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A survey of antibiotic resistance in *Streptococcus pneumoniae* and *Haemophilus influenzae* in Turkey, 2004–2005

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***Objectives*: To determine the prevalence of antimicrobial resistance among *Streptococcus pneumoniae* and *Haemophilus influenzae* isolated in Turkey as part of Survey Of Antibiotic Resistance, a surveillance programme in the Africa and Middle East region examining the antimicrobial susceptibility of key bacterial pathogens involved in community-acquired respiratory tract infections (CARTIs).**

***Methods*: Susceptibility was evaluated against a range of antimicrobial agents using disc diffusion and Etest methods.**

***Results*: Six centres in five cities collected 301 *S. pneumoniae* and 379 *H. influenzae* isolates between October 2004 and November 2005. Among *S. pneumoniae*, the prevalence of isolates with intermediate susceptibility (MICs 0.12–1 mg/L) and resistance to penicillin (MICs ≥2 mg/L) was 24.6% and 7.6%, respectively; there was a wide variation between cities (2.4% to 36.9% intermediate and 0% to 23.8% resistant phenotypes). Macrolide-azalide resistance rates exceeded those of penicillin resistance in all cities. Overall, 5.0% of isolates were co-resistant to penicillin and erythromycin and 10.0% were multidrug-resistant (joint resistance to erythromycin, co-trimoxazole and tetracycline). Agents tested to which over 90% of countrywide *S. pneumoniae* isolates remained susceptible were amoxicillin/clavulanate (98.7%), chloramphenicol (94.7%) and cefprozil (90.6%). Overall, the percentage of *H. influenzae* isolates producing β-lactamase was 5.5%, differing widely across the country with the highest prevalence of β-lactamase production detected in Trabzon (14.0%) and no β-lactamase-positive isolates found in Izmir. *H. influenzae* had the highest per cent susceptibility to amoxicillin/clavulanate (99.5%) and ofloxacin (99.2%) while >20% were resistant to co-trimoxazole.**

***Conclusions*: Prevalence of penicillin and macrolide–azalide resistance among *S. pneumoniae* appears to be on the increase in Turkey while overall β-lactamase production in *H. influenzae* remains relatively low. To adequately monitor the spread of drug-resistant phenotypes among these two important CARTI pathogens, ongoing collection of resistance surveillance data is**

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required—where possible locally as resistance patterns can vary substantially between cities and institutions.

Keywords: pneumococci, surveillance, community-acquired respiratory tract infections

Introduction

Streptococcus pneumoniae and *Haemophilus influenzae* are the key bacterial pathogens implicated in community-acquired respiratory tract infections (CARTIs), which occur frequently and account for significant morbidity and mortality.[1–4] Because of the time required to establish the significance, identity and susceptibility of bacterial isolates from patients with CARTIs, antimicrobial therapeutic choices are usually empirical. The increasing prevalence of resistant organisms, however, complicates this choice and poses a serious threat to current and future treatment of these infections.[5–8] Surveillance studies provide an important tool for determining local and regional susceptibility patterns and guiding empirical antimicrobial therapy.[9]

S. pneumoniae exhibits resistance to penicillins and several other classes of antimicrobials including macrolides, co-trimoxazole and also fluoroquinolones, although levels of resistance to the latter remain low in most countries.[10–13] Among *H. influenzae*, increasing aminopenicillin resistance, usually occurring as the result of β-lactamase production, and co-trimoxazole resistance further underline the need for effective surveillance.[8,14,15] During the first Survey Of Antibiotic Resistance (SOAR) in *S. pneumoniae* and *H. influenzae* in 2002–2003, penicillin non-susceptibility among *S. pneumoniae* was documented in 25.3% of Turkish isolates (24.0% intermediate and 1.3% resistant) and, overall, 14.7% were non-susceptible to macrolides/azalides.[16] Penicillin non-susceptibility rates of up to 50% have been reported in Turkey in recent years, with prevalence of penicillin-resistant *S. pneumoniae* (PRSP) ranging from 0.7% to 19.4%.[17–21] In these studies, the prevalence of macrolide resistance in *S. pneumoniae* varied from 2.1% to 21.1%. In the SOAR study from 2002 to 2003, 4.5% of *H. influenzae* isolates from Turkey were β-lactamase positive.[16] Similar rates of β-lactamase production in clinical isolates of *H. influenzae* (3.8–7.0%) have been reported by other surveillance programmes.[17,21–24]

In October 2004, the second phase of SOAR was initiated in the Africa and Middle East region to provide contemporary antimicrobial susceptibility data for the key respiratory pathogens *S. pneumoniae* and *H. influenzae*. Here we report findings from the programme in Turkey during 2004–2005.

Materials and methods

Collaborating centres

The following centres took part in the study: Ankara, Hacettepe University; Antalya, Akdeniz University; Istanbul, Istanbul University and Marmara University; Izmir, Ege University; Trabzon, Karadeniz Technical University.

Bacterial isolates and antimicrobial susceptibility testing

Isolates of *S. pneumoniae* and *H. influenzae* were obtained from fresh clinical material taken primarily from adult and paediatric patients with clinical indications of community-acquired respiratory tract infections using routine clinical collection methods. Duplicate isolates from the same patient were not accepted.

Organisms were identified using conventional methods (optochin susceptibility for *S. pneumoniae* and X and V factor requirement for *H. influenzae*). Organisms were stored frozen at −70°C until tested. β-Lactamase production of *H. influenzae* isolates was determined by a chromogenic cephalosporin (nitrocefin) disc method.[25] β-Lactamase-negative, ampicillin-resistant isolates were defined as those organisms having a negative β-lactamase result and an ampicillin MIC of ≥4 mg/L.[26]

MICs were determined using the Etest susceptibility testing method according to the manufacturer's instructions (AB Biodisk, Solna, Sweden). Disc susceptibility testing was performed according to CLSI (formerly NCCLS) guidelines.[27] Briefly, frozen isolates were subcultured twice on blood-supplemented Mueller–Hinton agar (*S. pneumoniae*) or Haemophilus Test Medium (*H. influenzae*) before susceptibility testing was performed. For susceptibility testing, a 0.5 McFarland standard dilution of each isolate was prepared by direct colony suspension and inoculated onto appropriate agar plates to produce a confluent lawn of growth. Etests and antibiotic discs were applied and plates incubated for 20–24 h (16–18 h for *H. influenzae* agar disc diffusion) at 35°C in a 5% CO_2 atmosphere. For azithromycin and clarithromycin Etests, *S. pneumoniae* isolates were incubated in ambient air due to the adverse effect of CO_2 on the activity of macrolide/azalide antibiotics. Etest MICs and inhibition zone diameters were read in accordance with AB Biodisk's instructions and CLSI guidelines for disc susceptibility testing, respectively.[27]

The antimicrobials tested using Etest included: penicillin (*S. pneumoniae* only), ampicillin (*H. influenzae* only), amoxicillin/clavulanate (2/1), cefaclor, cefprozil, clarithromycin, azithromycin and ofloxacin. In addition, susceptibility to erythromycin and clindamycin (*S. pneumoniae* only), tetracycline, co-trimoxazole (trimethoprim/sulfamethoxazole, 1/19) and chloramphenicol was determined by agar disc diffusion.

Quality control and data analysis

Quality control strains recommended by CLSI were used on each day of testing, and results of isolate testing were accepted if results of the control strains were within published limits.

Any Etest MIC results that were between doubling dilutions were rounded up to the next doubling dilution MIC for data analysis. MICs and zone diameters were interpreted qualitatively using CLSI interpretive standards; MICs were also analysed using pharmacokinetic/pharmacodynamic (PK/PD) breakpoints helping to predict the clinical and bacteriologic efficacy of antimicrobial dosing regimens (Table 1).[8,26,28] To interpret azithromycin and clarithromycin MICs for *H. influenzae*, revised breakpoints were used to account for incubation in a CO_2 atmosphere (AB Biodisk Etest package insert, Table 1 'Summary of performance, interpretive criteria and quality control ranges'). The respective PK/PD breakpoints were adjusted accordingly, i.e. raised by one doubling dilution, for interpretation of *H. influenzae* susceptibility. Statistical significance was determined by χ^2 or Fisher's exact test analysis and P values of ≤0.05 were regarded as significant.

Table 1. Breakpoints (mg/L) used to determine susceptible (S), intermediate (I) and resistant (R) categories based on PK/PD and CLSI interpretive breakpoints[8,26,28]

	PK/PD breakpoints[a]		CLSI breakpoints[b]					
			S. pneumoniae			*H. influenzae*		
Antimicrobial	S	R	S	I	R	S	I	R
Penicillin	NA	NA	≤0.06	0.12–1	≥2	NA	NA	NA
Ampicillin	NA	NA	NA	NA	NA	≤1	2	≥4
Amoxicillin/clavulanate	≤2	≥4	≤2	4	≥8	≤4	—	≥8
Cefaclor	≤0.5	≥1	≤1	2	≥4	≤8	16	≥32
Cefprozil	≤1	≥2	≤2	4	≥8	≤8	16	≥32
Azithromycin	≤0.12	≥0.25	≤0.5	1	≥2	≤8	—	—
Clarithromycin	≤0.25	≥0.5	≤0.25	0.5	≥1	≤16	32	≥64
Ofloxacin	≤2	≥4	≤2	4	≥8	≤2	—	—

NA, not available.
[a]PK/PD breakpoints for azithromycin of S ≤ 0.25 mg/L, R ≥ 0.5 mg/L and for clarithromycin of S ≤ 0.5 mg/L, R ≥ 1 mg/L were used to interpret susceptibility of *H. influenzae* as CLSI breakpoints were also raised by one doubling dilution for incubation in CO_2 (see footnote b).
[b]Azithromycin and clarithromycin breakpoints for *H. influenzae* are those provided by AB Biodisk for incubation in CO_2 (Etest package insert Table 1). Standard CLSI breakpoints for *H. influenzae* are S ≤ 4 mg/ for azithromycin and S ≤ 8 mg/L, I = 16 mg/L and R ≥ 32 mg/L for clarithromycin.

Results

A total of 301 isolates of *S. pneumoniae* and 379 isolates of *H. influenzae* were collected largely from patients with indications of community-acquired respiratory tract infections from October 2004 to November 2005. Isolates were from sputum (66.3%), bronchoalveolar lavage (10.1%), throat (5.9%), tracheal aspirate (4.6%), blood (2.4%), CSF (2.1%) and other sources. The patient age was known in 95.0% of cases; of these, 38.2% were paediatric patients (<18 years). Overall gender distribution was 60.4% male and 39.6% female with the proportion of females being higher in the paediatric than in the adult group (47.8% versus 35.1%).

S. pneumoniae

Antimicrobial susceptibility and $MIC_{50/90}$s of all 301 isolates of *S. pneumoniae* are shown in Table 2. Overall, 32.2% of isolates were non-susceptible to penicillin, 24.6% were intermediate (PISP) and 7.6% were resistant to penicillin (PRSP). Based on CLSI breakpoints, the most active antimicrobial tested against *S. pneumoniae* was amoxicillin/clavulanate with 98.7% susceptibility. Of the cephalosporins tested, cefprozil was more active than cefaclor (90.6% versus 78.7% susceptibility). Substantial resistance was observed with azithromycin and clarithromycin (17.2% and 17.3%, respectively), and susceptibility to azithromycin was as low as 40.2% when PK/PD breakpoints were applied. Overall susceptibility to azithromycin was lower than to clarithromycin due to 14 isolates (4.7%; 13 from Istanbul and one from Ankara) that tested azithromycin-intermediate by Etest although disc susceptibility results indicated that these isolates were azithromycin-susceptible (data not shown). Within the country and in each city, resistance levels to macrolide/azalide antibiotics exceeded the prevalence of penicillin resistance (penicillin MIC >1 mg/L). Cross-resistance between clindamycin and erythromycin can be used as an approximation of prevalence of the *erm*(B)-mediated methylation mechanism (MLS_B-phenotype) of *S. pneumoniae* macrolide resistance versus the *mef*(A)-mediated efflux mechanism (M-phenotype). Based on disc diffusion data, cross-resistance between erythromycin and clindamycin was 72.3% (34/47). Resistance to co-trimoxazole was very high (43.2%) and only 72.1% of *S. pneumoniae* were susceptible to ofloxacin, with the vast majority of non-susceptible isolates being ofloxacin-intermediate. The eight ofloxacin-resistant isolates, four of which surprisingly were from paediatric patients (<18 years), were not tested against newer fluoroquinolones or examined for potential quinolone resistance-determining region mutations. All ofloxacin-resistant isolates were susceptible to amoxicillin/clavulanate.

In vitro activity was also analysed based on penicillin susceptibility category of the isolates (Table 3). Using CLSI breakpoints, generally higher levels of resistance to cephalosporins, macrolides and other antibiotics were detected in penicillin non-susceptible compared with penicillin-susceptible *S. pneumoniae*. Of PRSP, 87.0% remained susceptible to amoxicillin/clavulanate. Only 34.8% of PRSP and 59.5% of PISP were susceptible to erythromycin, and overall 5.0% of isolates were co-resistant to penicillin and erythromycin. Joint resistance to erythromycin, co-trimoxazole and tetracycline was 10.0%; one-third of these isolates were also resistant to penicillin. For isolates where patient age information was available, a higher prevalence of PISP/PRSP were detected in paediatric patients (<18 years) than in adults (29.4%/10.8% versus 21.0%/5.9%; $P = 0.05$) while there was no difference in macrolide–azalide resistance rates between these two patient groups. There were no notable differences in penicillin and macrolide non-susceptibility associated with the gender of the patient.

Table 4 shows susceptibility of *S. pneumoniae* to all antimicrobials tested for each centre. Penicillin resistance was highest in Ankara (13.8%) and Antalya (23.8%) although only 21 isolates were tested in Antalya. The proportion of penicillin-intermediate and penicillin-resistant strains in these two cities (50.8% and 47.6%, respectively) was significantly higher than in

Table 2. Susceptibility of all *S. pneumoniae* and *H. influenzae* isolates from Turkey to 13 antimicrobials based on CLSI[26] and PK/PD[8,28] interpretive breakpoints and MIC_{50}s and MIC_{90}s

	S. pneumoniae						*H. influenzae*					
		CLSI		PK/PD	MIC_{50}	MIC_{90}		CLSI		PK/PD	MIC_{50}	MIC_{90}
Antimicrobial	*n*	S (%)	R (%)	S (%)	(mg/L)	(mg/L)	*n*	S (%)	R (%)	S (%)	(mg/L)	(mg/L)
Penicillin	301	67.8	7.6	—	0.032	1	0	—	—	—	—	—
Ampicillin	0	—	—	—	—	—	379	90.8	4.7	—	0.25	1
Amoxicillin/ clavulanate	301	98.7	0.3	98.7	0.032	1	379	99.5	0.5	97.6	0.5	1
Cefaclor	301	78.7	19.3	70.4	0.5	16	378	96.3	2.1	8.5	1	4
Cefprozil	299	90.6	3.3	84.9	0.064	2	378	96.8	1.6	56.1	1	4
Erythromycin	301	83.1	15.6	—	—	—	—	—	—	—	—	—
Azithromycin	296	78.0	17.2	40.2	0.25	256	370	98.9	—	4.1	2	4
Clarithromycin	301	82.7	17.3	82.7	0.064	32	378	95.2	1.6	0.8	8	16
Clindamycin	301	87.7	11.3	—	—	—	—	—	—	—	—	—
Ofloxacin	301	72.1	2.7	72.1	2	4	379	99.2	—	99.2	0.032	0.064
Co-trimoxazole	301	53.2	43.2	—	—	—	375	76.5	22.9	—	—	—
Tetracycline	301	81.4	16.9	—	—	—	378	78.0	8.5	—	—	—
Chloramphenicol	300	94.7	5.3	—	—	—	378	94.4	2.1	—	—	—

S, susceptible; R, resistant.
Data for penicillin, ampicillin, amoxicillin/clavulanate, cefaclor, cefprozil, azithromycin, clarithromycin and ofloxacin are based on Etest. Erythromycin, clindamycin, co-trimoxazole, tetracycline and chloramphenicol were tested using disc diffusion.

Trabzon where intermediate resistance was 2.4% and no PRSP were isolated ($P < 0.001$ and $P < 0.01$, respectively). Susceptibility to amoxicillin/clavulanate was 100% in Antalya, Istanbul and Trabzon. Cephalosporin resistance prevalence was mirrored by the levels of penicillin non-susceptibility, and cefaclor was less active than cefprozil in all centres. Macrolide susceptibility was lowest in Ankara with only 72.8%, 73.8% and 73.8% of isolates susceptible to azithromycin, clarithromycin and erythromycin, respectively. Macrolide–azalide susceptibility was significantly higher in Trabzon at 97.6% compared with the other four cities. The unusually low level of azithromycin susceptibility of isolates collected in Istanbul is due to 13 isolates tested azithromycin-intermediate by Etest (see above). Except for ofloxacin and co-trimoxazole, susceptibility levels were high (>90%) in Trabzon.

H. influenzae

Antimicrobial susceptibility data for all 379 isolates of *H. influenzae* and $MIC_{50/90}$s are shown in Table 2. Of these, 5.5% produced β-lactamase and 4.7% were resistant to ampicillin (>2 mg/L). Of the β-lactamase producers, five isolates were found to be intermediate-resistant to ampicillin; two isolates were tested β-lactamase-negative and ampicillin-resistant (BLNAR) (0.5%). *In vitro* activity was high for most antimicrobials tested, with susceptibility of >99% detected for amoxicillin/clavulanate and ofloxacin; only susceptibility to tetracycline and co-trimoxazole was <90%. Although CLSI breakpoints for cefaclor, azithromycin and clarithromycin show 96.3%, 98.9% and 95.2% of *H. influenzae* susceptible to these agents, respectively, based on PK/PD breakpoints, the susceptibility was <10%. Prevalence of β-lactamase production and antimicrobial susceptibility of *H. influenzae* isolates from Ankara, Antalya, Istanbul, Izmir and Trabzon are shown in Table 5. The highest prevalence of β-lactamase-positive isolates was detected in

Table 3. Susceptibility (%) of penicillin-susceptible (PSSP), -intermediate (PISP) and -resistant (PRSP) *S. pneumoniae* to 12 antimicrobials using CLSI interpretive breakpoints

	All		PSSP		PISP		PRSP	
Antimicrobial	*n*	S (%)	*n*	S (%)	*n*	S (%)	*n*	S (%)
Penicillin	301	67.8	204	100	74	0	23	0
Amoxicillin/ clavulanate	301	98.7	204	100	74	98.6	23	87.0
Cefaclor	301	78.7	204	100	74	44.6	23	0
Cefprozil	299	90.6	203	100	74	86.5	22	18.2
Erythromycin	301	83.1	204	97.1	74	59.5	23	34.8
Azithromycin	296	78.0	199	92.0	74	55.4	23	30.4
Clarithromycin	301	82.7	204	96.6	74	59.5	23	34.8
Clindamycin	301	87.7	204	98.0	74	73.0	23	43.5
Ofloxacin	301	72.1	204	78.4	74	62.2	23	47.8
Co-trimoxazole	301	53.2	204	62.7	74	36.5	23	21.7
Tetracycline	301	81.4	204	93.1	74	59.5	23	47.8
Chloramphenicol	300	94.7	204	98.5	74	91.9	22	68.2

S, susceptible.
Data for penicillin, amoxicillin/clavulanate, cefaclor, cefprozil, azithromycin, clarithromycin and ofloxacin are based on Etest. Erythromycin, clindamycin, co-trimoxazole, tetracycline and chloramphenicol were tested using disc diffusion.

Table 4. Susceptibility (%) of *S. pneumoniae* to 12 antimicrobials [susceptible (*S*), intermediate (*I*) and resistant (*R*) shown for penicillin] by city using CLSI interpretive breakpoints

City	*n*	Penicillin			Amoxicillin/clavulanate	Cefaclor	Cefprozil	Erythromycin	Azithromycin	Clarithromycin	Clindamycin	Ofloxacin	Co-trimoxazole	Tetracycline	Chloramphenicol
		S	I	R											
Ankara	65	49.2	36.9	13.8	98.5	66.2	83.1	73.8	72.3	73.8	81.5	53.8	55.4	75.4	92.3
Antalya	21	52.4	23.8	23.8	100	66.7	85.7	76.2	76.2	76.2	85.7	81.0	61.9	76.2	95.2
Istanbul	102	69.6	25.5	4.9	100	83.3	94.0	85.3	71.1	84.3	94.1	78.4	61.8	79.4	94.1
Izmir	71	69.0	25.4	5.6	95.8	76.1	88.7	81.7	81.7	81.7	81.7	76.1	56.3	83.1	97.2
Trabzon	42	97.6	2.4	0.0	100	97.6	100	97.6	97.6	97.6	92.9	73.8	19.0	95.2	95.2
Total	301	67.8	24.6	7.6	98.7	78.7	90.6	83.1	78.0	82.7	87.7	72.1	53.2	81.4	94.7

Data for penicillin, amoxicillin/clavulanate, cefaclor, cefprozil, azithromycin, clarithromycin and ofloxacin are based on Etest. Erythromycin, clindamycin, co-trimoxazole, tetracycline and chloramphenicol were tested using disc diffusion.

Trabzon (14.0%) and Istanbul (6.2%). In Istanbul, we saw a notable difference between the two participating centres (10.3% at Istanbul University versus 2.4% at Marmara University). No β-lactamase-positive *H. influenzae* were isolated in Izmir, which was significantly lower than in Trabzon ($P < 0.001$). Based on CLSI breakpoints, susceptibility was >90% for most antibiotics although considerable non-susceptibility was seen against co-trimoxazole (up to 33.3%) and tetracycline (up to 52.0%) in some cities.

Discussion

The increasing prevalence of antimicrobial resistance among the major pathogens responsible for CARTI is a serious global problem that complicates the management of these infections. SOAR was established to provide information on local resistance patterns among the two most common pulmonary pathogens, *S. pneumoniae* and *H. influenzae*, in African and Middle Eastern countries for some of which resistance surveillance data have been poorly documented. The Turkish SOAR programme provides contemporary surveillance data from six centres in five cities for the years 2004 and 2005. Penicillin non-susceptibility is common among *S. pneumoniae*; overall, 32.2% of strains were penicillin non-susceptible. However, there were marked differences in prevalence of penicillin non-susceptible isolates varying from 2.4% to ~50% highlighting the need to obtain and monitor local susceptibility data. Similar differences in penicillin susceptibility between centres and cities were detected in a study conducted in 1996–1997: the prevalence of penicillin non-susceptible *S. pneumoniae* was higher in Istanbul and Ankara than in Trabzon.[17] Overall penicillin resistance (>1 mg/L) nearly doubled from 3.9% in 1996–1997 to 7.6% in 2004–2005. However, lower as well as higher penicillin resistance rates have been reported in other recent surveillance studies conducted in Turkey.[29] As found in other programmes, higher penicillin non-susceptibility levels were detected in *S. pneumoniae* isolated from paediatric patients compared with those from adult patients.[30] Macrolide–azalide resistance also appears to be on the increase with only 2.1% of *S. pneumoniae* resistant to azithromycin in 1996–1997 compared with 17.2% in this study.[17] Based on co-resistance to erythromycin and clindamycin, *S. pneumoniae* macrolide resistance was predominantly due to the *erm*(B)-mediated methylation mechanism as also shown by a recent analysis of erythromycin-resistant *S. pneumoniae* collected during 1994–2002 in Ankara.[31] The overall prevalence of resistance to cefaclor, co-trimoxazole and tetracycline was high (19.3%, 43.2% and 16.9%, respectively) but the majority of isolates remained susceptible to amoxicillin/clavulanate (98.7%). The problem of multidrug resistance is an increasing worry although multidrug-resistant *S. pneumoniae* may be still relatively uncommon in Turkey compared with some other regions and countries.[12] In this study, combined resistance to erythromycin, co-trimoxazole and tetracycline was 10.0% while 3.3% of isolates were also resistant to penicillin.

Ofloxacin resistance, a marker for fluoroquinolone resistance, was at a low prevalence (2.7%) although intermediate resistance was common. The first treatment failure due to fluoroquinolone-resistant *S. pneumoniae* was reported in Turkey in 2003.[32] Among invasive *S. pneumoniae* isolated during

Table 5. β-Lactamase production (%) and susceptibility (%) of *H. influenzae* to 10 antimicrobials by city using CLSI interpretive breakpoints

City	*n*	β-lactamase-positive	Ampicillin	Amoxicillin/clavulanate	Cefaclor	Cefprozil	Azithromycin	Clarithromycin	Ofloxacin	Co-trimoxazole	Tetracycline	Chloramphenicol
Ankara	76	3.9	89.5	100	89.5	92.1	98.7	94.7	100	78.7	82.9	98.7
Antalya	22	4.5	95.5	95.5	95.5	95.5	88.9	86.4	100	86.4	86.4	95.5
Istanbul	162	6.2	91.4	99.4	98.1	98.1	99.4	93.8	98.8	77.4	78.9	93.2
Izmir	69	0.0	94.2	100	97.1	97.1	100	100	98.6	66.7	89.9	98.6
Trabzon	50	14.0	84.0	100	100	100	100	98.0	100	80.0	48.0	86.0
Total	379	5.5	90.8	99.5	96.0	96.8	98.9	95.2	99.2	76.5	78.0	94.4

Data for ampicillin, amoxicillin/clavulanate, cefaclor, cefprozil, azithromycin, clarithromycin and ofloxacin are based on Etest. Co-trimoxazole, tetracycline and chloramphenicol were tested using disc diffusion.

2000–2001, only 3.5% of isolates were ofloxacin non-susceptible, all of the intermediate-resistant type.[18]

β-Lactamase production in *H. influenzae* remains below 10% and seems to have been relatively stable over recent years as our data were comparable with prevalence rates found by other surveillance programmes. However, β-lactamase production and corresponding ampicillin resistance rates varied considerably between cities, with the high rates detected in Trabzon. BLNAR strains of *H. influenzae* were rare (0.5%) which is consistent with other surveillance studies.[17,23,24] Using CLSI breakpoints, susceptibility was >90% for all tested antibiotics except co-trimoxazole and tetracycline. However, <10% of *H. influenzae* were susceptible to cefaclor, azithromycin and clarithromycin based on PK/PD breakpoints.

Overall, the data presented here are consistent with other surveillance projects conducted during recent years in Turkey. Ongoing collection of resistance surveillance data is however required to provide further data especially for those cities and areas where only low numbers of isolates were collected such as Antalya and to adequately monitor the spread of drug-resistant phenotypes among CARTI pathogens, including penicillin, macrolide and multidrug-resistant *S. pneumoniae* and β-lactamase-positive *H. influenzae*. This study also highlights the need to collect and utilize local susceptibility data wherever possible as resistance patterns can vary substantially between cities and even institutions within the same city.

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Transparency declarations

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