EVOLUTION OF FLUOROQUINOLONE-RESISTANCE IN CLINICAL ISOLATES OF *STREPTOCCUS PNEUMONIAE* ISOLATED IN BELGIUM FROM 1995 TO 2005.

R. Vanhoof[1], S. Damée[1], S. De Craeye[1], E. Van Bossuyt[1], L.Avrain[2], P.M. Tulkens[2], J. Van Eldere[3], J. Verhaegen[3] and the Belgian SP Study Group*.

[1]Pasteur Institute Brussels, Engelandstraat 642, B-1180 Brussels, [2]Université catholique de Louvain, B-1200 Brussels, [3]University Hospital Gasthuisberg, B-3000 Leuven.

Pasteur Institute
BRUSSELS

* M. Carpentier (Liège), O. Fagnart, B. Mulongo (Bruxelles), Y. Glupczynski (Yvoir), P. Goffinet (Arlon), D. Govaerts (Montigny-le-Tilleul), P. Lefèvre (Marche-en-Famenne), M. Lontie (Leuven), K. Magerman, R. Cartuyvels (Hasselt), F. Meunier (Haine-St.Paul), I. Philippart (Mons), F. Moonens (Baudour), I. Surmont (Roeselare), M. Van De Vyvere, K. Camps (Antwerpen), H. Van Landuyt, B. Gordts (Brugge), L. Van Nimmen (Gent), R. Van Noyen, J. Frans (Bonheiden).

RICAI
26th interdisciplinary meeting on anti-infectious chemotherapy
Paris, December 7-8, 2006

Abstract

A total of 2118 clinical isolates of *Streptococcus pneumoniae* were collected by 15 laboratories in 7 surveys, i.e.: 1995 (143), 1997 (162), 1999 (227), 2001 (334), 2003 (391), 2004 (424) and 2005 (447) and tested for their susceptibility to ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), ofloxacin (OFL), by a CLSI microdilution technique. The following rates of insusceptibility (I+R)/resistance(R) (%) were found in the 7 surveys: CIP: 7.7/0; 13.5/1.9, 15.0/1.8, 10.2/3.6, 13.8/4.3, 9.0/2.4, 7.3/1.3; LEV 0/0, 1.2/0, 1.8/0, 2.7/0.3, 3.3/1.5, 2.8/0.2, 0.7/0.2; MOX: 0/0, 0/0, 0/0, 0.3/0, 0.6/0.3, 0.2/0, 0.2/0; OFL: 7.7/0, 16.6/1.2, 15.0/1.8, 10.2/3.6, 13.5/4.3, 9.0/2.4, 7.3/1.3. IR rates increased significantly between 1995 and 1999 for CIP (7.7% to 15.0%, 0.05>P>0.02) and between 1995 and 1997 for OFL (7.7% to 16.6%, 0.02>P>0.01). Afterwards, a significant decrease in IR rate was found for CIP (1997-2005, 13.5% to 7.3%, 0.02>P>0.01), LEV (2001-2005, 2.7% to 0.6%, 0.05>P>0.02) and OFL (1997-2005, 16.6% to 7.3%, P<0.001). The FQ had a one-modal MIC distribution and the mode did not shift markedly throughout the years (CIP, LEV: 0.5-1 µg/ml; MOX: 0.06; OFL: 1). CIP and LEV MIC distributions were comparable. The mode for the FQ non-susceptible isolates did not change significantly (CIP, MOX: 2; LEV, OFL: 4). Overall, OFL was 1 dilution less active than CIP while LEV and MOX were 1 and 3 dilution respectively more active than CIP. Following EUCAST breakpoints, nearly all isolates are considered as non susceptible to CIP and OFL, while rates of LEV and MOX are comparable with CLSI rates. There were only minor non significant differences in IR rates according to age, admission type, sampling site and gender. Significant geographic differences in IR rates between North (N), South (S) and Brussels (B) existed only for CIP and OFL in 2005 (N:1.6%, S: 13.2%, B: 0%; S/N = P<0.001) and S/B = 0.01>P>0.001). Cross-resistance between CIP and OFL was practically complete while the CIP-IR isolates remained mostly fully susceptible to LEV (68.4%-100%) and MOX (96.3%-100%).

Introduction and Purpose

S. pneumoniae still is a major cause of upper respiratory tract infections and invasive infections. For decades, Penicillin G has been considered as the drug of choice. The incidence of isolates with reduced susceptibility to penicillin and other antimicrobials increased world-wide. In this study we present data on the evolution of FQ non-susceptibility for the period 1995-2005.

Methods

ISOLATES: A total of 2118 consecutive, unduplicated isolates of *S. pneumoniae* were collected by the 15 participating laboratories during 7 surveus: 1995 (143), 1997 (162), 1999 (227), 2001 (334), 2003 (391), 2004 (424), 2005 (447).

SUSCEPTIBILITY TESTING: Susceptibility was determined by using a micro-dilution technique following CLSI recommendations. *S. pneumoniae* ATCC 49619 was used for quality control.

ANTIMICROBIAL AGENTS: The following fluoroquinolones were tested: Ciprofloxacin (CIP), Levofloxacin (LEF), Moxifloxacin (MOX), Ofloxacin (OFL).

RESISTANCE RATES: Resistance rates were determined by using the CLSI breakpoints (I=Intermediate; R=high level: expressed in µg/ml). CIP: I/R = 2/4 (no separate CLSI breakpoint; the breakpoint is in general one dilution lower than that of LEV), LEV: I/R = 4/8, MOX: I/R = 2/4, OFL: I/R = 4/8.

Table I: rates of non-susceptibility (I+R in %) to fluoroquinolones found in the various surveys. (R rate between brackets).

COMPOUND	1995	1997	1999	2001	2003	2004	2006
Ciprofloxacin	7.7 (0)	13.5 (1.9)	15.0 (1.8)	10.2 (3.6)	13.8 (4.3)	9.0 (2.4)	7.3 (1.3)
Levofloxacin	0 (0)	1.2 (0)	1.8 (0)	2.7 (0.3)	3.3 (1.5)	2.8 (0.2)	0.7 (0.2)
Moxifloxacin	0 (0)	0 (0)	0 (0)	0.3 (0)	0.6 (0.3)	0.2 (0)	0.2 (0)
Ofloxacin	7.7 (0)	16.6 (1.2)	15.0 (1.8)	10.2 (3.6)	13.5 (4.3)	9.0 (2.4)	7.3 (1.3)

Table II : Rates (%) of non-susceptibility following CLSI and EUCAST (EUC) breakpoints

	CIP		LEV		MOX		OFL	
	CLSI	EUC	CLSI	EUC	CLSI	EUC	CLSI	EUC
1995	7.7	96.5	0	0	0	0	7.7	100
1997	13.5	100	1.2	1.2	0	0	16.6	100
1999	15.0	99.1	1.8	1.8	0	0.9	15.0	99.6
2001	10.2	99.1	2.7	2.7	0.3	0.9	10.2	100
2003	13.8	96.4	3.3	3.3	0.6	0.5	13.5	99.5
2004	9.0	96.7	2.8	2.8	0.2	0.2	9.0	98.8
2005	7.3	96.2	0.7	0.7	0.2	0.2	7.3	97.3

Fig.1: One Modal MIC distributions of different FQ in various surveys

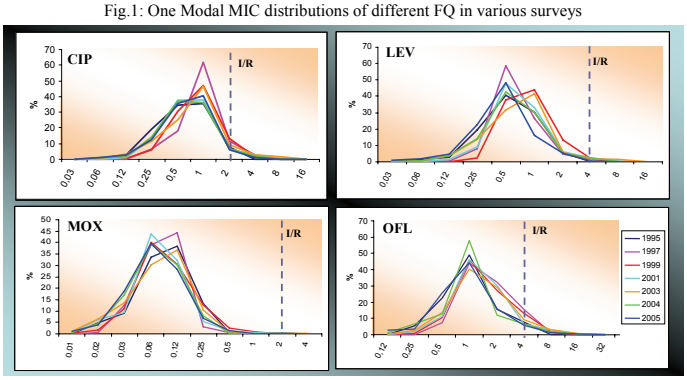
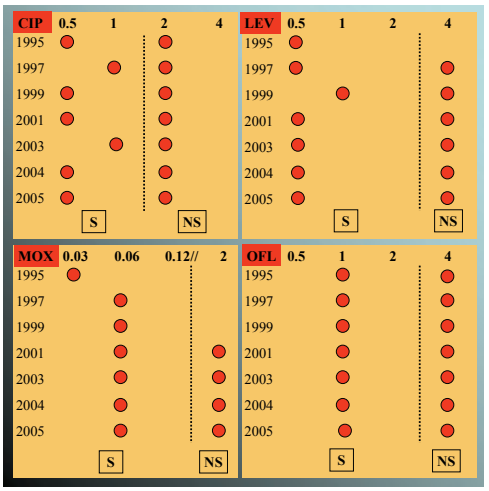


Fig.2: Evolution of MIC50 ● (µg/ml) for FQ in susceptible (S) and non-susceptible (NS) populations.



Results (1)

RATES OF NON-SUSCEPTIBILITY: see Tables I and II. Significant increase for CIP between 1995-1999 and for OFL between 1995-1997. Afterwards, significant decrease for CIP, LEV and OFL. Most of the isolates are intermediate and high level resistance is rarely found. LEV and MOX rates following EUCAST are comparable to those following CLSI.

Distributions: see Figs 1 and 2. One modal distributions. No shift in time for the modus. The MIC50 for susceptible and non-susceptible populations did not change significantly during the years. MIC distributions for CIP and LEV are comparable. Intrinsically, MOX is the most active compound.

Fig. 3: Geographic differences in CIP non-susceptibility rates (%) found in the North (No), South (So) or Brussels Capital (BS). NAT is the national level.

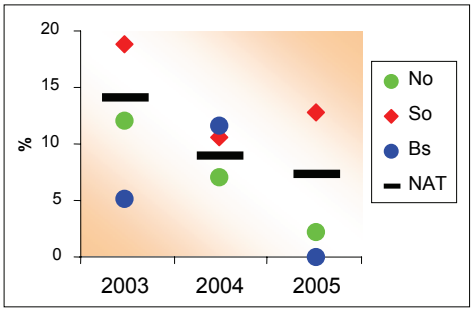


Table III:
% of CIP non-susceptible isolates remaining susceptible to other FQ

	LEV	MOX	OFL
1995	100	100	0
1997	90.9	100	31.8
1999	88.2	100	0
2001	73.5	97.1	0
2003	75.9	96.3	1.9
2004	68.4	97.4	0
2005	90.9	97.0	0

Results (2)

DIFFERENCES IN RATES OF NON-SUSCEPTIBILITY: see Fig 3. Significant difference between rates from North, South and Brussels were only found for CIP in 2005. Geographic rates were based on the postal code of the patients and are only available since 2003 the survey. Differences is rates according to age, admission type, sampling side and gender were minor and not significant.

CROSS-RESISTANCE: see Table III. Cross-resistance between the FQ was incomplete. The majority of the CIP non-susceptible isolates remained fully susceptible to LEV (68.4-100%)and MOX (96.3-100%).