Chapter VI-5
Resistance to antimicrobials in France: statistical data from ONERBA's networks

1 Comments

1.1 Subpopulation analysis of major bacterial species, according to their susceptibility level (type 1 information, chapter 6.1)

Data in humans

Figures 1.1, 1.2, 1.10, 1.11 compare the activity of amoxicillin + clavulanate (AMC) to amoxicillin alone (AMX) against *Escherichia coli*. The behaviour of this species with respect to AMX (Figure 1.1) is bimodal, with a susceptible subpopulation (mode, 24-26 mm) and a clearly resistant one (mode, 6 mm) widely separated by the two critical values. *E. coli* behaviour toward AMC shows an unimodal distribution (mode, 21 mm) spread over a wide zone on either side of « D » (21 mm), the upper critical diameter (Figures 1.2 and 1.11). Stratification on AMX susceptibility (susceptible strains (S) *versus* non-susceptible strains, i.e. intermediate susceptibility and resistant, R) shows two distinct subpopulations (Figures 1.10 and 1.11). The behaviour of AMX-S strains toward AMC is comparable to that of AMX alone, with unimodal distribution (mode, 24-26 mm). However, for AMX-R strains, AMC diameters distribution is highly heterogeneous. AMC restored susceptibility (diameter ≥21 mm) in a very small proportion of AMX-R strains, suggesting high level of resistance to amoxicillin. The observed distributions are similar to those observed in 2005 and 2006 [1,2].

Figure 1.3 shows that *E. coli* susceptibility to cefotaxime is highly homogenous, most strains being very susceptible (inhibition diameter ≥35 mm). As it has been observed in previous years, a small proportion of strains is highly resistant, possibly due to the emergence of strains producing ESBL of CTX-M type [3,4].

Figure 1.4 shows *E. coli* behaviour toward imipenem. The distribution is unimodal (mode, 31 mm), although there is a small peak at 35 mm relative to the upper detection limit of some automated cameras.

Figure 1.5 shows that *E. coli* susceptibility to nalidixic acid (NAL) is bimodal: a susceptible subpopulation with 26 mm modal inhibition diameter, a highly resistant subpopulation (mode, 6 mm) still increasing (reaching 25% in 2007) as reported in 2005 and 2006 [1,2]. Figure 1.7 shows the behaviour of *E. coli* isolates toward ciprofloxacin (CIP). Three populations are delineated. Highly resistant isolates to CIP are stable in 2006 (10%) marking a pause in the increase observed for several years (+4% in 2005). All isolates susceptible to NAL are also fully susceptible to CIP (Figure 1.8), but the distribution is bimodal (modes, 26-34 mm et >34 mm) suggesting the presence of an acquired mechanism of resistance in the least susceptible population. For NAL non-susceptible isolates (Figure 1.9), there are 3 subpopulations (modes: 6 mm, 8-15 mm, 24-33 mm). More than half of NAL-R isolates are CIP-resistant. There was no 4th hypersensitive subpopulation in distributions (>35 mm), as compared to 2006 [2].

Figure 1.12 shows *E. coli* susceptibility to cotrimoxazole to be trimodal: a susceptible population with 28 mm modal inhibition diameter, a highly resistant population (mode, 6 mm) and an intermediate population located between « d » and « D » as it was in 2006.

Figure 1.6 displays *E. coli* behaviour towards gentamicin. The distribution of diameters is trimodal, with a susceptible population (mode, 25 mm), a resistant to intermediate population located between 8 and 15 mm, and a highly resistant population (mode, 6 mm). The latter prevalence (1.8% of all isolates) is slightly lower than in 2006 (3.5%).

Data from food animals

For bovine, *E. coli* resistant to amoxicillin, associated or not with clavulanic acid, are frequent (Figures 1.13 and 1.14). Figure 1.15 shows the susceptibility of *E. coli* cattle isolates to ceftiofur (third generation cephalosporin used in veterinary medicine). Data in 2007 are in line with those gathered in the previous years and confirm the existence of an animal reservoir of strains harbouring decreased susceptibility (or resistance) to this compound. ESBL-producing *E. coli* are mainly responsible for this phenotype (CTX-M group, [5,6] even though AmpC-type producers were also identified in France, sometimes harbouring co-resistances (on the same plasmid) to others antibiotics [7]. This latter point argues also in favour of the selective role of other molecules in the co-selection process. More than 80% of *E. coli* are susceptible to gentamicin (Figure 1.16). Also, figure 1.17 shows 20% of *E. coli* isolates of bovine origin displaying a decreased susceptibility (or resistance) to enrofloxacin. All these data emphasize the constant need for a prudent use of beta-lactams and fluoroquinolones in veterinary medicine, even though co-selection with other antimicrobials should not be excluded. Figures 1.18 to 1.21 show that around 10% of *S. uberis* isolates of bovine origin are resistant to erythromycin, lincomycin, spiramycin and tetracycline.

1.2 Summary statistics of antibiotic resistance for the major bacterial species of medical interest (type 2 information, chapter 6.2)

Staphylococcus aureus

Tables 2.25, 2.29 to 2.31 show susceptibility rates of *S. aureus*. In the MedQual network of private laboratories (Table 2.25),

around 15% of *S. aureus* isolated in the community are resistant to methicillin (MRSA). This does not mean that these strains are community-acquired MRSA as previous history of patients is not recorded herein. Most of *S. aureus* strains (99%) are gentamicin-susceptible, and 86 % are kanamycin and 87% tobramycin-susceptible. Of interest, 75% of the strains are susceptible to erythromycin and 90% to fusidic acid. Only 80% of the strains are susceptible to fluoroquinolones, suggesting that at least 4% of methicillin susceptible strains are fluoroquinolone-resistant.

Enterobacteria

Tables 2.1 to 2.12 and table 2.24 show susceptibility rates of enterobacterial species isolated in Human:

- to amoxicillin (AMX) : 50% and 54% of *E. coli* strains are susceptible to this antibiotic when considering the REUSSIR network of hospital laboratories (Table 2.1) and the MedQual network of private laboratories (Table 2.24);
- to the amoxicillin-clavulanic acid combination: 65,3% of *E. coli* strains are susceptible to this antibiotic when considering the REUSSIR network (Table 2.1) and 75% for the MedQual network (Table 2.22), resulting in only 14 to 20% more susceptible strains than for AMX in both networks ; 78% among *P. mirabilis* (Table 2.9), 81% among *K. pneumoniae* (Table 2.7) and 76% among *K. oxytoca* (Table 2.6);
- to cefotaxime for group 1 and 2 enterobacteria (susceptibility rates between 98% and 93%) compared to group 3 enterobacteria that naturally produce AmpC enzyme (susceptible rates 58% to 96%). Of note, the least susceptible species is *E. aerogenes* that display a susceptibility rate of only 58% (Table 2.4);
- to fluoroquinolones for group 1 and 2 enterobacteria (79% to 95%) compared to group 3 enterobacteria (34% to 84%). Some species remain susceptible (87%-98% of susceptibility for *E. coli*, Tables 2.1 and 2.22, 98% for *P. vulgaris*), while others are less susceptible (79% of susceptible for *P. mirabilis*, 78% for *E. cloacae*, 81% for *M. morganii*, 76% for *C. freundii*), and finally some species are rarely susceptible (62% of susceptible for *E. aerogenes*, 34% for *P. stuartii*).

Pseudomonas aeruginosa

This species is almost strictly hospital acquired, and is naturally resistant to aminopenicillin, 1rst and 2nd generation cephalosporins, and classical quinolones. *P. aeruginosa* (Table 2.33) is more susceptible to ceftazidime and imipenem (85%) than to ciprofloxacin (about 73%).

Susceptibility in strains isolated from animals

Amongst *E. coli* strains isolated from poultry and swine (Tables 2.26 and 2.27), the rates of susceptible strains are 43% and 38%, respectively. More than 95% of strains are susceptible to ceftiofur (third generation cephalosporin) with a slight decrease between 2002 and 2007. This decrease is also noted for oxolinic acid in these two animal productions. Between 86% and 91% of *E. coli* strains isolated from swine and poultry respectively are susceptible to fluoroquinolones and more than 93% of strains are susceptible to gentamicin in 2007. Rates of cotrimoxazole-susceptible *E. coli* are significantly different between poultry (65%) and swine (38%) ($p < 0.01$) with an increase between 2002 and 2007. Only 18% of *E. coli* isolated from poultry and swine are susceptible to tetracycline.

Comparison of data gathered from 2003 to 2007 (Table 2.28) shows a constant and very low level of susceptibility of cattle *E. coli* to amoxicillin (26.9% in 2007), which is poorly restored by clavulanic acid (48,1% of susceptible cattle isolates in 2007), albeit slightly increasing since 2003. Susceptibility to third generation cephalosporins demonstrated a slight worrying trend in the last years (98.4% in 2005 *versus* 96.3% in 2006), but results for 2007 appeared rather stable (96.5%). Susceptibility to fluoroquinolones remains stable as well, albeit at a level of 70 to 80% of susceptible strains, below the one observed in pork and poultry. Low levels of susceptibility to streptomycin (25.1%) and tetracycline (27.4%) are also to note.

Trends in susceptibility (Tables 2.13 to 2.21, 2.32, 2.34)

S. aureus

S. aureus susceptibility to methicillin was higher in 2007, climbing from 64% in 2000 to 74% in 2007. The susceptibility rate was also higher for lincomycin (71% in 2000, 83% in 2007), and rifampicin (about 85% in 2005 98% in 2007) (Table 2.32).

E. coli

Almost no trend in *E. coli* susceptibility was observed for most antibiotics during the last 7 years (Table 2.13). However, there is a slight decrease in fluoroquinolones susceptibility of *E. coli* isolates, from 95% in 2000 to 87% in 2007. In addition, no strain resistant to cefotaxime was recorded in 2000 when 3% of isolates are resistant to this antibiotic in 2006 and 2007.

E. aerogenes

E. aerogenes susceptibility rates to cefotaxime and fluoroquinolones (Table 2.15) increased from 35% in 2000 to 58% in 2007 for cefotaxime, from 36% to 62% for fluoroquinolones, respectively. Such an increase in susceptibility is probably related to a decrease in the number of ESBL-producing strains (Tables 4.13, chapter 6.4).

E. cloacae

In contrast to *E. aerogenes, E. cloacae* susceptibility to third generation cephalosporins has decreased from 2000 (78%) to 2007 (66%) (Table 2.16). Fluoroquinolones susceptibility decreased (87%) in 2000 to 78% in 2007). In addition, there was a slight decrease in cotrimoxazole susceptibility (93% in 2000 to 86% in 2007).

K. pneumoniae

K. pneumoniae susceptibility to most antibiotics did not vary much between 2000 and 2007 (Table 2.18). However, in 2006, there was a slight decrease in susceptibility to fluoroquinolones (3%) that was confirmed in 2007.

P. mirabilis

As for *E. cloacae*, there is a slight decrease in fluoroquinolones (87% in 2000 to 79% in 2007) and cotrimoxazole susceptibility (81% in 2000 to 71% in 2007) (Table 2.19).

S. marcescens

In contrast to *E. cloacae, S. marcescens* susceptibility to third generation cephalosporins has increased by 10% from 2000 (82%) to 2007 (92%) (Table 2.21). Fluoroquinolones susceptibility increased also (75% in 2000 to 84% in 2007). In addition, there was a light increase in cotrimoxazole susceptibility (79% in 2000 to 91% in 2007).

P. aeruginosa

There was no significant trend in *P. aeruginosa* susceptibility to ß-lactams from 2000 to 2007. On the opposite, there was an upward trend (Table 2.31) in susceptibility to flioroquinolones (70% in 2000 to 74% in 2007) and to tobramycin (74% in 2000 to 85% in 2007).

1.3 Bacterial resistance of isolates in well documented infection or in specific epidemiological settings (type 3 information, chapter 6.3)

Bacteraemia: trends in antibiotic susceptibility

The analysis of the distribution of bacteria implicated in nosocomial and community-acquired bacteraemia shows that the Gram negative species, the most frequent among community-acquired bacteraemia since 2001, are as well the most frequent ones among nosocomial bacteraemia since 2005 (Table 3.13). The frequency of anaerobic bacteria should be carefully monitored, including in the community setting (Tables 3.13a and b).

Among *S. aureus*, the percentage of methicillin-susceptible strains continues to increase, particularly among hospital-acquired isolates (Table 3.40 and Table 3.14); almost all methicillin-susceptible strains and 90% of MRSA strains are now susceptible to gentamicin. In the last ten years, this almost complete disappearance of gentamicin resistant MRSA is one of the most noteworthy epidemiological variation occurring in this species (Table 3.5). The MRSA invasive strains exhibiting a homogeneous or heterogeneous decreased susceptibility to glycopeptides seem to have disappeared; the emergence and spread of fluoroquinolone susceptible clones harbouring specific toxin genes as *tst-1* have to be carefully screened (Tables 3.9 and 3.10, chapter 4).

During the last decade, the antibiotic susceptibility of *E. coli*, the main bacterial species responsible for community-acquired and nosocomial infections, decreases markedly for first-line agents. Indeed the amoxicillin susceptibility rate exhibits a 8% decrease between 1996 and 2007; almost one half of *E. coli* strains are now resistant to this compound (Table 3.6 and Table 3.41). Similarly the percentage of ciprofloxacin susceptible strains reaches 85% in 2007, which leads to a 13% decrease comparing to 1996. This trend is also identified for nalidixic acid: in 2007 only 80% of the strains are fully susceptible to this compound, comparing to 90% in 2000 (Table 3.6). Hospital-acquired isolates are more prone to show such decreased antibiotic susceptibility than community-acquired ones (Table 3.19). This downward trend in fluoroquinolones susceptibility was also identified among *E. cloacae* (Table 3.7). Stratification on amoxicillin susceptibility shows that amoxicillin-resistant *E. coli* strains are less frequently susceptible to ciprofloxacin than susceptible strains (Table 3.8). In 2007 the percentage of extended-spectrum ß-lactamase producing strains reaches 1.9% among *E. coli*, a rate superior to the 1.6% reported in 1996. In 2007 a trend to increase of ESBL harbouring strains is identified among *K. pneumoniae* (Tableau 3.18). During the last decade, the decrease of cefotaxime susceptibility rate, whatever the biochemical mechanism, is sustained among *E. cloacae* (71% of fully susceptible strains in 2007) (Table 3.7). During the same period a similar trend was not identified among *P. mirabilis* strains.

Streptococcus pneumoniae

Between 2001 and 2007, the proportion of invasive strains (isolated from meningitis or bacteraemia), susceptible to beta-lactams or macrolides significantly increased among both children (<16 years) and adults ($p<10^{-3}$). When considering fluoroquinolone resistance, proportion remained stable between 2001 and 2007 (Table 3.35, Figure 3.22).

Analysis of *S. pneumoniae* resistance according to age and type of sample is presented in Tables 3.26 to 3.33. In 2007, among both adults and children, the proportion of strains with reduced susceptibility to penicillin, amoxicillin and cefotaxime were respectively about 30%, 15% and 7% of invasive strains (isolated from meningitis or bacteraemia). No strain resistant to cefotaxime has been isolated from invasive infections in children and two strains isolated from meningitis were resistant to amoxicillin. In adults, only one strain isolated from meningitis was resistant to cefotaxime, and two strains isolated from bacteraemia were resistant to amoxicillin. Despite the increase in the proportion of susceptible strains to macrolides since 2001, non-susceptible strains still represent nearly 35% of invasive pneumococcal strains in 2007 (36.0% in adults, 32.7% in children). The proportion of strains that have acquired a mechanism of resistance to fluoroquinolones (<1%) has not increased since 2001, those strains remaining more frequently observed in bacteraemia in adults.

Mycobacterium tuberculosis

The frequency of susceptibility of *M. tuberculosis* to first line drugs, i.e. isoniazid, rifampicin, and ethambutol, is given in Table 3.45.

For new cases of tuberculosis, i.e. patients without previous history of treatment or primary resistance, who represent a majority of patients, the frequency of susceptibility to the three drugs is 93.5%, very close from the proportion observed in 2006 [2]. The latter proportion is far higher than the proportion of susceptibility among cases with previous history of treatment (84.3%), or secondary resistance. As in the previous years, the most frequent resistance among new cases is observed for isoniazid (6.5%). The latter resistance rate is very close from the rate observed in other Western-European countries as Austria (6.2%), Belgium (5.0%), Germany (6.0%), Netherlands (5.2%), and UK (6.9%) [8]. Althoug the primary resistance rate to rifampicin is only 1%, all strains were multi-drug resistant strains. Secondary resistance to rifampicin is 9 times higher (8.8%) than the observed primary resistance.

Documented infections in animals

Neonatal diarrhoea in calves constitutes the major pathological setting for antimicrobial use in cattle. The main target species is *E. coli* (Table 3.36), and the particularly low and constant percentage of susceptible *E. coli* isolates to amoxicillin over years is to note (17.5% in 2007). Resistances to third generation cephalosporins and fluoroquinolones are identified in cattle.

Bacterial respiratory infections in cattle are mainly due to the two species *Pasteurella multocida* and *Mannheimia haemolytica*. Both of them retain very high susceptibility to all antimicrobials (Tables 3.37 et 3.38).

1.4 Surveillance of multidrug-resistant bacteria: prevalence, incidence, characteristics (type 4 information, chapter 6.4)

Methicillin-resistant *Staphylococcus aureus* (MRSA)

The overall proportion of MRSA among *S. aureus* is very homogenous in French hospitals: between 26 and 34% for most hospitals in 2007, regardless of the type of clinical sample (Tables 4.1 to 4.5). However, this proportion varies depending on the type of hospitalisation: between 21 and 29% in acute care, and between 56 and 78% in chronic or long-term facilities. The proportion of MRSA remained stable (around 40%) in the Paris and North region of the nosocomial network (CCLIN) between 1998 and 2004 and decreased afterwards (Table 4.1). This decrease was more noticeable in acute-care facilities of the « Assistance Publique-Hôpitaux de Paris » network. Indeed, the MRSA proportions fell from 39% in 1993 to 21% in 2007 (Table 4.2 and Figure 4.3). This decrease was even more drastic in Intensive Care Units of the AP-HP network, where MRSA proportions dropped from 55% in 1993 to 22% in 2007 (Figure 4.4). In the other networks, MRSA trends are encouraging, with a slight decreased MRSA proportions among *S. aureus*, although observed decreases are less pronounced. Of note, this downward trend is observed in an international, and particularly European, context of quasi-generalized rise of this indicator [9].

Most MRSA strains (between 92 and 96%) are gentamicin-susceptible, and the proportion of tobramycin-susceptible strains increased steadily since 2000, reaching 47% in 2007 (Tables 4.7 to 4.10). Between 47 and 63% of MRSA strains are erythromycin-susceptible. MRSA susceptibility to other antimicrobials such as fusidic acid, rifampicin, pristinamycin and cotrimoxazole is high, exceeding 90%. On the opposite, resistance to fluoroquinolones remains high, above 90%.

Extended-spectrum ß-lactamase-producing enterobacteria (ESBL)

In the past few years, the distribution of enterobacterial species producing extended-spectrum ß-lactamases has changed considerably, showing an increase in *Escherichia coli* species and a concomitant decrease in *Enterobacter aerogenes* and *Klebsiella pneumoniae*, depending on the network (Tables 4.13 to 4.17 and Figures 4.8 and 4.9). In 2007, in the AP-HP network, 50% of ESBL strains belong to *E. coli* species while it was only 10% in 1995. This trend is also observed in other regions of France, with a slight time lag. In the Paris and North region of the nosocomial network (CCLIN), 52% of ESBL strains belong to *E. coli* species (6% in 2000) and 15% to *Enterobacter aerogenes* species (56% in 2000). In REUSSIR network, the ESBL-producing *E. coli* proportion rose from 8% in 2000 to 48%. In 2007, in the South-West region of nosocomial network (CCLIN), the proportion of extended-spectrum ß-lactamase producing strains reaches 3,9% (1,9% in 2005) (Table 4.21). It occurs as a result of the spread of CTX-M producing strains resulting in an increase in the global ESBL-positive enterobacteria incidence. Risk of dissemination in the community and the situation observed in neighbouring countries such as Spain [10] and the United Kingdom must prompt us to the greatest vigilance concerning these MDR strains that require specific monitoring and control procedures.

In 2007, the rate of *Klebsiella pneumoniae* among ESBL-positive enterobacteria increased in the « Assistance Publique-Hôpitaux de Paris » network and in the South-West region of the nosocomial network (CCLIN). Overall, ESBL-positive strains remain highly resistant to all antimicrobials except carbapenems (Tables 4.18 to 4.20 and Figure 4.10).

Other multidrug-resistant bacteria

Multidrug-resistance among *Acinetobacter baumannii* isolates, as defined by resistance to all beta-lactams except imipenem, is similar between 2004 and 2007 (Table 4.25) around 40%. Among the resistant strains, 10% were also resistant to imipenem. Multidrug-resistant isolates are mainly isolated in ICUs (Table 4.26) and are observed in all departments under surveillance by the South-West network (Table 4.27).

Multidrug-resistance of *Mycobacterium tuberculosis* (defined as combined resistance to isoniazid and rifampicin) remained stable since 2002, with 1.2% to 1.4% of all strains being concerned (Table 4.28). However, in 2007 the rate fall below the 1% level (0.9%) returning to rates observed in the 1990s. This low rate of multidrug-resistance in 2007 has to be confirmed in the coming years, and it is among the lowest rates observed in other Western-European countries [8].