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

1 Methodology Review

Data presented in this report and discussed in this chapter are classified into four major information categories defined in ONERBA's methodological guidelines [1], and briefly reviewed below.

Subpopulations analysis of major bacterial species, according to their susceptibility level (type 1 information)

The objective is to identify and describe subpopulations of isolates according to their susceptibility level. This requires access to quantitative data (inhibition diameters or MICs). This type of data is useful for establishing the critical values that delimit clinical categories, and for detecting the emergence of strains with atypical susceptibility level that would remain undetected by qualitative S, I, or R classification; for example, strains with reduced susceptibility level remaining within the susceptible category, or highly-resistant strains.

Global statistics of antibiotic resistance for the major bacterial species of medical interest (type 2 information)

The objective is to assess the percentage of strains with acquired resistance, i.e. to identify susceptible, intermediate and resistant strains within a species. Strains that are considered are those isolated from diagnostic samples, without considering the existence of a documented infection.

Global resistance statistics for the major bacterial species are extracted from databases of the laboratories networks'.

This type of data is useful for defining the spectrum of activity of antimicrobial agents or their clinical indications.

Resistance of bacterial isolates from well-documented infections in specific epidemiological settings (type 3 information)

The objective is to determine, in specific epidemio-clinical settings, the probability of activity for the major antibiotics. This requires clinical data, except for close site samples (for example, cerebrospinal fluid) or blood cultures, whose interpretation is generally unambiguous aside from rare specific cases (for example, coagulase-negative staphylococci blood cultures).

This type of data is essential for defining indications for antibiotics as they appear in product description summaries. It is invaluable for clinicians who are prescribers, as well as for Scientific Societies and Health Authorities who establish good practice recommendations for antibiotic use.

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

The objective is to assess the magnitude of the problem presented by multidrug-resistant bacteria (MDR): methicillin-resistant *S. aureus* (MRSA), extended-spectrum beta-lactamase producing enterobacteria (ESBL), carbapenem-resistant enterobacteria, glycopeptide-resistant enterococci (GRE), etc.

Because of their frequency or therapeutic consequences, MDR bacteria warrant specific surveillance in individuals, hospitals and the community, and even in animals and the environment.

Several National Reference Centres or veterinarian networks are responsible for the monitoring of some community-acquired species (*Streptococcus pneumoniae, Mycobacterium tuberculosis, salmonella Typhimurium*). C-CLIN networks are in charge of the surveillance of MRSA and ESBL enterobacteria, and sometimes other MDR bacteria. Some indicators (incidence per 100 admissions and per 1000 patient-days, place of acquisition) have been standardised within the framework of the « Alert, Investigation and Surveillance of Nosocomial Infection Network » (RAISIN). The results generated by RAISIN are presented elsewhere [2]. Other indicators (percentage of MDR bacteria in the species, co-resistance to other antibiotics, etc.) are collected by some networks independently from RAISIN.

2 Presentation of statistical data

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

Data in humans:

Figures 1.1, 1.2, 1.10, 1.11, allow to 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 clearly 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). As expected, 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 2004 and 2005 [3,4].

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 [5,6].

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 trimodal as in the last previous years: a susceptible subpopulation with 26 mm modal inhibition diameter, a highly resistant subpopulation (mode, 6 mm) still increasing as reported in 2004 and 2005, and an intermediate subpopulation whose limits extend between both previous subpopulations. Figure 1.7 shows the behaviour of *E. coli* isolates toward ciprofloxacin (CIP). Three populations are delineated. Highly resistant isolates to CIP are stable since 2005 (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, 23-34 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, 8-10 mm, 24-33 mm). Over half of NAL-R isolates are CIP-resistant. There was no 4th « hyper-susceptible » subpopulation in distributions (>35 mm), as compared to previous years [3,4].

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 observed in 2005.

Figure 1.6 displays *E. coli* behaviour towards gentamicin. The distribution of diameters is trimodal, with a susceptible population (mode, 24 mm), a resistant to intermediate population located between 8 and 17 mm, and a highly resistant population (mode, 6 mm). The latter prevalence (3.5% of all isolates) is slightly higher than in 2005 (2.5%).

Data from food animals

Figure 1.13 shows the susceptibility to ceftiofur (a third generation cephalosporin used in veterinary medicine) of *E. coli* isolated in cattle. The 2006 data are in line with those gathered from the previous years and confirm the existence of an animal reservoir of strains harbouring decreased susceptibility (or resistance) to this molecule. ESBL-producing *E. coli* strains are mainly responsible for this phenotype (CTX-M group) [7,8], even if AmpC-type producers were also identified in France, the latter sometimes harbouring other mechanisms of resistance (on the same plasmid) to others antibiotics [9]. This latter point argues also in favour of other molecules that may have a role in the co-selection process for resistance. In addition, figure 1.14 shows that 20 % of *E. coli* strains of bovine origin are not susceptible to enrofloxacin. All these data emphasize the constant need for a prudent use of beta-lactams and fluoroquinolones in veterinary medicine, even if co-selection by other antimicrobials is possible. Figures 1.15, 1.16 and 1.17 show that 10% of *S. uberis* isolates of bovine origin are resistant to erythromycin, spiramycin and lincomycin.

2.2 Summary statistics of antibiotic resistance for the major bacterial species of medical interest (type 2 information)

Staphylococcus aureus

In the MedQual network of private laboratories (Table 2.23), 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 (99%) of *S. aureus* strains are gentamicin-susceptible, and 86.5% are tobramycin-susceptible. Of interest, only 79% of the strains are susceptible to fluoroquinolones, suggesting that at least 5 to 6% of methicillin-susceptible strains are fluoroquinolone-resistant. Furthermore, 9% of all *S. aureus* isolated in private laboratories are resistant to fusidic acid.

More data on MRSA are given in appendix 4 regarding multidrug-resistant organisms.

Enterobacteria

Tables 2.1 to 2.22 show susceptibility rates of enterobacterial species:

- to amoxicillin (AMX) : 52% 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 2.22);
- to the amoxicillin-clavulanic acid combination:
  - 66% of *E. coli* strains are susceptible to this antibiotic when considering the REUSSIR network (Table 2.1) and 81% for the MedQual network (Table 2.22), resulting in only 14 to 25% more susceptible strains than for AMX in both networks;
  - 76% 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 95% and 98%) compared to group 3 enterobacteria that naturally produce AmpC enzyme (susceptible rates 54% to 91%). Of note, the least susceptible species is *E. aerogenes* that displays a susceptibility rate of only 54% (Table 2.4);

- to fluoroquinolones (mainly ciprofloxacin) for group 1 and 2 enterobacteria (80% to 97%) compared to group 3 enterobacteria (32% to 84%). Some species remain very susceptible (88-93% of susceptibility for *E. coli*, tables 2.1 and 2.22, 97% for *P. vulgaris*), while others are susceptible in less than 90% of cases (80% of susceptible for *P. mirabilis* 78% *M. morganii*, 75% for *C. freundii*), and finally some species are rarely susceptible (56% of susceptible for *E. aerogenes*, 33% for *P. stuartii*);
- to amikacin for which it can be noticed that *E. aerogenes* and *S. marcescens* remain less frequently susceptible (77% and 72%, respectively) than other species (susceptible rates >95%).

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 2.24) is less frequently susceptible to piperacillin (80%) and imipenem (84%) than to ceftazidim (86%), and susceptibility to ciprofloxacin (about 69%) is less frequent than to beta-lactams.

Susceptibility in strains isolated from animals

Comparison of data gathered from 2003 to 2006 (Table 2.28) of *E. coli* strains isolated from cattle shows a constant and very low frequency of susceptibility to amoxicillin (around 20%), which is being poorly restored by clavulanic acid (41,1% of susceptible isolates in 2006). Susceptibility to third generation cephalosporins demonstrates a slight downward trend in our network (98.4% in 2005 *versus* 96.3% in 2006) that needs to be confirmed. Susceptibility to fuoroquinolones remains stable as well, albeit at a level of 70 to 80% of susceptible strains, below the one observed in pork and poultry. Low frequency of susceptibility to streptomycin (19,2%) and tetracyclin (25,2%) are also worrysome.

Amongst *E. coli* strains isolated from poultry and swine (Tables 2.26 and 2.27), between 43% and 44% are susceptible to amoxicillin in 2005. Susceptibility is often restored by clavulanic acid, and over 98% of strains are susceptible to ceftiofur (a third generation cephalosporin). Between 88% and 95% of *E. coli* strains isolated from swine and poultry respectively are susceptible to fluoroquinolones and more than 94% of strains are susceptible to gentamicin in these two animal productions. Percentages of cotrimoxazole-susceptible *E. coli* are significantly different between poultry (60%) and swine (36%) ($p < 0.01$). Only 15% and 20% of *E. coli* isolated from poultry and swine respectively are susceptible to tetracycline.

Trends in susceptibility (Tables 2.13 to 2.21)

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 88% in 2006. In addition, no strain resistant to cefotaxime was recorded in 2005 when 3% of isolates are resistant to this antibiotic in 2006.

E. aerogenes

E. aerogenes susceptibility rates to cefotaxime, amikacin and fluoroquinolones (Table 2.15) increased significantly, from 35% in 2000 to 54% in 2006 for cefotaxime, from 55% to 77% for amikacine, and from 36% to 57% for fluoroquinolones, respectively. Such an increase in susceptibility is probably related to a decrease in the number of ESBL-producing strains (Tables 4.12 to 4.16).

E. cloacae

In contrast to *E. aerogenes*, *E. cloacae* susceptibility to third generation cephalosporins has decreased by 9% from 2000 (78%) to 2006 (69%) (Table 2.16). Fluoroquinolones susceptibility decreased by 10% from 2000 (87%) to 2006 (77%). In addition, there was a slight decrease in cotrimoxazole susceptibility (93% in 2000 to 86% in 2006) over the years.

K. pneumoniae

K. pneumoniae susceptibility to most antibiotics did not vary much between 2000 and 2006 (Table 2.18). However, during 2006, a slight decrease of susceptibility was observed for third generation cephalosporins (2%) and fluoroquinolones.

P. mirabilis

As for *E. cloacae*, there is a slight decrease in fluoroquinolones (87% in 2000 to 80% en 2006) and cotrimoxazole susceptibility (81% en 2000 à 76% en 2006) in the last years (Table 2.19).

P. aeruginosa

There was no significant trend in *P. aeruginosa* susceptibility to ß-lactams and fluoroquinolones from 2000 to 2006. On the opposite, there was an upward trend (Table 2.25) in susceptibility to gentamicin, and to tobramycin (74% in 2006 to 83% in 2006).

2.3 Bacterial resistance of isolates in documented infection or in specific epidemiological settings (type 3 information)

Tables 3.1 to 3.55 provide examples of resistance statistics established within several networks for documented infections or in specific epidemiological settings (type of infection, nosocomial/community-acquired, etc.).

Bacteraemia: trends in antibiotic susceptibility

The analysis of the distribution of bacteria implicated in nosocomial and community-acquired bacteraemia shows that gram-negative species, known to be the most frequent organisms in community-acquired bacteraemia since 2001, are now also the most frequent in nosocomial bacteraemia since 2005 (Table 3.12).

Among *S. aureus*, the percentages of methicillin-susceptibjle strains increased, independently of their origin (Tables 3.13 and 3.51); almost all methicillin-susceptible strains and 90% of MRSA strains are now susceptible to gentamicin. In the last ten years, the almost complete disappearance of gentamicin-resistant MRSA is one of the most noteworthy epidemiological events occurring in this species (Table 3.5).

During the last decade, the antibiotic susceptibility of *E. coli*, the main bacterial species responsible for community-acquired and nosocomial infections, decreased markedly, especially for

some first-line agents. Indeed, the amoxicillin susceptibility rates exhibit a 12% decrease between 1996 and 2006; less than one half of *E. coli* strains are now fully susceptible to this compound (Table 3.6). Similarly the percentage of ciprofloxacin-susceptible strains reaches 89% in 2006, resulting in a 10% decrease as compared to 1996. Such a trend is also noticed for nalidixic acid: in 2006 only 79% of the strains are fully susceptible to this compound, compared to 90% in 2000 (Table 3.6). This downward trend in fluoroquinolones susceptibility was also identified among *E. cloacae* (Table 3.7). Stratification on amoxicillin susceptibility shows that amoxicillin-resistant strains are less frequently susceptible to ciprofloxacin than susceptible strains (Table 3.8). In 2006, the percentage of extended-spectrum ß-lactamase producing strains reaches 1.6% amongst *E. coli,* a rate similar to the 1.6% reported in 1996 (Table 3.6). Since 2001 an upward trend in ESBL-producing strains is identified among *E. coli, K. pneumoniae* and *E. cloacae* species (Table 3.17). During the last decade, the decrease in cefotaxime susceptibility rates, whatever the mechanism of resistance, is constant among *E. cloacae* (80% of fully susceptible strains in 2006) (Table 3.7). Such a trend was not identified among *K. pneumoniae* and *P. mirabilis* strains during the same period.

Community-acquired infections

Streptococcus pneumoniae

Analysis of *S. pneumoniae* resistance according to age and type of sample is presented in tables 3.25 to 3.32. Between 2005 and 2006, the proportion of strains with decreased penicillin susceptibility remained stable. In 2006, strains isolated from meningitis in children (<16 years) are more often susceptible to beta-lactams than strains isolated from meningitis in adults. The proportion of susceptible strains was significantly different in both groups of age for penicillin G (73.1% *versus* 63.1%; p = 0.038), but not for amoxicillin (83.7% *versus* 82.5%; p=0.4) or cefotaxime (98.1% *versus* 95.4%; p = 0.12).

In spite of an increase in susceptibility to erythromycin since 2001, about 40% of invasive pneumococcal strains are still resistant to erythromycin in 2006 (36.6% in adults, 39.5% in children <16 years). When considering fluoroquinolone resistance, the proportion of pneumococcal strains with acquired mechanism(s) of fluoroquinolone resistance (<1%) remained stable since 2001, those strains being more frequently observed in bacteraemia in adults.

Mycobacterium tuberculosis

The results of *Mycobacterium tuberculosis* drug resistance are presented after stratification on prior antituberculosis treatment as recommended by WHO because it is the most important risk factor for drug resistance.

Table 3.33 shows that the proportion of strains susceptible to isoniazid, rifampicin and ethambutol, three of the four first line drugs, reaches 93.9% (94.2% in 2005) in the absence of prior treatment history (« primary » or « initial » resistance). As expected, this proportion fall to 84.7% (84.8% in 2005) in case of prior treatment (« secondary » or « acquired » resistance) (Table 3.33). As in the previous years, the most prevalent resistance is isoniazid resistance (5.9% of primary resistance and 14.4% of secondary resistance). Primary resistance to rifampicin remains around 1%, and all of the resistant strains are multi-resistant strains (i.e. resistant to both rifampicin and isoniazid). Acquired resistance to rifampicin (12.6%) is 10 times more prevalent than among new patients. Patients with unknown or doubtful previous history of treatment have resistance rates similar or close to those of new patients. As in previous years, the region with the highest resistant rates is the « Ile-de-France » region (Tables 3.34 and 3.35). Primary and secondary resistance rates are relatively stable since 2000, and close to values observed in other Western European countries [10].

Documented infections in animals

Neonatal diarrhoea in calf constitutes the major pathological setting for antimicrobial use in cattle. The main target species is *E. coli* (Table 3.48), and the particularly low and constant percentages of susceptibility of *E. coli* strains to amoxicillin over years is to be noticed (around 10%). Resistances to third generation cephalosporins and fluoroquinolones are identified in cattle as well.

Bacterial respiratory infections in cattle are mainly due to the two species *Pasteurella multocida* and *Mannheimia haemolytica*. Even if both retain very high susceptibility rates to all antimicrobials (Tables 3.49 and 3.50), data from 2006 show a decreased susceptibility rate to tetracyclin (*Pasteurella multocida, Mannheimia haemolytica*), as well as to amoxicillin, sulfonamides and quinolones (*Mannheimia haemolytica*).

2.4 Surveillance of multidrug-resistant bacteria (type 4 information)

Methicillin-resistant *Staphylococcus aureus* (MRSA)

The overall proportion of MRSA among all *S. aureus* strains is very homogenous in French hospitals. Indeed, it is around 27% for a majority of networks in 2006, 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 33% in acute care, and between 62 and 71% in chronic or long-term care facilities. The proportion of MRSA remained stable (around 40%) in the Paris and North region of the nosocomial network (CCLIN) between 1998 and 2004, but decreased afterwards (Table 4.1). This decrease was more noticeable in acute-care hospitals of the « Assistance Publique-Hôpitaux de Paris » (AP-HP) network. Indeed, the MRSA proportion fell from 39% in 1993 to 20% in 2006 (Table 4.2 and Figure 4.3). The decrease was even more drastic in Intensive Care Units of the AP-HP network, where MRSA proportion dropped from 55% in 1993 to 22% in 2006 (Figure 4.4). A decrease was also observed in the South-West region of the nosocomial network (CCLIN), where the MRSA proportion dropped from 41% in 1998 to 28% in 2006 (Table 4.3). In the other networks, MRSA trends are encouraging, with a slight decrease in 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.

Most MRSA strains (between 92 and 94%) are gentamicin-susceptible, and the proportion of tobramycin-susceptible strains increased steadily since 2000, reaching 37% in 2006 (Tables 4.7 to 4.9). Between 45 and 57% 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 ESBL-producing *Escherichia coli* and a concomitant decrease in *Enterobacter aerogenes* and *Klebsiella pneumoniae*, depending on the network (Tables 4.12 to 4.16 and Figures 4.7 and 4.8). In 2006, in the AP-HP network, around 50% of ESBL strains belong to the *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), 43% of ESBL strains belong to *E. coli* species (6% in 2000) and 22% to *Enterobacter aerogenes* species (56% in 2000). In REUSSIR network, the ESBL-producing *E. coli* proportion rose from 8% in 2000 to 43% in 2006. This increase is linked to 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 and the United Kingdom [11-12] must prompt us to the greatest vigilance concerning these MDR strains that require specific monitoring and control procedures.

In the yearly cross-networks survey of Onerba, the overall prevalence of ESBL-positive enterobacteria was 1.1% among all enterobacteria isolated in urines of ambulatory patients during the study period and 67% of them were *E. coli* strains. Among 48 *E. coli* strains, 40 were CTX-M positive (Tables 4.25 and 4.27). Among ESBL carriers, 62% had history of previous hospitalisation. Among the 10 patients with no history of previous hospitalisation, chronic disease or contact with health care system, 80% were female and all harboured CTX-M positive *E. coli* (Table 4.26).

In 2006, 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 4.17 to 4.19 and Figure 4.9).

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 2006 (Table 4.21) around 40%. Among the resistant strains, 9.8% were also resistant to imipenem. Multidrug-resistant isolates are mainly isolated in ICUs (Table 4.22) and are observed in all departments under surveillance by the South-West network (Table 4.23).

Multidrug-resistance of *Mycobacterium tuberculosis* (defined as simultaneous resistance to isoniazid and rifampicin) remains stable since 2002, with 1.2% to 1.4% of all strains being concerned (Table 4.24). This low rate of multidrug-resistance in France is similar to rates observed in other European countries [10].

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