# Epidemiological survey of susceptibility to β-lactams (AMX, CFX, CRO), macrolides (CLR, TEL), and fluoroquinolones (LVX, MXF) in a Belgian collection of CAP isolates of *Streptococcus pneumoniae* (SP).

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## REVISED ABSTRACT

**Objectives** Evaluate current resistance trends in SP (including efflux) towards the main antibiotics used in the treatment of CAP.

**Methods** Collection of SP (n=133) isolated from patients upon hospitalization for CAP in 4 Belgian hospitals over the last 3 years. MIC determined by microdilution in CAMH broth + 2.5% horse blood using antibiotics of clinical interest (amoxycillin [AMX], cefuroxime [CFX], ceftriaxone [CRO], clarithromycin [CLR], telithromycin [TEL], levofloxacin [LVX], moxifloxacin [MXF]). Susceptibility assessed according to EUCAST and CLSI breakpoints.

**Results**

| AB | $MIC_{50}$ | $MIC_{90}$ | Range min | Range max | EUCAST [a] % I | EUCAST [a] % R | CLSI [b] % I | CLSI [b] % R |
|---|---|---|---|---|---|---|---|---|
| AMX | 0.06 | 1.5 | ≤ 0.03 | 2 | | | 0 | 0 |
| CFX | 0.06 | 8 | ≤ 0.03 | 16 | 1.5 | 12.8 | 1.5 | 12.8 |
| CRO | 0.06 | 1.5 | ≤ 0.016 | 3 | 11.3 | 0.8 | 10.5 | 0 |
| CLR | ≤ 0.06 | > 32 | ≤ 0.06 | > 32 | 0 | 35.3 | 0.8 | 34.6 |
| TEL | ≤ 0.06 | 0.25 | ≤ 0.06 | 2 | 4.5 | 3 | 1.5 | 0 |
| LVX | 0.75 | 1.5 | 0.375 | 12 | \ | 2.3 | 1.5 | 0.8 |
| MXF | 0.25 | 0.25 | 0.06 | 3 | \ | 0.8 | 0.8 | 0 |

a EUCAST bkpts: AMX: none proposed; CFX: S≤0.5, R>1; CRO: S≤0.5, R>2; CLR (proposed): S≤0.25, R>0.5; CLI (proposed): S≤0.5<R; TEL (proposed): S≤0.25, R>0.5; LVX: S≤2<R; MXF: S≤0.5<R.

b CLSI bkpts: AMX: S≤2, R≥8; CFX: S≤0.5, R≥2; CRO: S≤1, R≥4; CLR & CLI: S≤0.25, R≥1; TEL: S≤1, R≥4; LVX: S≤2, R≥8; MXF: S≤1, R≥4.

According to CLSI, all isolates are susceptible to AMX. Non susceptibility to CFX is observed in about 14% and to CRO, in about 10% of strains, whatever the bkpoint considered. More than 34% of isolates were resistant to CLR, among which 20% [7% of the total of isolates] were CLI-S (denoting efflux). A significant proportion of isolates (7.5%) could be categorized as TEL-NS using EUCAST bkpts but only 1.5% would appear as TEL-I according to CLSI. MIC of LVX were much higher than those of MXF, but non susceptibility to both drugs remains low, due to higher bkpts for LVX. Most isolates show no decrease in MIC in the presence of reserpine (only 0.8% remains LVX-R, no change for MXF)

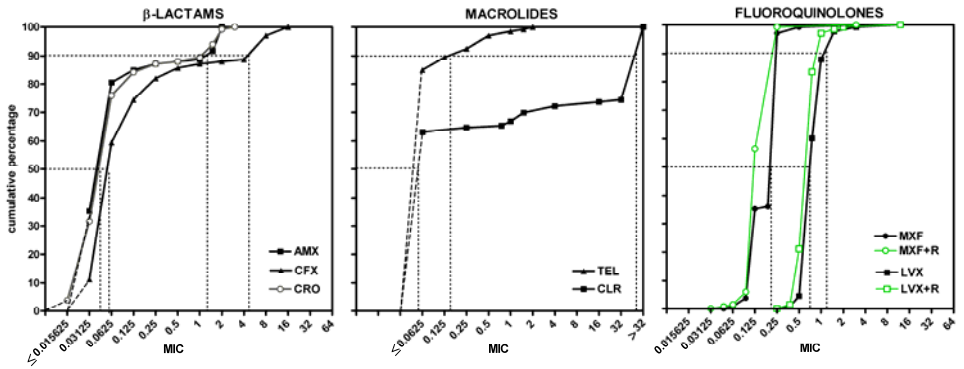
**Conclusion** The data show a decreased susceptibility of SP to cephalosporins, as well as a high prevalence of methylation-related resistance to macrolides, which starts to affect ketolides as well. Quinolone resistance remains low, based on current bkpts, even though LVX MICs are clearly increasing. Efflux significantly impacts on macrolide susceptibility but does not markedly affect LVX or MXF. These data underline the risk of empirical treatment of CAP and suggest the importance of setting appropriate bkpts.

## Background and Aim

- Respiratory tract infections represent the major reason for antibiotic prescription out of the hospital. It is therefore not surprising that the incidence of respiratory tract isolates with reduced susceptibility to antibiotics is increasing worldwide (1). Efflux may be an important but often neglected component of this reduction resulting in suboptimal therapies (2, 3).
- *Streptococcus pneumoniae* is the most frequent pathogen associated with respiratory tract infections, including in community-acquired pneumonia (CAP). This infection requires optimal antibiotic therapy especially in patients at risk.
- Epidemiological surveys are therefore needed to determine the local prevalence of resistance, including efflux, and to propose on this basis appropriate guidelines for treatment.
- In the present work we evaluate
  - current resistance trends
    - in a collection of *S. pneumoniae* isolated from CAP patients hospitalized in 4 major hospitals from the Brussels area,
    - towards three main antibiotic classes used in the clinics (β-lactams, macrolides, quinolones).
  - the prevalence of efflux for macrolides and fluoroquinolones

## Results

**Cumulative MIC distribution for 133 isolates of *S. pneumoniae* towards amoxycillin, cefuroxime, ceftriaxone, clarithromycin, telithromycin, levofloxacin and moxifloxacin.**




| | AMX | CFX | CRO | CLR | CLI | TEL | LVX Res | LVX (-) | LVX (+) | MXF (-) | MXF (+) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $MIC_{50}$ (mg/L) | 0.06 | 0.06 | 0.06 | ≤0.06 | 0.125 | ≤0.06 | | 0.75 | 0.75 | 0.25 | 0.125 |
| $MIC_{90}$ (mg/L) | 1.5 | 8 | 1.5 | >32 | >32 | 0.25 | | 1.5 | 1 | 0.25 | 0.25 |
| EUCAST bkpts S≤ (none proposed) | | 0.5 | 0.5 | | 0.25* | 0.5* | 0.25* | 2 | | 0.5 | |
| EUCAST bkpts R> | | 1 | 2 | | 0.5* | 0.5* | 0.5* | 2 | | 0.5 | |
| S: | | 85.7% | 88.0% | S: | 64.7% | 72.2% | 92.5% | 97.7% | 99.2% | 99.2% | 99.2% |
| I: | | 1.5% | 11.3% | I: | 0.0% | | 4.5% | | | | |
| R: | | 12.8% | 0.8% | R: | 35.3% | 27.8% | 3.0% | 2.3% | 0.8% | 0.8% | 0.8% |
| CLSI bkpts S≤ | 2 | 0.5 | 1 | | 0.25 | 0.25 | 1 | 2 | | 1 | |
| CLSI bkpts R≥ | 8 | 2 | 4 | | 1 | 1 | 4 | 8 | | 4 | |
| S: | 100.0% | 85.7% | 89.5% | S: | 64.7% | 72.2% | 98.5% | 97.7% | 99.2% | 99.2% | 99.2% |
| I: | 0.0% | 1.5% | 10.5% | I: | 0.8% | | 1.5% | 1.5% | 0% | 0.8% | 0.8% |
| R: | 0.0% | 12.8% | 0.0% | R: | 34.6% | 27.8% | 0.0% | 0.8% | 0.8% | 0.0% | 0.0% |

AB alone (black), + reserpine 10mg/L (green).
* Proposed EUCAST breakpoints for CLR, CLI & TEL.

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## Methods

**Bacteria:** 133 strains of *S. pneumoniae* have been isolated over the 2004-2007 period from patients admitted in 4 major hospitals from the Brussels area, with a diagnosis of CAP (confirmed by an in-depth analysis of the medical file).

**Susceptibility testing:** MICs were determined by microdilution following CLSI recommendations. *S. pneumoniae* ATCC 49619 was used as a quality control. Susceptibility was assessed according to EUCAST and CLSI breakpoints.

**Resistance due to active efflux** was evidenced
- for macrolides by comparison of the MICs of CLR and CLI, which is only affected by ribosomal mutations (4).
- for fluoroquinolones by determining the effect of an efflux pump inhibitor (reserpine, 10mg/L) on the MICs of LVX and MXF (5).

## Conclusions

- **β-lactams**: decreased susceptibility of SP to cephalosporins, with 12.8% full resistance to CFX.
- **Macrolides**: high prevalence of resistance to macrolides (~35%) with 20% of resistant strains remaining susceptible to CLI, suggesting active efflux. TEL susceptibility remains superior to 92%.
- **Fluoroquinolones**: low prevalence of resistance based on current breakpoints, but LVX MICs clearly higher than those of MXF, with evidence of efflux (0.5-1 dilution).

These data
(i) Underline the risk of empirical treatment of CAP with conventional macrolides;
(ii) reinforce the necessity to use β-lactams in large dose with constant control of susceptibility;
(iii) suggest the importance of setting appropriate breakpoints.

## References

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