteen percent of the *S. aureus* isolates were resistant to cotrimoxazole; this figure increased to 35.5% among MRSA. Methicillin-susceptible strains of *S. aureus* (MSSA) were also highly susceptible to telithromycin (97.7%), with a maximum MIC₉₀ of 0.06 mg/L, although 91 of the 93 MRSA strains (97.9%) were found to be resistant to this agent.

Table 2. PROTEKT 1999-2000: Penicillin, erythromycin and fluoroquinolone susceptibility in Latin American clinical isolates of *S. pneumoniae*

Center	Total no. of isolates	Penicillin susceptibility			Erythromycin susceptibility			Levofloxacin susceptibility		
		SUSC no.(%)	INT no.(%)	RES no.(%)	SUSC no.(%)	INT no.(%)	RES no.(%)	SUSC no.(%)	INT no.(%)	RES no.(%)
Argentina	55	40 (72.7)	6 (10.9)	9 (16.4)	49 (89.1)	0 (0.0)	6 (10.9)	55 (100.0)	0 (0.0)	0 (0.0)
Buenos Aires 50	52	38 (73.1)	5 (9.6)	9 (17.3)	48 (92.3)	0 (0.0)	4 (7.7)	52 (100.0)	0 (0.0)	0 (0.0)
Buenos Aires 51	3	2 (66.7)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	3 (100.0)	0 (0.0)	0 (0.0)
Brazil	260	172 (66.2)	67 (25.8)	21 (8.1)	242 (93.1)	1 (0.4)	17 (6.5)	259 (99.6)	0 (0.0)	1 (0.4)
Florianópolis 41	52	44 (84.6)	6 (11.5)	2 (3.8)	46 (88.5)	1 (1.9)	5 (9.6)	52 (100.0)	0 (0.0)	0 (0.0)
Brasília 45	20	11 (55.0)	3 (15.0)	6 (30.0)	17 (85.0)	0 (0.0)	3 (15.0)	20 (100.0)	0 (0.0)	0 (0.0)
São Paulo 40	58	34 (58.6)	21 (36.2)	3 (5.2)	57 (98.3)	0 (0.0)	1 (1.7)	58 (100.0)	0 (0.0)	0 (0.0)
São Paulo 42	70	36 (51.4)	27 (38.6)	7 (10.0)	64 (91.4)	0 (0.0)	6 (8.6)	69 (98.6)	0 (0.0)	1 (1.4)
São Paulo 44	4	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)
São Paulo 46	56	43 (76.8)	10 (17.9)	3 (5.4)	54 (96.4)	0 (0.0)	2 (3.6)	56 (100.0)	0 (0.0)	0 (0.0)
Mexico	203	88 (43.4)	66 (32.5)	49 (24.1)	147 (72.4)	0 (0.0)	56 (27.6)	200 (98.5)	0 (0.0)	3 (1.5)
México City 31	61	27 (44.3)	22 (36.1)	12 (19.7)	47 (77.1)	0 (0.0)	14 (23.0)	61 (100.0)	0 (0.0)	0 (0.0)
Mexico City 32	17	2 (11.8)	2 (11.8)	13 (76.5)	14 (82.4)	0 (0.0)	3 (17.6)	17 (100.0)	0 (0.0)	0 (0.0)
Monterrey 33	125	59 (47.2)	42 (33.6)	24 (19.2)	86 (68.8)	0 (0.0)	39 (31.2)	122 (97.6)	0 (0.0)	3 (2.4)
Latin America total	518	300 (57.9)	139 (26.8)	79 (15.3)	438 (84.6)	1 (0.2)	79 (15.3)	514 (99.2)	0 (0.0)	4 (0.8)

Penicillin breakpoints: susceptible, MIC \leq 0.06 mg/L; intermediate, MIC 0.12-1 mg/L; resistant, MIC \geq 2 mg/L.

Erythromycin breakpoints: susceptible, MIC \leq 0.25 mg/L; intermediate, MIC 0.5 mg/L; resistant, MIC \geq 1 mg/L.

Levofloxacin breakpoints: susceptible, MIC \leq 2 mg/L; intermediate, MIC 4 mg/L; resistant, MIC \geq 8 mg/L.

Figure 2a. PROTEKT 1999-2000: MIC distributions for telithromycin against *S. pneumoniae* isolated from Latin America in 1999-2000, according to penicillin susceptibility

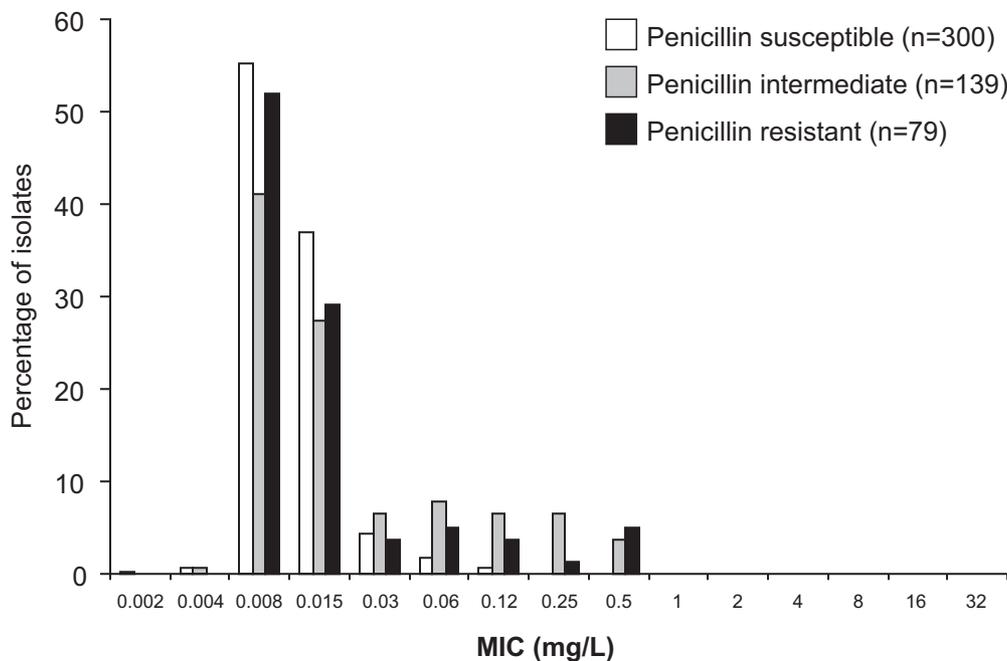


Figure 2b. PROTEKT 1999-2000: MIC distributions for telithromycin against *S. pneumoniae* isolated from Latin America in 1999-2000, according to erythromycin susceptibility

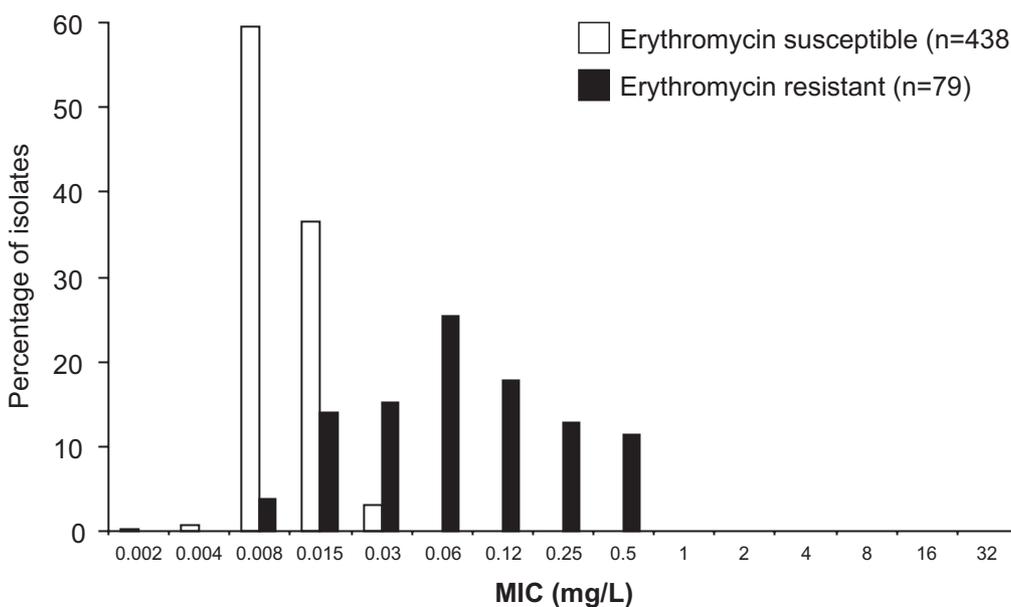


Table 3. PROTEKT 1999-2000: Activity of various antibacterials against clinical isolates of penicillin-susceptible (n=300), -intermediate (n=139) and -resistant (n=79) *S. pneumoniae* in Latin America, 1999-2000

Antibacterial	Susceptibility			MIC parameters	
	SUSC (%)	INT (%)	RES (%)	MIC ₉₀ (mg/L)	MIC range (mg/L)
Penicillin					
All isolates	300 (57.9)	139 (26.8)	79 (15.3)	2	0.008-8
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.06	0.008-0.06
Pen ^I	0 (0.0)	139 (100)	0 (0.0)	1	0.12-1
Pen ^R	0 (0.0)	0 (0.0)	79 (100)	4	2-8
Amoxicillin/clavulanate					
All isolates	511 (98.7)	4 (0.8)	3 (0.6)	2	0.008-8
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.03	0.008-0.06
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	1	0.03-2
Pen ^R	72 (91.1)	4 (5.1)	3 (3.8)	2	1-8
Cefaclor					
All isolates	330 (63.7)	55 (10.6)	133 (25.7)	64	0.5-128
Pen ^S	280 (93.3)	20 (6.7)	0 (0.0)	1	0.5-2
Pen ^I	50 (36.0)	35 (25.2)	54 (38.9)	32	0.5-128
Pen ^R	0 (0.0)	0 (0.0)	79 (100)	>64	32-128
Cefixime [?]					
All isolates	300 (57.9)			32	0.12-128
Pen ^S	300 (100)			1	0.12-8
Pen ^I	0 (0.0)			16	0.25-128
Pen ^R	0 (0.0)			64	16-128
Cefpodoxime					
All isolates	406 (78.4)	19 (3.7)	93 (18.0)	2	0.12-32
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.12	0.12-0.5
Pen ^I	106 (76.3)	16 (11.5)	17 (12.2)	2	0.12-32
Pen ^R	0 (0.0)	3 (3.8)	76 (96.2)	4	1-16
Cefuroxime					
All isolates	399 (77.0)	14 (2.7)	105 (20.3)	4	0.015-16
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.12	0.015-1
Pen ^I	99 (71.2)	14 (10.1)	26 (18.7)	4	0.03-16
Pen ^R	0 (0.0)	0 (0.0)	79 (100)	8	4-16
Azithromycin					
All isolates	439 (84.8)	4 (0.8)	75 (14.5)	8	0.03-128
Pen ^S	285 (95.0)	1 (0.3)	14 (4.7)	0.12	0.06-128
Pen ^I	93 (66.9)	1 (0.7)	45 (32.4)	>64	0.06-128
Pen ^R	61 (77.2)	2 (2.5)	16 (20.3)	8	0.03-128
Clarithromycin					
All isolates	439 (84.8)	4 (0.8)	75 (14.5)	4	0.015-64
Pen ^S	285 (95.0)	1 (0.3)	14 (4.7)	0.06	0.015-64
Pen ^I	93 (66.9)	1 (0.7)	45 (32.4)	>32	0.015-64
Pen ^R	61 (77.2)	2 (2.5)	16 (20.3)	8	0.03-64
Erythromycin					
All isolates	438 (84.6)	1 (0.2)	79 (15.3)	4	0.03-128
Pen ^S	285 (95.0)	0 (0.0)	15 (5.0)	0.06	0.03-128
Pen ^I	92 (66.2)	1 (0.7)	46 (33.1)	>64	0.03-128
Pen ^R	61 (77.2)	0 (0.0)	18 (22.8)	8	0.03-128

Antibacterial	Susceptibility			MIC parameters	
	SUSC (%)	INT (%)	RES (%)	MIC ₉₀ (mg/L)	MIC range (mg/L)
Telithromycin					
All isolates	N/A [#]	N/A [#]	N/A [#]	0.06	0.002-0.5
Pen ^S				0.015	0.002-0.12
Pen ^I				0.25	0.004-0.5
Pen ^R				0.12	0.008-0.5
Levofloxacin					
All isolates	514 (99.2)	0 (0.0)	4 (0.8)	1	0.5-16
Pen ^S	298 (99.3)	0 (0.0)	2 (0.7)	1	0.5-16
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	1	0.5-2
Pen ^R	77 (97.5)	0 (0.0)	2 (2.5)	1	0.5-16
Moxifloxacin					
All isolates	514 (99.2)	2 (0.4)	2 (0.4)	0.25	0.06-4
Pen ^S	298 (99.3)	1 (0.3)	1 (0.3)	0.25	0.06-4
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	0.25	0.06-0.25
Pen ^R	77 (97.5)	1 (1.3)	1 (1.3)	0.25	0.06-4
Clindamycin					
All isolates	482 (93.1)	0 (0.0)	36 (7.0)	0.12	0.03-8
Pen ^S	289 (96.3)	0 (0.0)	11 (3.7)	0.12	0.03-8
Pen ^I	120 (86.3)	0 (0.0)	19 (13.7)	>4	0.03-8
Pen ^R	73 (92.4)	0 (0.0)	6 (7.6)	0.12	0.03-8
Co-trimoxazole					
All isolates	189 (36.5)	93 (18.0)	236 (45.6)	16	0.12-32
Pen ^S	148 (49.3)	72 (24.0)	80 (26.7)	8	0.12-32
Pen ^I	35 (25.2)	18 (13.0)	86 (61.9)	>16	0.12-32
Pen ^R	6 (7.6)	3 (3.8)	70 (88.6)	>16	0.25-32
Tetracycline					
All isolates	389 (75.1)	16 (3.1)	113 (21.8)	>16	0.12-32
Pen ^S	243 (81.0)	10 (3.3)	47 (15.7)	16	0.12-32
Pen ^I	99 (71.2)	3 (2.2)	37 (26.6)	>16	0.12-32
Pen ^R	47 (59.5)	3 (3.8)	29 (36.7)	>16	0.12-32
Linezolid					
All isolates	518 (100)	0 (0.0)	0 (0.0)	2	0.12-2
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	2	0.5-2
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	2	0.5-2
Pen ^R	79 (100)	0 (0.0)	0 (0.0)	2	0.12-2
Teicoplanin					
All isolates	518 (100)	0 (0.0)	0 (0.0)	0.12	0.03-0.25
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.12	0.03-0.25
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	0.12	0.03-0.25
Pen ^R	79 (100)	0 (0.0)	0 (0.0)	0.12	0.03-0.12
Vancomycin					
All isolates	518 (100)	0 (0.0)	0 (0.0)	0.5	0.12-1
Pen ^S	300 (100)	0 (0.0)	0 (0.0)	0.5	0.25-0.5
Pen ^I	139 (100)	0 (0.0)	0 (0.0)	0.5	0.12-1
Pen ^R	79 (100)	0 (0.0)	0 (0.0)	0.5	0.25-0.5

NCCLS susceptibility breakpoints [9].

Pen^S = penicillin G susceptible (MIC ≤0.06 mg/L); Pen^I = penicillin G intermediate (MIC 0.12–1 mg/L); Pen^R = penicillin G resistant (MIC ≥2 mg/L).

[#] Breakpoint for telithromycin not available.

³Cefixime: Susceptibility based on penicillin susceptibility. There are no breakpoints for intermediate or resistant.

Figure 3a. PROTEKT 1999-2000: MIC distributions for azithromycin, clarithromycin, erythromycin and telithromycin against *H. influenzae* in 1999-2000 from Argentina

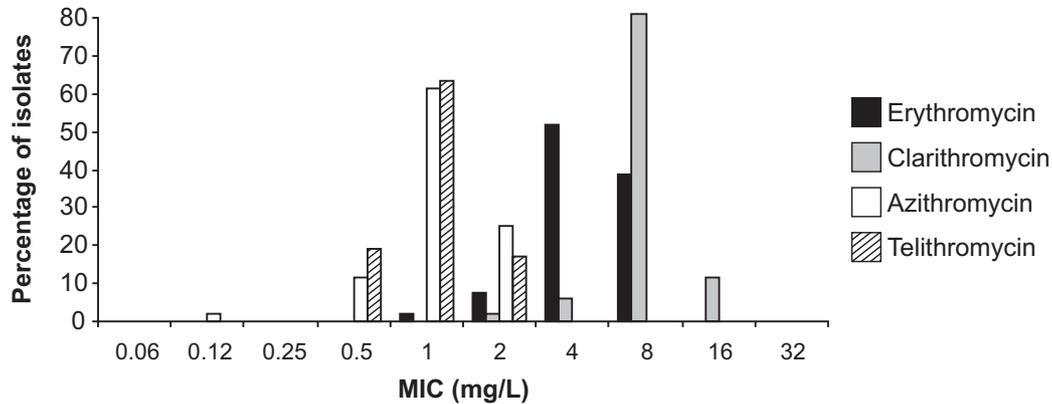


Figure 3b. PROTEKT 1999-2000: MIC distributions for azithromycin, clarithromycin, erythromycin and telithromycin against *H. influenzae* in 1999-2000 from Brazil

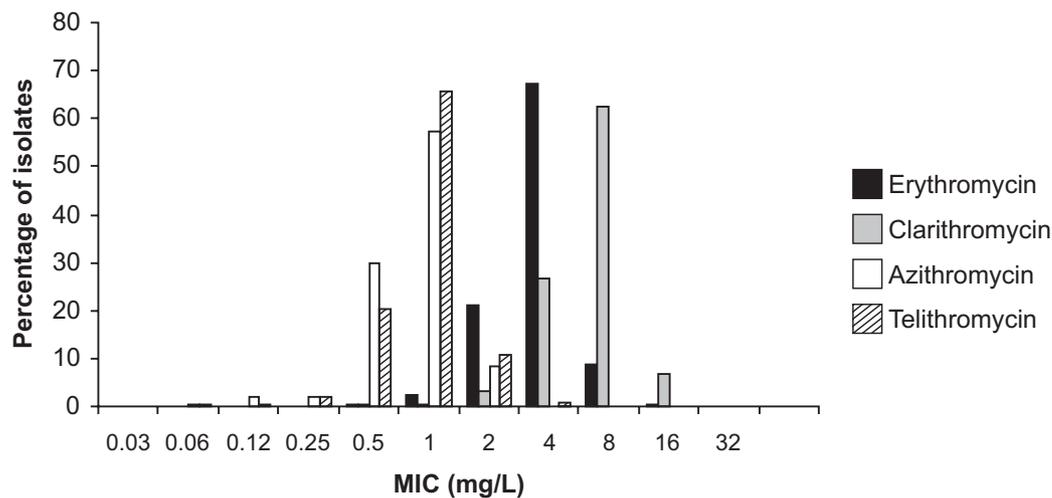


Figure 3c. PROTEKT 1999-2000: MIC distributions for azithromycin, clarithromycin, erythromycin and telithromycin against *H. influenzae* in 1999-2000 from Mexico

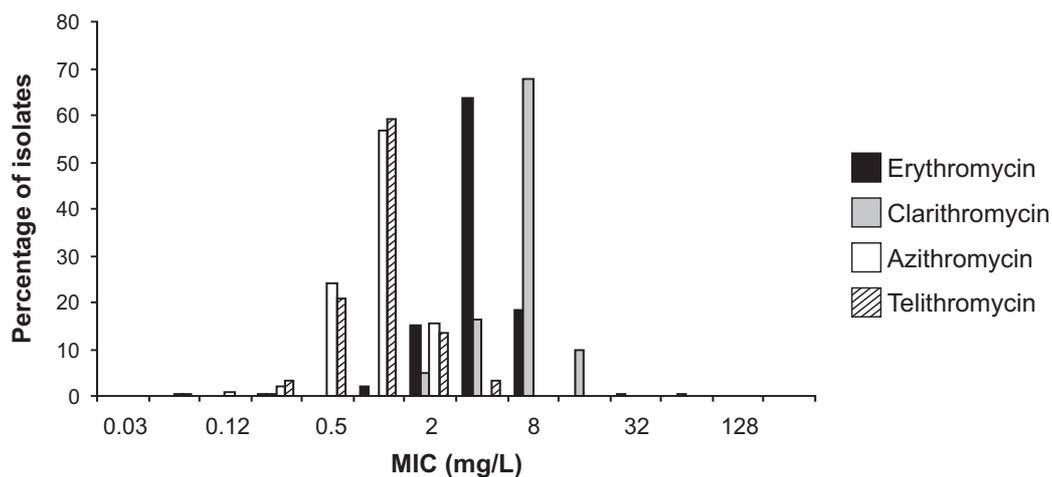


Table 4. PROTEKT 1999-2000: Distribution of macrolide resistance mechanisms among erythromycin-resistant (MIC \geq 1 mg/L) *S. pneumoniae* isolated from Latin America in 1999-2000

Center	Total no.of isolates tested	Erm(B)	Mef(A)	Negative for mechanisms	Total
Argentina	55				
Buenos Aires 50	52	1	3		4
Buenos Aires 51	3		2		2
Brazil	260				
Florianópolis 41	52	4			4
Brasilia 45	20	1	2		3
São Paulo 40	58	1			1
São Paulo 42	70	2	4		6
São Paulo 43	0				0
São Paulo 44	4				0
São Paulo 46	56	2			2
Mexico	203				
Mexico City 31	61	6	8		14
Mexico City 32	17	3			3
Monterrey 33	125	16	21	1	38
Latin America total	518	36	40	1	77

Discussion

PROTEKT data collected during the period 1999-2000 indicate that the prevalence of penicillin resistance (MIC \geq 2 mg/L) amongst pneumococci in Latin America is high, with 15.3% of the isolates being fully resistant and 26.8% having intermediate resistance to this antibacterial agent. This level of nonsusceptibility appears to be higher than that reported by Odland et al. [1], who analysed over 2,000 pneumococcal isolates as part of the SENTRY programme, of which 264 were from Latin American countries. Among these, 9.9% were fully resistant to penicillin and 45.8% were intermediate. Of the 1,100 *S. pneumoniae* isolates from seven Latin American and Caribbean countries surveyed by the LASER study group in 1997 [2], 23.5% were nonsusceptible to penicillin (6.9% resistant/16.6% intermediate). As in the PROTEKT study, a high multiple-resistance pattern towards co-trimoxazole (44.6%) was also observed. Similar resistance rates were observed in the Global SMART (GSMART)

surveillance study, during which 244 pneumococcal isolates from five Latin American countries were analysed in 1999-2000 [12]. Of these, 28% were nonsusceptible to penicillin and 5% were fully resistant. Rates of nonsusceptibility to penicillin varied between the Latin American countries participating in the PROTEKT study (Mexico, 56.6%; Brazil, 33.9%; Argentina, 27.3%). Corresponding rates reported in the LASER study were: Mexico (40.8%), Brazil (13%) and Argentina (19.1%) [2]. Intermediate and full resistance patterns in the PROTEKT study were as follows: Argentina (10.9% intermediate, 16.4% resistant), Brazil (25.8% intermediate; 8.1% resistant) and Mexico (32.5% intermediate; 24.1% resistant). In comparison, in the worldwide Alexander Project conducted between 1996 and 1997, a high rate of intermediate resistance (17.9%) and a low fully resistant rate of 2.1% were observed among 95 isolates of *S. pneumoniae* from Brazil; corresponding figures for Mexico were 31.4% and 15.7%, respectively [3]. In the SIREVA-vigía programme conducted in Latin

Table 5. PROTEKT 1999-2000: Activity of selected antibacterials against clinical isolates of *H. influenzae* and *M. catarrhalis* from Latin America (1999-2000) according to β -lactamase status

Antibacterial	<i>H. influenzae</i> (n=520)				<i>M. catarrhalis</i> (n=140)			
	INT (%)	RES (%)	MIC90 (mg/L)	MIC range (mg/L)	INT* (%)	RES* (%)	MIC90 (mg/L)	MIC range (mg/L)
Ampicillin								
All isolates	0 (0.0)	88 (16.9)	>16	0.12-32	11 (7.9)	116 (82.9)	16	0.12-32
β -lactamase –	0 (0.0)	0 (0.0)	0.5	0.12-1	0 (0.0)	0 (0.0)	- ^a	0.12
β -lactamase +	0 (0.0)	88 (100)	>16	4-32	116 (84.1)	116 (84.1)	16	0.12-32
Amoxicillin								
All isolates	7 (1.3)	90 (17.3)	>16	0.12-32	7 (5.0)	122 (87.1)	>16	0.12-32
β -lactamase –	6 (1.4)	3 (0.7)	0.5	0.12-4	0 (0.0)	0 (0.0)	- ^a	0.12
β -lactamase +	1 (1.1)	87 (98.9)	>16	2-32	7 (5.1)	122 (88.4)	>16	0.12-32
Amoxicillin/clavulanate								
All isolates	0 (0.0)	0 (0.0)	1	0.12-4	0 (0.0)	0 (0.0)	0.25	0.12-0.5
β -lactamase –	0 (0.0)	0 (0.0)	0.5	0.12-4	0 (0.0)	0 (0.0)	- ^a	0.12
β -lactamase +	0 (0.0)	0 (0.0)	1	0.25-4	0 (0.0)	0 (0.0)	0.25	0.12-0.5
Cefaclor								
All isolates	22 (4.2)	2 (0.4)	8	0.5-64	5 (3.6)	0 (0.0)	8	0.5-16
β -lactamase –	6 (1.4)	0 (0.0)	4	0.5-16	0 (0.0)	0 (0.0)	- ^a	0.5-1
β -lactamase +	16 (18.2)	2 (2.3)	16	1-64	5 (3.6)	0 (0.0)	8	0.5-16
Cefdinir								
All isolates	0 (0.0)	0 (0.0)	0.5	0.06-1	0 (0.0)	0 (0.0)	0.25	0.06-1
β -lactamase –	0 (0.0)	0 (0.0)	0.5	0.06-1	0 (0.0)	0 (0.0)	- ^a	0.06
β -lactamase +	0 (0.0)	0 (0.0)	0.5	0.06-1	5 (3.6)	0 (0.0)	0.25	0.06-1
Cefixime								
All isolates	0 (0.0)	0 (0.0)	0.06	0.008-0.5	0 (0.0)	0 (0.0)	0.5	0.03-0.5
β -lactamase –	0 (0.0)	0 (0.0)	0.06	0.008-0.5	0 (0.0)	0 (0.0)	- ^a	0.03-0.06
β -lactamase +	0 (0.0)	0 (0.0)	0.06	0.015-0.5	0 (0.0)	0 (0.0)	0.5	0.03-0.5
Cefpodoxime								
All isolates	0 (0.0)	0 (0.0)	0.12	0.015-0.5	0 (0.0)	0 (0.0)	1	0.06-2
β -lactamase –	0 (0.0)	0 (0.0)	0.12	0.015-0.5	0 (0.0)	0 (0.0)	- ^a	0.06-0.12
β -lactamase +	0 (0.0)	0 (0.0)	0.12	0.015-0.5	0 (0.0)	0 (0.0)	1	0.12-2
Cefprozil								
All isolates	12 (2.3)	4 (0.8)	4	0.5-128	6 (4.3)	1 (0.7)	8	0.5-32
β -lactamase –	3 (0.7)	0 (0.0)	4	0.5-16	0 (0.0)	0 (0.0)	- ^a	0.5
β -lactamase +	9 (10.2)	4 (4.5)	16	0.5-128	6 (4.3)	1 (0.7)	8	0.5-32
Cefuroxime								
All isolates	0 (0.0)	0 (0.0)	1	0.12-4	1 (0.7)	0 (0.0)	2	0.12-8
β -lactamase –	0 (0.0)	0 (0.0)	1	0.12-4	0 (0.0)	0 (0.0)	- ^a	0.12-0.5
β -lactamase +	0 (0.0)	0 (0.0)	2	0.25-4	1 (0.7)	0 (0.0)	2	0.5-8

Antibacterial	<i>H. influenzae</i> (n=520)				<i>M. catarrhalis</i> (n=140)			
	INT (%)	RES (%)	MIC90 (mg/L)	MIC range (mg/L)	INT* (%)	RES* (%)	MIC90 (mg/L)	MIC range (mg/L)
Azithromycin								
All isolates	0 (0.0)	0 (0.0)	2	0.06-2	0 (0.0)	0 (0.0)	0.06	0.06
b-lactamase –	0 (0.0)	0 (0.0)	2	0.06-2	0 (0.0)	0 (0.0)	- ^a	0.06
b-lactamase +	0 (0.0)	0 (0.0)	2	0.06-2	0 (0.0)	0 (0.0)	0.06	0.06
Clarithromycin								
All isolates	43 (8.3)	1 (0.2)	8	0.25-64	0 (0.0)	0 (0.0)	0.25	0.25
b-lactamase –	28 (6.5)	1 (0.2)	8	1-64	0 (0.0)	0 (0.0)	- ^a	0.25
b-lactamase +	15 (17.0)	0 (0.0)	16	0.24-16	0 (0.0)	0 (0.0)	0.25	0.25
Telithromycin								
All isolates	N/A [#]	N/A [#]	2	0.002-4	N/A [#]	N/A [#]	0.12	0.008-0.25
b-lactamase –			2	0.002-4			- ^a	0.008-0.06
b-lactamase +			2	0.12-4			0.12	0.03-0.25
Ciprofloxacin								
All isolates	0 (0.0)	0 (0.0)	0.015	0.008-1	N/A	N/A	0.03	0.015-0.25
b-lactamase –	0 (0.0)	0 (0.0)	0.015	0.008-1			- ^a	0.03
b-lactamase +	0 (0.0)	0 (0.0)	0.015	0.008-0.03			0.03	0.015-0.25
Levofloxacin								
All isolates	0 (0.0)	0 (0.0)	0.015	0.008-0.5	0 (0.0)	0 (0.0)	0.03	0.015-0.25
b-lactamase –	0 (0.0)	0 (0.0)	0.015	0.008-0.5	0 (0.0)	0 (0.0)	- ^a	0.03-0.06
b-lactamase +	0 (0.0)	0 (0.0)	0.015	0.008-0.03	0 (0.0)	0 (0.0)	0.03	0.015-0.25
Moxifloxacin								
All isolates	0 (0.0)	0 (0.0)	0.03	0.008-0.25	0 (0.0)	0 (0.0)	0.06	0.015-0.06
b-lactamase –	0 (0.0)	0 (0.0)	0.03	0.008-0.25	0 (0.0)	0 (0.0)	- ^a	0.06
b-lactamase +	0 (0.0)	0 (0.0)	0.03	0.008-0.03	0 (0.0)	0 (0.0)	0.06	0.015-0.06
Tetracycline								
All isolates	5 (1.0)	14 (2.7)	1	0.12-16	0 (0.0)	0 (0.0)	0.5	0.25-0.5
b-lactamase –	3 (0.7)	3 (0.7)	0.5	0.12-8	0 (0.0)	0 (0.0)	- ^a	0.25
b-lactamase +	2 (2.3)	11 (12.5)	8	0.25-16	0 (0.0)	0 (0.0)	0.5	0.25-0.5
Co-trimoxazole								
All isolates	23 (4.4)	181 (34.8)	8	0.03-32	6 (4.3)	2 (1.4)	0.5	0.06-4
b-lactamase –	21 (4.9)	130 (30.1)	8	0.03-32	0 (0.0)	0 (0.0)	- ^a	0.12
b-lactamase +	2 (2.3)	51 (58.0)	16	0.03-16	6 (4.3)	2 (1.5)	0.5	0.06-4
Chloramphenicol								
All isolates	1 (0.2)	13 (2.5)	0.5	0.12-16	0 (0.0)	0 (0.0)	0.5	0.25-1
b-lactamase –	0 (0.0)	3 (0.7)	0.5	0.12-8	0 (0.0)	0 (0.0)	- ^a	0.5
b-lactamase +	1 (1.1)	10 (11.4)	8	0.12-16	0 (0.0)	0 (0.0)	0.5	0.25-1

* Based on NCCLS breakpoints for *H. influenzae* [9].

Breakpoint not available.

^a Not applicable, only 2 isolates.

Table 6. PROTEKT 1999-2000: Distribution of macrolide resistance mechanisms among erythromycin-resistant (MIC \geq 1 mg/L) *S. pyogenes* isolated from Latin America in 1999-2000

Center	Total no. of isolates tested	<i>erm(B)</i>	<i>ermTR</i>	<i>mefA</i>	<i>erm(B)+mefA</i>	Total
Argentina	33					
Buenos Aires Center 50	23			3		3
Buenos Aires Center 51	10			1		1
Brazil	145					
Florianópolis Center 41	24	1		2		3
Brasília Center 45	19			2		2
São Paulo Center 40	27					0
São Paulo Center 42	37		2	2		4
São Paulo Center 43	6					0
São Paulo Center 44	21					0
São Paulo Center 46	11					0
Mexico	99					
Mexico City Center 31	58		3	5		8
Mexico City Center 32	10			2		2
Monterrey Center 33	29			1	0	1
Latin America total	277	1	5	18	0	24

America, 2% of *S. pneumoniae* isolates from Brazil were fully resistant to penicillin and 21.3% were intermediate; corresponding figures for Mexico were 20.8% and 28.6%, respectively [13]. Finally, in the SENTRY programme, Sader et al. [4] analysed 344 community-acquired RTI pathogens isolated from Brazilian hospitals in 1997-1998. Among these, 2.3% of the 176 pneumococcal isolates had full resistance to penicillin and 26.2% were intermediate. Considering all of these results together, the current PROTEKT findings suggest that nonsusceptibility to penicillin among pneumococci is increasing in Latin American countries. Furthermore, penicillin resistance appears to be shifting from intermediate towards full resistance in this region.

In addition to the increasing prevalence of penicillin resistance, we found considerable variation in resistance rates between centers within Brazil and Mexico. In Brazil, penicillin resistance ranged from <5% in three centers to 30.0% in Brasilia. Differences were even more marked in Mexico, where rates ranged from

19.2% in Monterrey to 76.5% in Mexico City. These differences may be explained because of the type of hospital involved, paediatric versus adult centers and primary or secondary care centers versus referral centers. Large inter-center variation in susceptibility has also been reported in other surveillance studies conducted in Latin America, including the LASER study [2], the Alexander Project [3], and the SENTRY programme [4]. In addition to inter-center variation, we detected a difference in susceptibility results attributable to methodology: two pneumococcal strains from center 41 (Florianópolis – Brazil) were reported as intermediate susceptibility to penicillin by E-test methodology when evaluated in the original center; however, when tested by the NCCLS broth microdilution method in the coordinating centre, both strains were classified as fully resistant towards penicillin. These findings re-affirm how important it is for physicians to be aware of local resistance patterns in order to ensure judicious use of antibacterials for

patients with community-acquired RTIs that may be attributable to *S. pneumoniae*.

Another important finding of our study is the high prevalence of macrolide (erythromycin) resistance amongst pneumococci in Latin America. Overall, 15.3% of the isolates were resistant to erythromycin, including 10.9% in Argentina, 6.5% in Brazil and 27.6% in Mexico. These values are comparable to the overall level of approximately 12% to 13% observed during the LASER study [2], the Alexander Project [3], and the SENTRY programme [4] and suggest that macrolide resistance is relatively stable in Latin America. However, as with penicillin resistance, marked intra-city/state variability was observed. Overall, macrolide resistance tended to be lower than penicillin resistance in most of the centers participating in the study, with the exception of the following: Florianópolis (Brazil), Monterrey and Mexico City Center 31.

We found the prevalence of macrolide resistance among *S. pneumoniae* to be high among isolates that were also resistant to penicillin (22.8%). However, despite this cross-resistance between the macrolides and other MLS antibiotics, the ketolide telithromycin remained highly active against pneumococci, irrespective of concomitant penicillin and/or erythromycin resistance. Indeed, telithromycin was the most potent of the oral agents tested against *S. pneumoniae* ($MIC_{90}=0.06$ mg/L). While fluoroquinolone resistance was absent in the Latin American centers participating in the SENTRY programme [4], the current PROTEKT findings indicate that the prevalence of *S. pneumoniae* resistance to fluoroquinolones may be increasing (0.8%) and multiple-resistance between the fluoroquinolones, β -lactams and a number of MLS antibacterial agents is apparent. This situation is of concern from the public health perspective and should be monitored carefully, particularly with the introduction of newer broad-spectrum fluoroquinolones for community-acquired RTIs.

Considering the other RTI pathogens monitored during the study, 16.9% of *H. influenzae* isolates in Latin America were $\hat{\alpha}$ -lactamase positive, ranging from 11.0% in Brazil to 24.6% in Mexico. With the exception of ampicillin, amoxicillin and co-trimoxazole, resistance against the antibacterials tested in Latin America was not observed, although a high multiple-resistance to co-trimoxazole

(34.8%) was detected. These rates of β -lactamase production and resistance patterns appear to be in agreement with those reported elsewhere [4,14,3]. In the SENTRY programme conducted in the same region during 1997-1998 [4], 12.7% of 361 *H. influenzae* isolates were found to be β -lactamase producers. Among the participating countries, rates of resistance were highest in Mexico (26%), followed by Argentina (17.1%), Chile (12.5%), and Brazil (9.3%). As in the PROTEKT study, a high rate of resistance to co-trimoxazole (40%) was also observed. Also during 1997-1998, 9.4% of the 223 Brazilian-isolates strains analysed by MRL were resistant to ampicillin and 2.2% were intermediate [14]. Resistance to co-trimoxazole (47.1%) was high in this study. Finally, in the Alexander Project, β -lactamase production was detected in 10.3% of Brazilian isolates [3]. Infrequent resistance to chloramphenicol (11.9%), along with a high frequency of resistance to co-trimoxazole (29.1%), was observed in this study.

These findings suggest that susceptibility to the macrolides, the ketolide telithromycin and the fluoroquinolones is universally high in Latin America at present. However, the relatively high level of intermediate susceptibility to clarithromycin observed in the PROTEKT study needs to be monitored carefully as it may indicate the emergence of resistance to this agent among *H. influenzae* in Latin America.

β -lactamase production was highly prevalent amongst *M. catarrhalis* in Latin America, affecting 97.5% of the isolates from Argentina, 98.6% from Brazil, and 100% of isolates from Mexico (98.6% overall). In comparison, data from the Alexander Project showed a rate of 90.4% in 1996 [3]; the corresponding rate of production in the SENTRY study in Latin America during 1997-1998 was 91.8% [4]. With the exception of ampicillin and amoxicillin (82.9% and 87.1% resistant isolates, respectively), *M. catarrhalis* was susceptible to the other antibacterial agents tested during the PROTEKT study. However, the apparent trend towards increasing β -lactamase production and the decreasing susceptibility of other $\hat{\alpha}$ -lactams and also co-trimoxazole among *M. catarrhalis* in Latin America should be monitored carefully in the future.

As anticipated, all Latin American *S. pyogenes* isolates remained susceptible to penicillin and most of the other β -lactams, with the exception of cefixime. In patients allergic to penicillins and other β -lactams, macrolides are useful agents for treating infections with this pathogen. However, recent reports have found that, in some countries, up to 30% of *S. pyogenes* isolates are resistant to macrolides [16,17]. In PROTEKT, the prevalence of macrolide resistance among *S. pyogenes* was found to be 8.3%. Telithromycin was active against 100% of Latin American *S. pyogenes* isolates, suggesting that it is a useful alternative to macrolides in the treatment of *S. pyogenes* infections in penicillin-allergic patients.

The PROTEKT findings also showed that the prevalence of methicillin resistance among isolates of *S. aureus* (MRSA, 26.5%) is similar to that reported by the Latin American centers participating in the SENTRY surveillance programme between 1997 and 1999 (34.9%) [18].

In summary, the current findings from the Latin American centers participating in the PROTEKT study confirm that antibacterial resistance among common community-acquired RTI pathogens is an emerging problem in Latin America. The results suggest that the already high levels of pneumococcal resistance to the β -lactam and macrolides reported from other large surveillance studies conducted in this region are now being exceeded. In particular, resistance to the β -lactams appears to be increasing and fluoroquinolone resistance in *S. pneumoniae* has been detected, albeit at a low level. These findings highlight the need for increased vigilance in monitoring and tracking changes in antibacterial susceptibility in order to guide empirical therapy. With this in mind, findings from the ongoing PROTEKT study are rapidly available and frequently updated on the World Wide Web (www.protekt.org), thereby providing up-to-date susceptibility data for physicians to facilitate local prescribing decisions. Such steps, along with the development of new agents that do not induce or create conditions for selection for resistance, for example the novel ketolide telithromycin, are vitally important in order to safeguard future antibacterial efficacy.

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