

## ORIGINAL ARTICLE

## National surveillance programme on susceptibility patterns of respiratory pathogens in South Africa: moxifloxacin compared with eight other antimicrobial agents

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**Aims:** The susceptibility patterns of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes* isolated from specimens submitted to 12 private laboratories in South Africa were determined.

**Methods:** Minimum inhibitory concentration (MIC) determinations were performed on the isolates in the microbiology laboratory at Tygerberg Hospital according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS).

**Results:** According to the NCCLS breakpoints, 24% of 729 *S pneumoniae* isolates were sensitive, 30% intermediate, and 46% resistant to penicillin. Rates of macrolide resistance were high, with 61% of the pneumococci being resistant to clarithromycin and azithromycin. Co-trimoxazole resistance was also high, with 28% of pneumococcal strains being sensitive, 21% intermediate, and 51% resistant.  $\beta$  Lactamase was produced by 7% of 736 *H influenzae* isolates and 91% of 256 *M catarrhalis* isolates. The quinolones, moxifloxacin and levofloxacin, were universally active against all isolates tested, which included *S pneumoniae*, *H influenzae*, *M catarrhalis*, *K pneumoniae*, and *S pyogenes*.

**Conclusions:** *Haemophilus influenzae* and *S pneumoniae* were the most commonly isolated organisms. Resistance to penicillin was one of the highest reported in the world (76%) in *S pneumoniae*, as was macrolide resistance in pneumococci, although surprisingly, only 14% of *S pyogenes* were resistant. The quinolones, moxifloxacin and levofloxacin, were active against all organisms tested, including the penicillin and macrolide resistant strains and moxifloxacin was more active than levofloxacin against pneumococci.

Resistance to conventional antimicrobial agents is rising worldwide, both in organisms that cause community acquired infections, and those that cause nosocomial infections. Because of the emergence of resistance to frequently prescribed antibiotics, it is necessary to have alternative agents available. When selecting an antimicrobial agent for empirical treatment of a respiratory tract infection, it is important to know the susceptibility patterns of the bacteria that frequently cause these infections in the particular geographical area concerned, because large variations occur.

Since 1976, there have been increasing reports of penicillin resistant pneumococci from many countries. The main foci of penicillin resistant pneumococci are currently South Africa, Spain, Eastern Europe, and the Asia Pacific region.<sup>1</sup> The problem is exacerbated by the tendency of penicillin resistant clones to spread easily from continent to continent. Recently (within the past decade), there has also been a rapid emergence of macrolide resistance among clinical pneumococcal isolates, which in some parts of the world has exceeded resistance to  $\beta$  lactams.<sup>1</sup>

Therapeutic options for infections caused by multiply resistant pneumococci are problematical, and there is a need for new agents for oral administration. Clinical resistance to fluoroquinolones is rare in respiratory pathogens. However, the inclusion of the fluoroquinolones into recent guidelines, such as those of the Infectious Diseases Society of America, the American Thoracic Society, and the joint Canadian Societies' guidelines reflects the need for alternative therapeutic agents.

"Since 1976, there have been increasing reports of penicillin resistant pneumococci from many countries"

No surveillance data from South Africa on the susceptibility of respiratory tract pathogens (non-sterile sites) to fluoroquinolone are available in the medical literature. Here, we present the results of a national multicentre surveillance study conducted during 2000 to 2001. The susceptibilities of common respiratory tract pathogens to the new methoxyfluoroquinolone moxifloxacin were compared with eight other antimicrobials. Strains of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae* isolated from specimens submitted to 12 private laboratories in South Africa were sent to the microbiology laboratory at Tygerberg Hospital for susceptibility testing.

## MATERIALS AND METHODS

Twelve private clinical laboratories representing six of the nine provinces of South Africa participated in this multicentre study. Table 1 shows the location of participating laboratories and the total number of viable isolates collected. Specimens included in our study were obtained from patients of all ages, with both community and hospital acquired infections.

**Abbreviations:** CAMHB, cation adjusted Mueller-Hinton broth; HTM, haemophilus test medium; MIC, minimum inhibitory concentration; NCCLS, National Committee for Clinical Laboratory Standards

**Table 1** Distribution of participating laboratories and number of isolates collected

Province	Location	Laboratory	Number of isolates
Gauteng	Johannesburg	BARC	165
		Tripath	307
	Pretoria	BARC	60
		Tripath	240
		Niehaus and Botha	1539
Western Cape	Cape Town	Pathcare	296
Eastern Cape	George	Pathcare	30
	East London	Pathcare	51
	Port Elizabeth	Pathcare	7
KwaZulu Natal	Durban	BARC	43
Mpumalanga	Nelspruit	Tripath	14
Orange Free State	Bloemfontein	Tripath	67

Sputum samples were only cultured if they satisfied Bartlett's criteria. Previous antibiotic treatment was not known.

Non-replicate isolates of *S pneumoniae* (729), *S pyogenes* (66), *H influenzae* (736), *M catarrhalis* (256), and *K pneumoniae* (87) were cultured from the following specimen types: broncho-alveolar lavage (26), bronchial brush (one), sputum (1233), pleural fluid (six), sinus tap (183), middle ear fluid (497), and pharyngeal swabs (151).

Isolates were subcultured on to Dorset egg transport medium, and dispatched by courier to the central laboratory—the microbiology laboratory at Tygerberg Hospital. Isolate identification and purity were confirmed using routine laboratory methods. Strains were stored at  $-70^{\circ}\text{C}$  in glycerol nutrient broth supplemented with 5% blood for streptococci and *H influenzae* until susceptibility testing was performed.

### Susceptibility testing

Minimum inhibitory concentrations (MICs) of moxifloxacin, levofloxacin, penicillin, amoxicillin, amoxicillin/clavulanate, clarithromycin, azithromycin, cefuroxime, and co-trimoxazole were determined by the broth microdilution method according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS).<sup>2</sup> Co-trimoxazole was

**Table 2** Summary of minimum inhibitory concentration (MIC) data of antimicrobials tested against respiratory tract pathogens

Organism	Antimicrobial agent	MICs (mg/l)			Per cent sensitive	Per cent intermediate	Per cent resistant
		MIC <sub>50</sub>	MIC <sub>90</sub>	MIC range			
<i>Streptococcus pneumoniae</i> (729)	Moxifloxacin	0.12	0.25	$\leq 0.002$ to 1	100	–	–
	Levofloxacin	1	1	0.03 to 2	100	–	–
	Penicillin	1	4	$\leq 0.008$ to $>8$	24	30	46
	Amoxicillin	1	4	$\leq 0.03$ to $>32$	86	7	7
	Amox/clav	1/0.5	4/2	$\leq 0.015/0.008$ to $>16/8$	87	8	5
	Cefuroxime	4	8	$<0.03$ to $>32$	41	6	53
	Azithromycin	8	$>32$	$<0.03$ to $>32$	38	1	61
	Clarithromycin	4	$>32$	$\leq 0.015$ to $>32$	38	1	61
	Cotrimoxazole	4/76	4/76	0.12/2.37 to 4/76	28	21	51
	<i>Streptococcus pyogenes</i> (66)	Moxifloxacin	0.12	0.25	0.06 to 0.5	100	–
Levofloxacin		0.5	1	0.25 to 2	100	–	–
Penicillin		$\leq 0.008$	$\leq 0.008$	$\leq 0.008$	100	–	–
Amoxicillin		$\leq 0.03$	$\leq 0.03$	$\leq 0.03$	100	–	–
Amox/clav		$\leq 0.015/0.008$	$\leq 0.015/0.008$	$\leq 0.015/0.008$ to 0.03/0.015	100	–	–
Cefuroxime		0.03	0.03	$\leq 0.03$ to 0.25	100	–	–
Azithromycin		0.12	4	$\leq 0.03$ to 8	86	3	11
Clarithromycin		0.03	4	$\leq 0.015$ to 8	86	2	12
Cotrimoxazole		0.12/2.37	0.5/9.5	$\leq 0.12/2.37$ to 1/19	100	–	–
<i>Haemophilus influenzae</i> (736)	Moxifloxacin	0.03	0.03	0.008 to 0.5	100	–	–
	Levofloxacin	0.015	0.03	$\leq 0.004$ to 2	100	–	–
	Amoxicillin	0.5	4	0.12 to $>32$	93	–	7
	Amox/clav	0.5/0.25	2/1	$\leq 0.015/0.008$ –4/2	100	–	–
	Cefuroxime	1	4	$\leq 0.03$ to 16	95	4	1
	Azithromycin	1	2	$\leq 0.03$ to $>32$	99	–	1
	Clarithromycin	8	16	0.03 to $>16$	81	19	–
	Cotrimoxazole	0.12/2.37	4/76	$\leq 0.12/2.37$ to $>4/76$	64	10	26
<i>Klebsiella pneumoniae</i> (87)	Moxifloxacin	0.12	0.25	0.06 to 1	100	–	0
	Levofloxacin	0.06	0.12	0.03 to 1	100	–	0
	Amoxicillin	32	$>32$	2 to $>32$	1	–	99
	Amox/clav	2/1	16/8	1/0.5 to $>16/8$	86	–	14
	Cefuroxime	4	$>32$	1 to $>32$	73	–	27
	Cotrimoxazole	0.12/2.37	$>4/76$	$\leq 0.12/2.37$ to $>4/76$	88.5	–	11
	<i>Moraxella catarrhalis</i> (256)	Moxifloxacin	0.06	0.06	$\leq 0.002$ to 0.25	–	–
Levofloxacin		0.03	0.06	$\leq 0.004$ to 1	–	–	–
Penicillin		8	$>8$	$\leq 0.008$ to $>8$	–	–	–
Amoxicillin		4	8	$\leq 0.03$ to $>32$	–	–	–
Amox/clav		0.12/0.06	0.25/0.1	$\leq 0.015/0.008$ to 2/1	–	–	–
Cefuroxime		2	2	0.25 to 8	–	–	–
Azithromycin		0.03	0.03	$\leq 0.03$ to 2	–	–	–
Clarithromycin		0.12	0.03	$\leq 0.015$ to 16	–	–	–
Cotrimoxazole		0.12/2.37	4/76	$\leq 0.12/2.37$ to 4/76	–	–	–

Amox/clav, amoxicillin/clavulanate.

tested as a combination of trimethoprim and sulfamethoxazole at a ratio of 1.25 : 23.75. Microtitre trays containing the required concentrations of the antimicrobials were prepared by TREK Diagnostic Systems Limited, UK and stored at room temperature until used. Haemophilus test medium (HTM), and cation supplemented Mueller-Hinton broth containing 2–5% (vol/vol) lysed horse blood was used for susceptibility testing of *H influenzae* and streptococci, respectively. Cation adjusted Mueller-Hinton broth (CAMHB) was used for non-fastidious organisms. HTM and CAMHB were prepared by TREK Diagnostic Systems.

The appropriate ATCC control strains were included in each batch. The ATCC strains used were: *Escherichia coli* 25922, *E coli* 35218, *S pneumoniae* 49619, and *H influenzae* 49247. MICs were interpreted using breakpoints published by the NCCLS.<sup>2</sup>

Isolates of *H influenzae* and *M catarrhalis* were examined for  $\beta$  lactamase activity. Any strains in which amoxicillin/clavulanate produced a fourfold or more decrease in amoxicillin MICs were considered to produce  $\beta$  lactamase.

### Data analysis

MIC data were analysed centrally. MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC range values were determined. The percentage of isolates with “intermediate”, “resistant”, and “susceptible” susceptibility was calculated according to breakpoints defined by the NCCLS.<sup>2</sup>

### RESULTS

Of the total number of isolates cultured (n = 1874), *H influenzae* (n = 736) was the most commonly isolated respiratory pathogen, closely followed by *S pneumoniae* (n = 729). Table 2 presents the MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC range values, together with per cent susceptibility values. Co-trimoxazole was tested as a combination of trimethoprim/sulfamethoxazole at a ratio of 1 : 19.

No percentage susceptibility values are presented for *M catarrhalis* because no NCCLS breakpoints are recommended (table 2).

The 729 *S pneumoniae* isolates (38%) were predominantly isolated from sputum. Penicillin resistance was seen in 46% of isolates, 30% of strains showed intermediate susceptibility, and only 24% were susceptible to penicillin. Cefuroxime susceptibility was 41%, whereas amoxicillin and amoxicillin/clavulanate susceptibilities were higher after the introduction of the revised NCCLS breakpoints (2002). The in vitro activity of amoxicillin and amoxicillin/clavulanate were similar, with 86% and 87% susceptible, respectively. Macrolide resistance was high, with only 38% of pneumococci tested susceptible to both clarithromycin and azithromycin. Although the MIC<sub>50</sub> for clarithromycin and azithromycin was 4 and 8 mg/litre, respectively, high level resistance (MIC  $\geq$  32 mg/litre) to both agents was seen in 47% of the isolates tested. All strains were fully susceptible to both fluoroquinolones tested. Moxifloxacin (MIC<sub>50</sub>, 0.12 mg/litre) was more active than levofloxacin (MIC<sub>50</sub>, 1 mg/litre).

Other streptococci, represented by *S pyogenes* were not commonly isolated. In contrast to *S pneumoniae*, susceptibility was greatly maintained in this species, with all strains tested being susceptible to penicillin, amoxicillin, amoxicillin/clavulanate, cefuroxime, moxifloxacin, and levofloxacin. Resistance to macrolides was less evident, with 86% of strains susceptible to both clarithromycin and azithromycin.

Of the 736 strains of *H influenzae* tested, 7% produced  $\beta$  lactamase. Resistance to co-trimoxazole was evident. The MIC<sub>50</sub> of azithromycin was 1 mg/litre, whereas that of clarithromycin was 8 mg/litre. Of the 256 *M catarrhalis* isolates tested, 91% produced  $\beta$  lactamase. Most strains were highly susceptible to all antimicrobials tested.

The only antimicrobial agents active against all the *K pneumoniae* isolates were moxifloxacin and levofloxacin.

### DISCUSSION

Clinicians prescribe antibiotics more frequently for community acquired respiratory tract infections than any other type of infection. Worldwide, approximately 80% of total antibiotic usage occurs in the community rather than in hospitals, of which in turn about 80% is for the treatment of respiratory tract infections.<sup>3</sup> With increased rates of resistance, appropriate and informed antimicrobial use becomes crucial for successful treatment. Many cases of community acquired respiratory tract infections are treated empirically, and it is therefore necessary to know the antimicrobial susceptibility patterns of the frequently isolated bacterial pathogens in any particular community.

Despite limitations in available surveillance data, some robust trends are evident. Resistant pneumococci have a worldwide distribution, which varies from country to country. Isolates may also be resistant to multiple antibiotics, and some are susceptible only to parental agents,<sup>4</sup> posing a threat to the effective treatment of pneumococcal disease.

When the breakpoints listed in the 2002 NCCLS guidelines were applied to our data, somewhat confusing results were obtained. Although the breakpoints for amoxicillin and amoxicillin/clavulanate against *S pneumoniae* have been raised, that for penicillin remains unchanged.<sup>3</sup> With these breakpoints, only 24% of the 729 pneumococcal isolates collected were sensitive to penicillin, with 86% being fully susceptible to amoxicillin. However, although reporting pneumococci as resistant to penicillin, respiratory tract infections caused by these strains would probably respond to treatment with either penicillin or amoxicillin.<sup>6,7</sup> Irrespective of clinical relevance, the high prevalence of penicillin resistant strains in South Africa, and the rapid rate of increase over the past few years, particularly with respect to the highly resistant strains (MICs  $\geq$  2 mg/litre), is very worrying. In the Alexander project, the percentages of intermediate and resistant strains detected during 1996 to 1997 were 25.8% to 31.3% and 3.6% to 4.5%, respectively.<sup>8</sup> This has increased to 30% and 46%, respectively, during the present study period. Furthermore, the present prevalence of penicillin non-susceptible strains in South Africa (76%) is one of the highest in the world. It is far higher than that reported from the UK (9–13%),<sup>3</sup> USA (33.5–36.2%),<sup>9–11</sup> Canada (21–22.2%),<sup>12,13</sup> Western Europe (25–30%),<sup>1,8,14</sup> Central and Eastern Europe (< 5% to > 40%),<sup>1</sup> Spain (41–52%),<sup>4</sup> and Australia (25%).<sup>15</sup>

“Of great concern is the rapid increase in macrolide resistance seen over the past few years in South African isolates of pneumococci”

The South African figures approximate some of those from the Asia Pacific region. In the PROTEKT study, the percentage of penicillin non-susceptible strains varied from 68% in Asia, to 81% in South Korea, compared with the 76% seen in our study in South Africa.<sup>1</sup> In contrast to the high levels of resistance seen in South Africa, where reported, resistance levels are lower in the rest of Africa. For example, in Egypt 25% of strains were resistant during the period 1991 to 1993.<sup>16</sup>

Of great concern is the rapid increase in macrolide resistance seen over the past few years in South African isolates of pneumococci. Only 6–7% of the strains tested in the Alexander study, which were collected during 1996 to 1997, were macrolide resistant.<sup>8</sup> In our present study, 61% of the pneumococci tested were resistant to both clarithromycin and azithromycin, with 47% having MICs of  $\geq$  32 mg/litre. Again, the South African pneumococci have one of the highest macrolide resistance rates in the world. Both the PROTEKT and Alexander project reported an overall prevalence of macrolide resistance of 25% across Europe.<sup>1,8</sup> Macrolide resistance in other countries is as follows: UK, 0.1% (1992), 13.6% (1996), 7.2% (1997)<sup>3,8</sup>; USA, 19–24%<sup>9,10</sup>; Canada, 1–17%<sup>12,13</sup>; Spain, 19.1–32.6%<sup>8</sup>; and Australia, 16%.<sup>15</sup>

**Take home messages**

- The present prevalence of penicillin non-susceptible strains of *Streptococcus pneumoniae* in South Africa (76%) is one of the highest in the world
- Macrolide resistance in pneumococci in South Africa (61%) is also one of the highest in the world, although surprisingly, only 14% of *S pyogenes* were resistant
- The quinolones, moxifloxacin and levofloxacin, showed good activity against all the organisms tested, including the penicillin and macrolide resistant strains and *K pneumoniae*
- Moxifloxacin was more active than levofloxacin against pneumococci
- With the ever increasing prevalence of resistant bacteria, it is necessary to have ongoing national surveillance programmes to monitor the susceptibility patterns of frequently isolated pathogens

Resistance rates higher than those in South Africa have been reported from the Asia Pacific region. In the PROTEKT study, 81% of the pneumococcal isolates were macrolide resistant.<sup>1</sup> Of these, 11% showed intermediate resistance, whereas 70% were fully resistant to these agents.<sup>1</sup>

In addition, 21% of the South African pneumococcal isolates demonstrated intermediate resistance and 51% full resistance to co-trimoxazole.

The massive increase in both macrolide and penicillin resistant isolates may reflect bias introduced into our present study because only clinical isolates from specimens submitted to the private laboratories were tested. In the private sector many patients are treated empirically initially, and frequently specimens are only submitted for culture in severely ill patients or patients who do not respond to initial treatment. Such infections are more likely to be caused by a resistant strain. However, it is very important to know the sensitivity patterns of the more resistant organisms present in any community to be able to select the appropriate treatment.

It is surprising that although high level macrolide resistance was seen in so many pneumococci, only 14% of *S pyogenes* isolates tested were macrolide resistant. Levels of macrolide resistance in *S pyogenes* vary throughout the world. The levels of macrolide resistant *S pyogenes* in Europe as reported in the PROTEKT study varied between 0% in Austria, Belgium, Netherlands, and the UK, to 21–24.5% in Spain, Portugal, and Italy.<sup>1</sup>

In addition, although  $\beta$  lactamase was produced by nearly all the *M catarrhalis* isolates, only 7% of *H influenzae* strains tested were  $\beta$  lactamase producing. The prevalence of  $\beta$  lactamase producing strains of *H influenzae* isolated in our study is considerably lower than that reported from Europe. In the Alexander study, up to 14% of isolates from London and more than 15% of isolates from the Republic of Ireland, France, and Belgium were  $\beta$  lactamase producing.<sup>8</sup> These figures are very similar to the PROTEKT data, where  $\beta$  lactamase production occurred in 11–19% of isolates tested from Western Europe.<sup>1</sup> In Spain, rates are as high as 31.7%.<sup>8</sup> In the USA, 33.4% of isolates produced  $\beta$  lactamase during 1996 to 1997<sup>9</sup> and 26.2% during 1999 to 2000,<sup>11</sup> whereas in Canada 21.7% were  $\beta$  lactamase producing.<sup>12</sup>

The quinolones, moxifloxacin and levofloxacin, showed good activity against all the organisms tested, including the penicillin and macrolide resistant strains and *K pneumoniae*. None of the *H influenzae* or *M catarrhalis* isolates were resistant to these agents. Moxifloxacin was more active than levofloxacin against pneumococci. This is in accordance with similar studies reported in the literature.<sup>10 11 17–19</sup> These new fluoroquinolones are also active against *Chlamydia pneumoniae*,

*Mycoplasma pneumoniae*, and *Legionella pneumophila* and are good alternatives to  $\beta$  lactams and macrolides for the treatment of respiratory tract infections.

With the ever increasing prevalence of resistant bacteria, it is necessary to have ongoing national surveillance programmes to monitor the susceptibility patterns of frequently isolated pathogens.

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