# Chapter VI

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

## 1 Methodology

The data presented in this report and the comments in this chapter are classified in the four major categories defined in ONERBA's methodological guidelines *(1)* and summarised below.

### Subpopulation analysis of isolates according to their level of susceptibility in major bacterial species of medical interest (type 1 information)

The goal is to identify and describe subpopulations of strains according to their level of susceptibility.

To do so, quantitative data (inhibition zone diameters or MICs) are required. This type of data is useful for establishing the critical values that define clinical categories, or for detecting the emergence of strains with unusual behaviour, not detectable by using the qualitative S, I, R classification: for example, reduced susceptibility strains still within the susceptibility category, or highly resistant strains.

### Global statistics for antimicrobial resistance in major bacterial species of medical interest (type 2 information)

The goal is to assess the percentage of strains with acquired resistance. This is the percentage of susceptible, intermediate or resistant strains within the species. Strains are those isolated in clinical diagnostic samples, whether or not there is documented infection (colonization, carriage).

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

This type of data is useful for establishing spectrums of activity or clinical indications for antimicrobials.

### Resistance of bacterial isolates from well defined infections in specific epidemiological situations (type 3 information)

The goal is to determine, in particular epidemiological situations, the probability of activity of the major antimicrobials. This requires clinical information, except for closed site samples (such as cerebro-spinal fluid) or blood cultures whose interpretation does not generally create confusion (except in rare cases such as blood cultures with coagulase negative staphylococci).

These data are essential in defining indications for antimicrobials as they appear in the summaries of product characteristics (RCP), and provides valuable information for clinicians, as well as for scientific societies and health agencies who draw up recommendations for the proper use of antimicrobials.

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

The goal is to assess the magnitude of the problem presented by multidrug-resistant bacteria (MDR): methicillin-resistant *Staphylococcus aureus* (MRSA), enterobacteria producing extended-spectrum betalactamases (ESBL) or resistant to carbapenems, glycopeptide-resistant enterococci (GRE), etc.

Given their frequency and therapeutic consequences, MDR bacteria warrant specific surveillance in human, in hospital and community settings, as well as surveillance in animals and in the environment.

Several national reference centres (NRC) and veterinary networks monitor multidrug resistance of certain community-acquired species (*Streptococcus pneumoniae, M. tuberculosis, Salmonella* Typhimurium). C-CLIN networks monitor MRSA, ESBL enterobacteria and sometimes other MDR bacteria. Some indicators (incidence per 100 admissions and per 1 000 hospital-days, place of acquisition) have been standardised within the *Réseau Alerte Investigation et Surveillance des Infections Nosocomiales* (RAISIN). RAISIN results are published elsewhere *(2)*. Other indicators (percentage of MDR in the species, co-resistance to other antimicrobials, etc.) are collected by some networks independently from RAISIN.

## 2 Presentation of statistical data

### 2.1 *Subpopulation analysis, in major bacterial species of medical interest, of isolates according to their level of susceptibility (type 1 information) [Appendix 1]*

*Figures 1.1, 1.2, 1.10 and 1.11* make it possible to compare activity of the amoxicillin-clavulanate combination (AMC) to amoxicillin alone (AMX) in *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 subpopulation (mode, 6 mm) distinctly separated by the critical values. *Escherichia coli* behaviour with respect to AMC shows unimodal distribution (mode, 21 mm) very spread out and on both sides of "D" (21 mm), critical upper diameter *(figure 1.2)*. Stratification on amoxicillin susceptibility (susceptible strains, S, and non-susceptible strains, i.e. intermediate and resistant, R) shows two distinct populations *(figures 1.10 and 1.11)*. Behaviour of AMX-S strains toward AMC is similar to that with AMX, with unimodal distribution (mode, 21-22 mm). However, for AMX-R strains, AMC diameter distribution is very heterogeneous. AMC made it possible to restore susceptibility (diameter $\geq$ 21 mm) in a very small proportion of AMX-R strains, suggesting high level of resistance to amoxicillin. Distributions observed were similar to those seen in 2002 *(3)*.

If we compare distributions to those observed for strains isolated from bovines with respect to AMC *(figure 1.45)*, distribution is bimodal with presence of a highly resistant population (mode, 6 mm), which is not the case in man.

*Figure 1.3* shows that the behaviour of *E. coli* with respect to cefotaxime is very homogenous, with most strains being very susceptible (inhibition zone diameter $\geq$ 35 mm). Compared to 1999, the proportion of strains with < 26 mm diameter is greater *(4)*. However, the characteristics of the two networks (REUSSIR and AZAY-resistance) are not identical for the two years, making it necessary to place this result in perspective.

As for strains isolated in bovines *(figure 1.46)*, we observe strains with intermediate susceptibility to third generation cephalosporins (ceftiofur), possibly due to emergence of CTX-M strains *(5)*.

*Figure 1.4* shows the behaviour of *E. coli* with respect to imipenem. Distribution is unimodal (modal inhibition zone diameter: 31 mm), although there is a peak at 35 mm related to upper limit detection of some automated systems.

*Figure 1.5* shows that the behaviour of *E. coli* with respect to nalidixic acid (NAL) is trimodal, as it was in 2002: a susceptible population with a modal inhibition zone diameter of 25-27 mm, a highly resistant population (mode, 6 mm) and an intermediate population distributed between these two poles. *Figure 1.7* shows the behaviour of the same strains with respect to ciprofloxacin (CIP) and identifies three populations, with almost all strains (95%) susceptible to CIP. *Figures 1.8 and 1.9*, after stratification on susceptibility to nalidixic acid, show the presence of four populations. Strains susceptible to NAL are all susceptible to CIP. By contrast, strains resistant to NAL are much less susceptible to CIP, and we observe three distinct populations (trimodal distribution of inhibition zone diameters: 6 mm, 9-10 mm, 25-28 mm). Finally, half of the NAL-R strains are CIP-resistant. There is no distribution change compared to 1999 or 2002 *(3, 4)*.

*Figures 1.14, 1.20 and 1.25* show the behaviour of *Morganella morganii, Proteus mirabilis* and *Proteus vulgaris* with respect to nalidixic-acid. For *M. morganii* and *P. mirabilis*, distribution is trimodal, while for *P. vulgaris* it is bimodal, with absence of an intermediate population with mode 10-15 mm. The susceptible population of *P. mirabilis* strains has a mode (23-25 mm) inferior to that of the susceptible populations of the other two species (27-30 mm). This distribution difference is not observed when analysing inhibition diameters for ciprofloxacin *(figures 1.15-1.17, 1.21-1.23, 1.26)*.

Distributions of inhibition zone diameters for *Salmonella* Enteritidis are very different from those observed for *S.* Typhimurium in terms of amoxicillin *(figures 1.27 and 1.31)*, nalidixic-acid *(figures 1.29 and 1.33)* and ciprofloxacin *(figures 1.30 and 1.34)*, with lower values for diameters and modes related to *S.* Typhimurium.

As for *Pseudomonas aeruginosa*, the population susceptible to piperacillin (mode, 30 mm) *(figure 1.36)* is better defined in relation to "D" than the population susceptible to ticarcillin, which is distributed on both sides of "D" *(figure 1.35)*. The behaviour of *P. aeruginosa* with respect to piperacillin *(figure 1.36)* and to the combination piperacillin + tazobactam *(figure 1.37)* is only slightly different. This difference is highlighted in *figures 1.40 and 1.41*, which show behaviour toward the drug combination in strains susceptible or non-susceptible to piperacillin. Very few strains resistant to piperacillin are susceptible to the combination piperacillin-tazobactam.

*Figure 1.42* shows the behaviour of *Streptococcus pneumoniae* with respect to the three main β-lactams : penicillin G, amoxicillin and cefotaxime. Distribution is bimodal for all three β-lactams. The mode of the susceptible population is identical for the three drugs (< 0.01 mg/L), but the mode of the non-susceptible population is different for each drug, but identical to that observed in 2002.

*Figure 1.43* shows the behaviour of *S. pneumoniae* with respect to fluoroquinolones. Distribution is homogenous and unimodal for the two drugs tested, levofloxacin and moxifloxacin, with a mode at 0.12-0.25 mg/L for moxifloxacin, and at 1 mg/L for levofloxacin. Like in 2002, only a few rare strains are resistant to fluoroquinolones.

*Figures 1.53 to 1.55* show the behaviour of *Streptococcus uberis* strains isolated from bovine mammitis with respect to macrolides and related drugs. For the three antibiotics tested (erythromycin, lincomycin and spiramycin), behaviour is heterogenous and roughly trimodal, with results not significantly different from those obtained in 2002.

## 2.2 *Global statistics of acquired resistance for the major bacterial species (type 2 information) [Appendix 2]*

### Staphylococcus aureus

Methicillin-resistant *S. aureus* (MRSA) will be reviewed below (appendix 4, Multidrug-resistant bacteria). Overall, 10% of *S. aureus* strains isolated in hospital are susceptible to penicillin G *(table 2.1)* and 32% are MRSA. Most strains are susceptible to gentamicin (97%), and two thirds are susceptible to kanamycin (and therefore to amikacin) and to tobramycin. Two thirds of strains are susceptible to erythromycin and to fluoroquinolones, and over 90% are susceptible to pristinamycin, to fusidic acid, to cotrimoxazole and to rifampicin. Resistance to glycopeptides is still very rare (less than 0.5%). These results are similar to those obtained in 2002.

MRSA is much more rarely susceptible to all antibiotics than methicillin-susceptible *S. aureus* strains (MSSA): aminoglycoside (10% *versus* 94% to kanamycin, 13% *versus* 96% to tobramycin and 93% *versus* 99% to gentamicin), erythromycin (35% *versus* 78%) and fluoroquinolones (10% *versus* 90%) *(tables 2.2 and 2.3)*.

### Enterococci

*E. faecalis* is isolated more often than *E. faecium* (1 513 strains *versus* 109 in 2003 in the REUSSIR Network *(tables 2.4 and 2.5)*.

*E. faecalis* remains more susceptible to penicillins A (> 99%) than *E. faecium* (56%).

The same is true for furanes (96% *versus* 34%). Resistance to glycopeptides in *E. faecium* was very rare in 2003 in France (< 1%), as opposed to other European countries like Portugal (50%), Italy (25%), Greece (23%) and Ireland (19%), based on EARSS data *(6)*.

### Enterobacteria

*Tables 2.6 to 2.17* show differences in proportion of susceptible strains among enterobacterial species:

– To amoxicillin (AMX) among group-1 strains naturally susceptible to this antibiotic: about 54% of *E. coli* strains are susceptible.

– To amoxicillin-clavulanate, which restores AMX activity: 68% of *E. coli* strains are susceptible to AMC (a little over 10% more than to AMX), 79% of *P. mirabilis*, 80% of *K. pneumoniae* and 75% of *K. oxytoca*.

– To cefotaxime for group-1 enterobacteria (about 98% of *E. coli*) compared to those in group-2 (between 96% and 98%), and especially those in group-3 which naturally produce a cephalosporinase (44% to 97%). The least susceptible species is *E. aerogenes* (44%).

– To fluoroquinolones (particularly ciprofloxacin) for group-1 and 2 enterobacteria (from 85% to 95%) compared to group-3 enterobacteria (from 97% to 36%). Frequency of susceptibility to ciprofloxacin is higher than that to other fluoroquinolones. Some species are very susceptible (92% in *E. coli*, 97% in *P. vulgaris*), others are susceptible in less than 90% of the cases (85% in *P. mirabilis*, 81% in *C. freundii*), while others are rarely susceptible (43% for *E. aerogenes*, 36% for *P. stuartii*).

– To amikacin for *E. aerogenes* and *S. marcescens* (62% and 63%) compared to other, much more frequently susceptible enterobacteria (most often > 95%).

### *Pseudomonas aeruginosa and* Acinetobacter baumannii

These species are almost exclusively isolated in the hospital setting. They are naturally resistant to penicillin A, first and second-generation cephalosporins and classical quinolones. In addition, these species have often acquired resistance to other antimicrobials.

*P. aeruginosa* is a little less often susceptible to piperacillin (80%) and to imipenem (81%) than to ceftazidime (84%). The tazobactam-piperacillin association is only slightly more active than piperacillin alone (81.0% versus 79.8%).

**Susceptibility to ciprofloxacin is less frequent (about 70%).**

*A. baumannii* is more susceptible to ticarcillin (54%) than to piperacillin (50%). Ceftazidime activity (28% of strains are susceptible) is significantly inferior to that of broad-spectrum penicillins like ticarcillin (54%) or ticarcillin-clavulanate (57%). Imipenem remains the antibiotic to which this species is the most susceptible (95%) *(table 2.19)*.

### *Susceptibility of isolates from animals*

Susceptibility to amoxicillin is less frequent for *E. coli* strains isolated in bovine samples than for human isolates (18% *versus* 54%). The same is true for susceptibility to amoxicillin-clavulanate (32% *versus* 68%) *(table 2.37)*.

This does not apply to samples from poultry and pork, for which susceptibility differences compared to human samples are smaller: 42% strains susceptible to amoxicillin in animals *versus* 54% in man; 73% strains susceptible to amoxicillin-clavulanate in animals *versus* 68% in man *(table 2.39)*.

### *Stratified analysis*

ONERBA guidelines *(1)* and European recommendations *(7)* emphasize the advantages of stratifying global statistics by parameters available in the laboratory (type of patient, type of sample...). Among *Haemophilus influenzae* strains from communities and institutions isolated in outpatient laboratories, 66% are susceptible to amoxicillin. Over 80% of resistant strains produce penicillinase. Restoration of amoxicillin activity by clavulanic acid is still very satisfactory (100% of strains seem susceptible).

### Trends in susceptibility

The advisability of monitoring global susceptibility statistics regularly is illustrated in *tables 2.20 to 2.35*. The $chi^2$ trend test was used to perform statistical analysis of annual percentages of susceptibility for the most representative antimicrobial/bacterial species couples.

#### S. aureus

Global susceptibility to methicillin in *S. aureus* increased gradually, but significantly, between 2000 and 2003, rising from 64% to 68% *(table 2.20)*; $p < 0.01$, $chi^2$ trend).

In 2003, susceptibility to gentamicin is still rising ($p < 0.01$); this is due to increased susceptibility in MRSA strains, as shown in *table 2.22* ($p < 0.01$), but not in MSSA that is usually susceptible to gentamicin ($p = 0.6123$) *(table 2.21)*.

#### E. faecalis

Although *E. faecalis* susceptibility to ampicillin remains very frequent (> 99%), frequency of high-level resistance to gentamicin is increasing and has risen from 19% in 2000 to nearly 30% in 2003 ($p < 0.01$) *(table 2.23)*.

#### E. coli

Variations in *E. coli* susceptibility to major antimicrobials are minor. However, we observe a regular reduction in susceptibility to some specific antibiotics; for example, ciprofloxacin, for which susceptibility over the past four years has decreased from 95% to 92% ($p < 0.01$).

#### K. pneumoniae

Susceptibility of *K. pneumoniae* to cefotaxime and ceftazidime has decreased significantly since 2000, dropping from 99% to 96% for cefotaxime ($p < 0.01$ for cefotaxime and ceftazidime) *(table 2.30)*. Susceptibility to ciprofloxacin remains stable, around 95%.

#### E. aerogenes

Susceptibility of *E. aerogenes* to cefotaxime, to ceftazidime and to ciprofloxacin *(table 2.27)* was greater in 2002 and 2003 than it had been in 2000 and 2001 ($p < 0.01$ for all three antimicrobials). This is probably due to a decrease in the proportion of ESBL producing strains *(tables 4.13 and 4.14)*.

#### E. cloacae

By contrast to *E. aerogenes*, *E. cloacae* susceptibility to third generation cephalosporins and ciprofloxacin remains stable *(table 2.28)*.

#### P. aeruginosa

*P. aeruginosa* susceptibility to ceftazidime is remarkably stable but for imipenem *(table 2.34)*. Indeed, there was a statistically significant reduction in susceptibility to imipenem over the four-year surveillance period (84.6% to 81.1%; $p < 0.01$).

### A. baumannii

The trend in *A. baumannii* susceptibility is a cause for concern *(table 2.35)*: susceptibility to ceftazidime started to decrease in 2001 and remained low until 2003 ($p < 0.01$). In 2003, susceptibility to imipenem dropped drastically compared to previous years (95% *versus* 99 to 100%). Susceptibility to ciprofloxacin also decreased between 2000 and 2003, dropping from 47% to 33% ($p < 0.01$).

## 2.3 *Antimicrobial resistance in infections isolated in well-defined epidemiological settings : statistics and risk factors (type 3 information) [Appendix 3]*

Examples of resistance statistics established by several networks for documented infections in specific epidemiological settings (type of infection, nosocomial/community, etc...) are presented in *tables 3.1 to 3.41*.

### Bacteraemia: trends in susceptibility to antimicrobials

The data in *table 3.7* show that between 1996 and 2003 susceptibility to gentamicin in *S. aureus* strains isolated from blood cultures has increased, approaching 100%. This can be explained by the clear rise in susceptibility to gentamicin, in MRSA, which has increased from 53% to 97% between 1996 and 2003. In the same period, susceptibility to gentamicin in *S. aureus* strains susceptible to methicillin has remained stable.

Between 1996 and 2003, susceptibility of *E. coli* strains isolated from blood cultures has remained stable with respect to most antimicrobials except amoxicillin (60% to 48%) and ciprofloxacin (98% to 92%) *(figure 3.2 and table 3.8)*. Stratification of strains based on susceptibility to amoxicillin (AMX) shows that AMX-R strains are susceptible to gentamicin a little less frequently than AMX-S strains *(table 3.10)*. In addition, there is a greater reduction of susceptibility to ciprofloxacin in AMX-R strains (96% to 87%) than in AMX-S strains (100% to 97%).

This trend is reversed for *K. pneumoniae* *(table 3.9 and figure 3.4)*. In fact, frequency of susceptibility to ciprofloxacin has increased from 86% to 95% between 1996 and 2003. This increase is probably related to the reduction of *K. pneumoniae* strains that produce ESBL *(tables 4.12 to 4.14)*. This hypothesis is reinforced by an increased frequency in the susceptibility of this species to cefotaxime *(table 3.9 and figure 3.3)*.

Comparison of susceptibility frequency in *E. coli* strains isolated in community-acquired bacteraemia *(table 3.16)* with susceptibility in strains isolated from urine samples of community-acquired infections in women *(table 3.2)* shows that susceptibility percentages in strains isolated from blood cultures are globally similar to those for strains from urine samples. This is due to the fact that *E. coli* bacteraemia is very often of urinary origin.

### Bacteraemia in hospital settings: relation between nosocomial/community origin and susceptibility to antimicrobials

The distribution of micro-organisms isolated in community and nosocomial bacteraemia was very different *(tables 3.11 and 3.23)*: *S. aureus* accounted for over 20% of bacteria isolated in nosocomial bacteraemia, and about 10% from community bacteraemia. By contrast, *E. coli* accounted for almost 40% of micro-organisms isolated in community bacteraemia, and 15% to 20% of those isolated in nosocomial bacteraemia. *P. aeruginosa* and fungi were almost exclusively isolated in nosocomial bacteraemia, while *Salmonella* bacteraemia were most always community-acquired.

For *S. aureus* bacteraemia, it is well known that nosocomial acquisition exposes to a much higher risk of resistance to β-lactams (MRSA) than community acquisition *(table 3.12)*.

Nosocomial MSSA strains did not seem more resistant to aminoglycosides, macrolides, rifampicin, fusidic acid and fluoroquinolones than community-acquired MSSA *(table 3.13)*. However, as expected, MSSA strains were much more often susceptible to these antibiotics (82-100%) than MRSA strains (10-86%), whatever the origin as shown in *table 3.3*.

Susceptibility of enterobacteria isolated in community-acquired bacteraemia to the major antibiotics used to treat severe infections (third generation cephalosporins, aminoglycosides fluoroquinolones) was almost constant (95-100%). However, susceptibility to these antibiotics in enterobacteria from nosocomial bacteraemia was only about 90% (87-95%), thereby exposing patients to a risk of treatment failure in case of first-line monotherapy with these antibiotics *(tables 3.16 and 3.24)*.

This is related primarily to susceptibility differences within the same species when comparing

community versus nosocomial strains. For example, this was the case for *E. coli* *(table 3.16)*, whether strains were susceptible or not to amoxicillin *(table 3.17)* or to nalidixic acid *(table 3.18)*. This is due to a much higher proportion of nosocomial species with a high frequency of resistance (*Enterobacter* spp., *Serratia* spp., etc...) in

nosocomial as opposed to community bacteraemia *(tables 3.11 and 3.23)*.

## Infections in the community

### *Streptococcus pneumoniae*

The analysis of *S. pneumoniae* resistance as a function of age and type of sample is presented in *tables 3.28 to 3.37*. Strains isolated in children (< 16 years) with meningitis or bacteraemia in 2003 were not more often resistant to $\beta$-lactams than strains from adult meningitis or blood cultures. However, strains are more resistant to macrolides and cyclines.

In children, strains isolated from acute otitis media (AOM) are much more often antibiotic-resistant than strains isolated from meningitis. This is the case for penicillin G (34,8% *versus* 92.8%; p < 0,01), erythromycin (27.2% *versus* 43.0%; p < 0.01) and cotrimoxazole (53,4% versus 73.8%; p = 0.03). This is due to the fact that in France tympanocentesis is performed mainly in case of AOM treatment failure.

### *Mycobacterium tuberculosis*

For *Mycobacterium tuberculosis*, the species for which there is no saprophytism or commensalism, and for which isolation is equivalent to tuberculosis infection, the WHO recommends stratifying resistance statistics according to history of antituberculous treatment.

*Table 3.38* shows that the percentage of strains susceptible to isoniazid, rifampicin and ethambutol, three of the four first line drugs, is close to 94% in the absence of previous treatment ("primary" or "initial" resistance), but decreased to 82% in previously treated patients ("secondary" or "acquired" resistance). There is more frequent resistance to isoniazid (5.4% primary resistance and 13.6% secondary resistance) than to rifampicin. The only region where resistant strains were more frequent was the Paris metropolitan area *(table 3.39)*, although it is possible that the proportion of resistant strains may be higher in other regions, due to the small number of strains isolated. In 2003, rates of primary and secondary resistance to first-line antituberculous drugs were not statistically different than in previous years.

### Coagulase-positive staphylococci and *Streptococcus uberis* in cattle

Strains of coagulase-positive staphylococci isolated in bovine mammitis *(table 3.40)* were globally less often resistant to antibiotic than *S. aureus* human strains, showing 55.2% susceptibility to penicillin, 98% to methicillin, almost 90% to erythromycin and tetracycline, and 100% to fluoroquinolones. By contrast, *Streptococcus uberis* strains isolated in bovine mammitis *(table 3.41)* were more often resistant to macrolides and associated drugs (susceptibility < 50%) than human strains.

### *Nota bene*

It is best to be able to identify both the epidemiological context (nosocomial/community, antibiotic treatment history), and the settings in which strains were collected in order to use resistance statistics efficiently. It is important to remember that global resistance statistics (type 2 information) originate in part from difficult cases, relapses, treatment failures, nosocomial and iatrogenic infections, therefore providing a biased picture that exaggerates resistance frequency in community-acquired infections, and resulting, *in fine*, in over-consumption of certain antimicrobials. For example, since urine analysis is not recommended for uncomplicated urinary tract infections in young women, it is likely that this type of test is used more often in case of treatment failure or relapse, two factors that may be related to frequency of antibiotic resistance. This is why close attention must be paid to study characteristics regarding resistance rates before making recommendations concerning probabilistic antibiotic treatment.

2.4 *2.4 Surveillance of multidrug-resistant bacteria (type 4 information) [Appendix 4]*

### *Methicillin-resistant Staphylococcus aureus* (MRSA)

The overall percentage of MRSA within the *S. aureus* species was very homogenous in French hospitals: 35% in 2003 in most hospitals, for all types of clinical samples *(tables 4.1 to 4.4)*. However, this percentage varies according to type of hospitalisation: between 63 and 66% for rehabilitation and long-term care hospitals. MRSA percentages remained stable in the C-CLIN Paris-Nord Network between 1998 and 2003, at about 40% *(table 4.1)*, but declined in short-stay hospitals of the public network (AP-HP Network) during the same period. In fact, this percentage fell from 39% in 1993 to 27% in 2003 *(table 4.2 and figure 4.2)*. This decline was even more significant in the intensive care units of the AP-HP Network: 55% in 1993 to 30% in 2003 *(figure 4.4)*.

In the same network, trends were less favourable in rehabilitation and long-term care departments, increasing from 54% to 63%. In other networks, such as the Franche-Comté Network, we observed a decrease in the percentage of MRSA in rehabilitation and long-term care departments: from 58% in 1999 to 48% in 2003 *(table 4.4)*.

Overall, MRSA trend in French hospitals was rather encouraging, with considerable reduction, in some regions, in acute care hospitals and particularly in intensive care units.

Most MRSA strains (85% to 95%) are susceptible to gentamicin; the percentage of strains susceptible to tobramycin increases regularly since 2000, finally reaching 15% *(tables 4.5 to 4.8)*.

The great majority of MRSA strains have remained resistant to fluoroquinolones, but the proportion of susceptible strains tends to increase. Observation of erythromycin susceptibility shows that susceptibility of MRSA strains is high (between 42 and 50%).

Overall, we observe a return to susceptibility of MRSA strains to all antimicrobials except β-lactams and fluoroquinolones.

### *Extended-spectrum beta-lactamase (ESBL)-producing enterobacteria*

Over the past few years, distribution of enterobacteria species producing ESBL has changed considerably, due to increase in *E. coli* strains and concurrent decrease in *E. aerogenes* and *K. pneumoniae* which, depending on the network, were the most frequently isolated species *(tables 4.12 to 4.15)*. In 2003, in the AP-HP network, over 50% of ESBL enterobacteria were strains of *E. coli*. This trend was also seen in other regions of France, and was concurrent with an increase in ESBL enterobacteria incidence with dissemination of CTX-M producing *E. coli* strains. Risk of dissemination in the community, and the situation observed in neighbouring countries like Spain *(8)*, should prompt greater vigilance with respect to this MDR bacteria, and warrants a specific surveillance system.

ESBL enterobacteria strains have remained globally very resistant to all antimicrobials except carbapenems *(tables 4.17 and 4.18)*.

### *Other multidrug-resistant bacteria*

Multidrug-resistance in *Mycobacterium tuberculosis* (defined by simultaneous resistance to isoniazid and rifampicin) remains rare: 1.4% of all strains isolated in 2003 *(table 4.19)*. The significant increase in multidrug-resistance observed between 2001 and 2002 was confirmed in 2003, but did not become any more pronounced *(9)*.

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# Notes