Chapter VI

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

1 Methodology

The data presented in this report and the themes discussed in this chapter are classified into the four major information categories defined in ONERBA's methodologcal guidelines *(1)*, 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; that is, to identify susceptible, intermediate and resistant strains within a species. The strains are isolated from diagnostic samples, whether or not there is a documented infection (colonization, carrier-state).
Global resistance statistics for the major bacterial species are extracted from databases of the laboratories of the 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, blood cultures yielding coagulase-negative *staphylococci*).
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 and 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 one clearly susceptible subpopulation (24-26 mm mode) and a clearly resistant one (6 mm mode) widely separated by the two critical values. *E. coli* behaviour toward AMC shows an unimodal distribution (21 mm mode) over a wide zone spread on either side of "D" (21 mm), the upper critical diameter *(figure 1.2)*. 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, with unimodal distribution (21-22 mm mode). However, for AMX-R strains, AMC diameter 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 2003 *(3)*.

Figure 1.3 shows that *E. coli* susceptibility to cefotaxime is highly homogenous, most strains being very susceptible (inhibition diameter ≥ 35 mm). However, a small proportion of strains (higher than in 2003) is highly resistant, possibly due to the emergence of strains producing ESBL of CTX-M type.

Figure 1.4 shows *E. coli* behaviour toward imipenem. The distribution is unimodal (modal inhibition diameter: 31 mm), despite a drop at 35 mm relative to the upper detection limit of some automated cameras. Similar results are observed for *E. cloacae (figure 1.34)* (modal inhibition diameter: 28 mm) and *E. aerogenes (figure 1.24)* (modal inhibition diameter: 29 mm). However, in the *E. aerogenes* subpopulation resistant to cefotaxime *(figure 1.28)*, we observe some rare isolates I or R to imipenem, with inhibition diameters ranging between 12 and 20 mm.

Figure 1.5 shows that *E. coli* susceptibility to nalidixic acid (NAL) is trimodal, as it was in 2003: a susceptible subpopulation with 26 mm modal inhibition diameter, a highly resistant subpopulation (6 mm mode) and an intermediate subpopulation whose limits extend between both previous subpopulations. *Figure 1.7* shows the behaviour of the same isolates toward ciprofloxacin (CIP) It also distinguishes three populations, with almost all (93%) isolates being susceptible to CIP. After stratification on susceptibility to nalidixic acid, *figures 1.8 and 1.9* on the one hand and *1.16 and 1.18* on the other hand, distinguish four subpopulations. All isolates susceptible to NAL are also fully susceptible to CIP. For NAL-resistant isolates, there are 3 subpopulations (modes: 6 mm, 9-10 mm, and 25-28 mm). Finally, over half of NAL-R isolates are CIP-resistant. There is no change in distributions compared to 2002 and 2003 *(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 (6 mm mode) and an intermediate population located between "d" and "D".

Figures 1.19 and 1.21 show the susceptibility of ESBL-producing *E. coli* strains to third generation cephalosporins (cefotaxime, ceftazidime, cefepime). Overall, there are two subpopulations, one highly resistant with a modal diameter of 6 mm, and one that is very spread with modal diameters depending on the cephalosporin tested: below "D" for cefotaxime and ceftazidime, and above "D" for cefepime.

Drawing inhibition diameters of these three cephalosporins for ESBL-producing *E. cloacae* and *E. aerogenes* isolates shows drastically different distributions depending on the compound and the species. Most *E. cloacae* species are highly resistant to cefotaxime and to ceftazidime, while most ESBL *E. aerogenes* populations extend on either side of "D". However, ESBL strains of the two species show the same susceptibility to cefepime: most of the population has a 27-28 mm modal inhibition diameter and could therefore be considered susceptible according to the breakpoints.

For *Pseudomonas aeruginosa*, the piperacillin-susceptible population with 30 mm mode *(figure 1.46)* is more clearly defined in relation to " D " than the ticarcillin-susceptible population, which extends on either side of " D " *(figure 1.45)*. *P. aeruginosa* susceptibility to piperacillin *(figure 1.46)* is quite similar to that for the piperacillin-tazobactam combination *(figure 1.47)*. The small difference existing between both drugs is illustrated in *figures 1.51 and 1.52* which show susceptibility to the combination in piperacillin-susceptible and non-susceptible strains. The susceptibility to the combination of piperacillin-resistant isolates is restored for only a small number of isolates; distribution is bimodal: a highly resistant population (6 mm mode) and a 15-16 mm mode population on either side of "d" and "D".

Animal Data

Figures 1.57 and 1.59 show *E. coli* susceptibility to ceftiofur, a third generation cephalosporin used in veterinary medicine. The 2004 data make it possible to identify strains with reduced susceptibility and even ceftiofur-resistant strains, whose number shows a slight increase compared to 2003

data in bovines, swine and poultry. This observation might be linked to increased emergence of ESBL-producing strains of animal origin. *Figure 1.60* shows that nearly 20% of *E. coli* strains isolated from bovine are intermediate or resistant to enrofloxacin. Two subpopulations seem to be present: one very spread and spanning the susceptible and intermediate categories, and one highly resistant. *Figure 1.61* shows *S. uberis* strain susceptibility to tetracycline. We observe three subpopulations, one of which is susceptible, with a 27-28 modal diameter, and another highly resistant with a 6 mm modal diameter.
Figures 1.55 and 1.56 show cotrimoxazole susceptibility in *E. coli* isolated from poultry or swine. *Figure 1.55* display three subpopulations: one susceptible (28 mm mode), one resistant (6 mm mode) and one situated around the upper critical threshold (16-17 mm mode); these three subpopulations are not present in strains isolated from swine. *Figure 1.56* shows that most of the population is resistant (6 mm mode).

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

Staphylococcus aureus
S. aureus resistance to methicillin (MRSA) will be reviewed in appendix 4 (multidrug-resistant bacteria). Overall, 11% of *S. aureus* strains isolated in the hospital are penicillin G-susceptible *(table 2.1)* and 32% are MRSA. Most strains are susceptible to gentamicin (97%), while 70% are susceptible to kanamycin (and therefore to amikacin) and to tobramycin. Two thirds of the strains are susceptible to erythromycin and to fluoroquinolones, and > 90% are susceptible to pristinamycin, fusidic acid, cotrimoxazole and rifampicin. Resistance to glycopeptides remains rare (0.1%). These results are comparable to those observed in 2003.
MRSA strains are far less susceptible to all antibiotics than methicillin susceptible *S. aureus* strains (MSSA), including aminoglycosides (15% *versus* 96% to kanamycin, 17% *versus* 97% to tobramycin and 93% *versus* 99% to gentamicin), erythromycin (43% *versus* 79%) and fluoroquinolones (9% *versus* 91%) *(tables 2.2 and 2.3)*.

Enterococcus
Enterococcus faecalis is more often isolated than *Enterococcus faecium* (2283 strains *versus* 159 in 2004) in the REUSSIR network *(tables 2.4 and 2.5)*.
E. faecalis remains more susceptible to penicillin A (> 99%) and furans (96%) than *E. faecium* (33% and 34%, respectively). Glycopeptide-resistance in *E. faecium* remains very rare (< 1%) in 2004 in France, as in previous years. In the EARSS network, glycopeptide-resistance among *E. faecium* strains isolated in France is reported to be 5% in 2004. The difference with the present report is due to the fact that one of the hospitals submitting data to EARSS was facing an outbreak while resistance rates in the other hospitals was < 1%. Several European countries such as Portugal (42%), Italy (21%), Greece (20%) and Ireland (22%) have very high glycopeptide-resistance rates in 2004 *(5)*. Belgium reports 5% resistance to vancomycin in *E. faecium* in 2004, and Germany reports 11% of VRE among *E. faecium (5)*.

Enterobacteria
Tables 2.6 to 2.17 show differences in susceptibility rates among enterobacterial species:
– to amoxicillin (AMX): about 54% of *E. coli* strains are susceptible;
– to the amoxicillin-clavulanic acid combination: 68% of *E. coli* strains are susceptible (slightly over 10% more than for AMX alone), 78% of *P. mirabilis*, 82% of *K. pneumoniae* and 75% of *K. oxytoca strains*;
– to cefotaxime for groups 1 and 2 enterobacteria (susceptible rates between 96% and 98%) compared to group 3 enterobacteria that naturally produce ampC (susceptible rates 46% to 90%). *E. aerogenes* is the species least frequently susceptible to cefotaxime (46%);
– to fluoroquinolones (particularly ciprofloxacin) for groups 1 and 2 enterobacteria (85% to 94%) compared to group 3 enterobacteria (36% to 87%). Ciprofloxacin is more often active than other fluoroquinolones. Some species are very susceptible (91% of susceptibility for *E. coli*, 99% for *P. vulgaris),* while others are susceptible in less than 90% of cases (85% of susceptible for *P. mirabilis*, 84% for *M. morganii*, 80% for *C. freundii*), and finally some species are rarely susceptible (49% of susceptible for *E. aerogenes*, 36% for *P. stuartii*);
– to amikacin where it can be noticed that *E. aerogenes* and *S. marcescens* remain less frequently susceptible (67% and 64%, respectively) than other species (susceptible rates > 95%).

Pseudomonas aeruginosa* and *Acinetobacter baumannii
These species are almost exclusively acquired in the hospital setting.
P. aeruginosa (table 2.18) is slightly less often susceptible to piperacillin (79%) and to imipenem (82%) than to ceftazidime (83%). Ciprofloxacin susceptibility rate is as low as 71%.
A. baumannii (table 2.19) is more often susceptible to ticarcillin (65%) than to piperacillin (58%). Ceftazidime is less often active than broad-spectrum penicillins such as ticarcillin (36% *vs* 65%, respectively) or ticarcillin in combination with clavulanic acid (70%). Imipenem remains the most active antibiotic against this species (97%).

Susceptibility in strains isolated from animals
Comparison of 2003 with 2004 data *(table 2.39)* shows stability of very low levels of *E. coli* susceptibility to amoxicillin and to

the amoxicillin-clavulanic acid combination in bovines (15.9% in 2004). It must be noted that susceptibility rates to streptomycin (19%) and to tetracycline (21.9%) are low as well.
Amongst *E. coli* strains isolated from poultry and swine *(tables 2.41 and 2.42)*, about 45% are susceptible to amoxicillin. Susceptibility is often restored by clavulanic acid, and over 99% of strains are susceptible to ceftiofur (third generation cephalosporin). About 90% to 95% of *E. coli* strains isolated from poultry and swine are susceptible to fluoroquinolones; as in bovine species, while tetracyclin shows lowest susceptible rates (12% to 20%).

Trends in susceptibility

S. aureus

Global *S. aureus* susceptibility to methicillin was 68% in 2004 *(table 2.20)*, a figure identical to that for 2003. Susceptibility to gentamicin is also stable at 97%. Gentamicin-resistant strains are mainly found among methicillin-resistant strains (7.4%) as compared to 0.8% among methicillin-susceptible strains *(tables 2.21 and 2.22)*.

E. faecalis

Although *E. faecalis* susceptibility to ampicillin remains high (99%), frequency of high resistance level to gentamicin has decreased from 30% in 2003 to 20.5% in 2004 ($p < 0.01$), reverting back to levels close to those found in 2000 *(table 2.23)*.

E. coli

No trend in *E. coli* susceptibility was observed for most antibiotics but for fluoroquinolones *(table 2.25)*. Indeed, there is a continuous decrease in susceptibility to quinolones; e.g. susceptibility to ciprofloxacin has fallen from 95% to 91% ($p < 0.01$) in five years.

K. pneumoniae

K. pneumoniae susceptibility to cefotaxime and to ceftazidime has decreased significantly between 2000 and 2003, dropping from 99% to 96% for cefotaxime ($p < 0.01$ for both cefotaxime and ceftazidime) *(table 2.30)*. However, the percentage of susceptibility to cefotaxime in 2004 is identical to that for 2003. Susceptibility to ciprofloxacin remains close to that for 2003, at 94%.

E. aerogenes

E. aerogenes susceptibility rates to cefotaxime, ceftazidime and fluoroquinolones *(table 2.27)* are higher in 2003 and 2004 than they were in 2000 and 2001 ($p < 0.01$ for all three antibiotics);this is probably due to a decrease in the number of ESBL-producing strains *(tables 4.13 and 4.14)*.

E. cloacae

In contrast to *E. aerogenes*, *E. cloacae* susceptibility to third generation cephalosporins and to fluoroquinolones has remained very stable since 2000 *(table 2.28)*.

P. aeruginosa

P. aeruginosa susceptibility to ceftazidime is relatively stable at 83% in 2004 compared to 84% in 2000 *(table 2.34)*. The trend toward statistically significant decrease in susceptibility to imipenem between 2000 and 2003 (84.6% to 81.1%; $p < 0.01$) seems to have been reversed in 2004, but this observation has to be confirmed.

A. baumanii

Trends in *A. baumannii* susceptibility, which declined constantly until 2003, has increased for several drugs in 2004 *(table 2.35)*: susceptibility to ceftazidime increased from 28% in 2003 to over 35% in 2004. Similarly, susceptibility to imipenem shows a slight increase (95.4% in 2003 *versus* 97% in 2004). Susceptibility to ciprofloxacin, which had decreased from 47% in 2000 to 33% in 2003 ($p < 0.01$), rose to 41.6% in 2004.

2.3 *Bacterial resistance of infection isolates documented in specific epidemiological settings: statistics and risk factors (type 3 information)*

Tables 3.1 to 3.53 present 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

Table 3.8 shows that, between 1996 and 2004, there was a constant increase in S. aureus susceptibility to gentamicin, that now reached nearly 100%. This is clearly linked to the increase in MRSA susceptibility to gentamicin: from 53% in 1996 to 95% in 2004, while susceptibility to gentamicin in MSSA strains remained stable, at nearly 100% during the same period of time.
Between 1996 and 2004, susceptibility of E. coli strains isolated from blood cultures remained stable for most antibiotics, except two for which there was a decrease in susceptibility: a drop from 60% to 48% for amoxicillin and a drop from 98% to 90% for ciprofloxacin *(table 3.10 and figure 3.2)*. Of interest, 1.7% of E. coli strains isolated from bacteraemia in 2004 produced extended-spectrum β-lactamases, while in 2001 this proportion was only 0.2%.
Stratification on amoxicillin susceptibility shows that amoxicillin-resistant strains are less frequently susceptibility to gentamicin, cefotaxime and fluoroquinolones than susceptible strains *(tables 3.10 and 3.12)*.
Table 3.16 shows that susceptibility rates of E. coli strains isolated between 2001 and 2004 from community-acquired bacteraemia remained stable;on the contrary, there was a decreased in rates of antibiotic susceptibility for strains isolated in hospital-acquired bacteraemia during the same

period. Among the latter, less than 70% of amoxicillin-resistant strains are susceptible to ciprofloxacin *(table 3.17)* and less than 20% of nalidixic acid-resistant strains are susceptible to ciprofloxacin *(table 3.18)*.

Place of acquisition and antibiotic susceptibility

Distribution of microorganisms isolated from community- and hospital-acquired bacteraemia is drastically different *(tables 3.11 and 3.23)*; *S. aureus* represents about 20% of organisms isolated from hospital-acquired bacteraemia, and 10% of community-acquired bacteraemia; *E. coli* represents nearly 40% of organisms isolated from community-acquired bacteraemia, and about 20% of hospital-acquired bacteraemia. *Streptococcus pneumoniae* is most often isolated from community-acquired bacteraemia, while *Pseudomonas aeruginosa* and fungi are almost exclusively isolated from hospital-acquired bacteraemia.
For *S. aureus* bacteraemia, it is well known that nosocomial origin is closely linked to a higher risk of resistance to beta-lactams *(table 3.12)*. Overall, nosocomial MSSA strains are as susceptible to aminoglycosides, macrolides, rifampicin and fusidic acid than community-acquired strains, but less often susceptible to fluoroquinolones (85% *versus* 96%) *(tables 3.3 and 3.13)*.
The frequency of resistance in coagulase-negative staphylococci isolated from bacteraemia is a cause for concern, since over 60% of these strains are methicillin-resistant *(table 3.14)*. In addition, susceptibility rates to other antimicrobials are seldom over 50% with the exception of vancomycin and pristinamycin susceptibility.
For enterobacteria isolated from community-acquired bacteraemia, susceptibility to the major antimicrobials used in the treatment of serious infections (third generation cephalosporins, aminosides, fluoroquinolones) remains almost stable (95 to 100%). However, susceptibility to these antimicrobials in enterobacteria isolated from hospital-acquired bacteraemia only reaches 85%. Therefore, the risk of failure may not be overlooked when these antimicrobials are used in monotherapy *(tables 3.16 and 3.39)*. The difference is linked to two factors. First, differences in susceptibility rates within a species, whether strains are community- or hospital-acquired, as it is the case for *E. coli* *(tables 3.16 to 3.18)*. Second, it is also linked to the much higher proportion of "hospital" species with usually higher resistance rates (*Enterobacter spp, Serratia spp*…) in hospital-acquired than in community-acquired bacteraemia *(tables 3.11 and 3.23)*.

Community-acquired infections

Streptococcus pneumoniae
Analysis of *S. pneumoniae* resistance according to age and type of sample is presented at *tables 3.28 to 3.35*. In 2004, strains isolated from paediatric (< 16 years) meningitis or bacteraemia are more often resistant to beta-lactams and macrolides than strains isolated from meningitis or bacteraemia in adults. Fluoroquinolone-resistant strains are more frequent in adults, although their proportion remains very low.

Mycobacterium tuberculosis
The WHO recommends that *Mycobacterium tuberculosis* resistance statistics be stratified on prior antituberculosis treatment.
Table 3.36 shows that the percentages of strains susceptible to isoniazid, rifampicin and ethambutol, three of the four first line drugs reach nearly 96% in the absence of prior treatment history ("primary" or "initial" resistance). This percentages fall around 80% in case of prior treatment ("secondary" or "acquired" resistance). The most frequent resistance is isoniazid resistance (4.1% of primary resistance and 17.5% of secondary resistance). As in previous years, the region with higher resistant rates is the "Île-de-France" region *(table 3.37)*. Observed proportion of resistance could be higher in some regions due to the small number of strains isolated. Primary and secondary resistance rates are relatively stable since 2000, and close to values observed in other Western European countries *(7)*.

Documented infections in animals
Neonatal diarrhoea in calf is a major pathological setting for the use of bovine antibiotics. The main targeted species is *E. coli* *(table 3.50)*. It should be noted that the percentage of *E. coli* strains susceptible to amoxicillin (9.3%), and to the amoxicillin-clavulanic acid combination (33.7%) are extremely low. Resistance to the newer cephalosporins and fluoroquinolones is now emerging.
In bovines, bacterial respiratory infections are mainly due to two species: *Pasteurella multocida* and *Mannheimia haemolytica;* both species retain very high susceptibility to all antibacterials *(tables 3.51 and 3.52)*.

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

Methicillin-resistant Staphylococcus aureus (MRSA)
The global MRSA percentage among *S. aureus* is very homogenous in French hospitals: between 30 and 40% for most hospitals in 2004, regardless of the type of clinical sample *(tables 4.1 and 4.4)*. However, this percentage varies depending on the type of hospitalisation: between 25 and 33% in acute care, and between 58 and 66% in chronic or long-term facilities. MRSA percentage remained stable circa 40% in the Paris and North region of the nosocomial network (CCLIN) between 1998 and 2004 *(table 4.1)*, but it decreased in acute-care facilities of the "Assistance Publique-Hôpitaux de Paris" network during the same period. In fact, this percentage fell from 39% in 1993 to

25% in 2004 *(table 4.2 and figure 4.2)*. This decrease was even more significant in Intensive Care Units of the AP-HP network, where MRSA proportions fell from 55% in 1993 to 25% in 2004 *(figure 4.4)*. In the other networks, MRSA trends is encouraging, with a decreased MRSA percentage among *S. aureus* for most networks, although observed decreases are less pronounced. This downward trend is observed in an international, and particularly European, context of quasi-generalized rise of this indicator.
Most MRSA strains (between 85 and 95%) are gentamicin-susceptible, and the percentage of tobramycin-susceptible strains has shown constant increase since 2000, reaching 25% in 2004 *(tables 4.5 and 4.8)*. Between 45 and 50% of MRSA strains are erythromycin-susceptible. MRSA susceptibility to other antimicrobials such as fusidic acid, rifampicin, pristinamycin and cotrimoxazole is high, exceeding 90%; however, resistance to fluoroquinolones remains high, above 90%.

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

In the past few years, the distribution of enterobacterial species producing extended-spectrum β-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 4.11 to 4.13)*. In 2004, in the AP-HP network, 55% of ESBL strains belong to *E. coli* species. This trend is also observed in other regions of France, with a slight time lag. 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 and the United Kingdom *(8)* must prompt us to the greatest vigilance concerning these MDR strains that requires specific monitoring and control procedures. Overall, ESBL-positive strains remain highly resistant to all antimicrobials except carbapenems.

Other multidrug-resistant bacteria

In *Mycobacterium tuberculosis*, multidrug-resistance (defined as simultaneous resistance to isoniazid and rifampicin) remains stable since 2002, with 1.3% to 1.4% of all strains being concerned *(table 4.21)*. This low rate of multidrug-resistance in France, is similar to rates observed in other European countries such as Hungary, Sweden or Poland (1.6% in each country), but lower than rates observed in Italy (3.1%) or Spain (3.6%) (7).

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