Chapter VI

Resistance to antimicrobials in France: statistical data from Networks federated in ONERBA

1 Methodology

The data presented in this report and the comments in this chapter follow the four categories of information defined in ONERBA's methodological recommendations [www.onerba.org] *(1)*. These four categories are briefly reviewed below.

Subpopulation analysis of isolates according to their level of susceptibility (type 1 information)

The goal is to identify and describe subpopulations of strains according to their level of susceptibility. In this purpose, quantitative data (inhibition zone diameters or MICs) are required. This type of data is useful in establishing the critical values that define the clinical categories or in detecting the appearance of strains with an abnormal behaviour that will not be detected by the qualitative S, I, R classification. For example, strains with reduced susceptibility but still in the susceptible category, or strains with a very high level of resistance will not be distinguished from strains of the same categories.

Summary statistics of antimicrobial resistance for the main bacterial species of medical interest (type 2 information)

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

Summary resistance statistics are extracted from laboratory information systems. These results may be stratified according to simple parameters, generally available in the laboratory database: outpatient or hospitalised patient, hospitalisation ward, type of sample, and, whenever possible, length of hospitalisation, etc.

This type of data is useful in establishing the clinical spectrum of activity or clinical indications of antimicrobials.

Statistics of antimicrobial resistance in well defined infections or in specific epidemiological situations (type 3 information)

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

This information is necessary in defining indications for antimicrobials as presented in summaries of the product characteristics (RCP) and provide important information for clinicians as well as for scientific societies and health agencies in the establishment of recommendations relating to the proper use of antimicrobials.

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

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

MDR isolates warrant specific surveillance in man, in the hospital as well as in the community settings, and even in animals or in the environment. Indeed, MDR can be frequently isolated both in the hospital (MRSA) and in the community (for example: betalactam-resistant pneumo-

cocci, *Mycobacterium tuberculosis* resistant to rifampicine and isoniazid, etc.) where they may have major therapeutic consequences.

Several national reference centres (NRCs) or veterinary networks monitor the multidrug-resistance of community species *(Streptococcus pneumoniae, M. tuberculosis, Salmonella typhimurium)*. The C-CLIN microbiological networks monitor MRSA and ESBL-producing enterobacteria and, for some of it, other MDR. 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). Results of the RAISIN have been published elsewhere *(2)*. Other indicators (percentage of MDR in the species, co-resistance to other antimicrobials, etc.) are collected independently from RAISIN by some networks and are presented herein.

2 Data analysis

2.1 *Subpopulation analysis of isolates according to their level of susceptibility (type 1 information)*

Figures 1, 2, 4 and *5* enable comparison of the activity of the amoxicillin-clavulanate association (AMC) with that of amoxicillin alone (AMX) against *Escherichia coli*. The behaviour of this species with respect to AMX *(figures 1 and 4)* is clearly bimodal, with a susceptible subpopulation (mode, 24-26mm) and a resistant subpopulation (mode, 6mm) that are well separated by the critical values. The behaviour of *E. coli* with respect to AMC displays an unimodal distribution (mode, 21-24mm) that is very spread out and on both sides of D (≥21mm), the upper critical diameter *(figures 2 and 5)*. The stratification between susceptible strains (S) and nonsusceptible strains (intermediate and resistant, I+R) to AMX *(figures 7 and 8)* separates two populations. The behaviour of the AMX-S strains with respect to AMC is similar to that with AMX, with an unimodal distribution (mode, 24-25mm). However, for the AMX-R strains, the distribution of AMC diameters is bimodal, with a highly resistant subpopulation on which AMC has no visible activity (mode, 6mm) and a subpopulation with a spread out distribution centred on D, the upper critical diameter (mode, 21mm, range 7 to 36mm). AMC enabled the restoration of susceptibility (diameter ≈ 21mm) for a little over one third of the strains, but about one quarter remains nonsusceptible (diameter < 21mm).

There is no difference between the distribution of diameters of strains isolated from bacteraemia and those of strains isolated from all clinical samples. In addition, diameter distributions are similar to those observed in 1999 *(3)*.

Figures 3 and 6 show the behaviour of *E. coli* with respect to cefotaxime. Most of the strains are very susceptible (inhibition zone diameter ≥ 36mm). A small fraction is less susceptible (inhibition zone diameter: 23-32mm) or even intermediate or resistant (inhibition zone diameter < 21mm). The latter strains are amoxicillin-resistant by a mechanism partially inactivating the third generation cephalosporins (cephalosporinase overproduction, ESBL).

Figure 10 shows the behaviour of *E. coli* with respect to imipenem. The distribution is unimodal (mode: 31mm) although there is a peak at 35mm related to the upper detection limit of some automated systems.

Figures 9 and 12 show that the behaviour of *E. coli* with respect to gentamicin is trimodal: susceptible (modal inhibition zone diameter: 19-23mm), intermediate or mildly resistant (distribution of the diameters ranging from 8 to 15mm) and highly resistant (diameter: 6mm).

Figure 11 shows that the behaviour of *E. coli* with respect to nalidixic-acid (NAL) is trimodal, the susceptible population having a modal inhibition zone diameter of 27mm. *Figures 6 and 7* show the importance of separately considering *E. coli* strains susceptible or resistant to classical quinolones (NAL) in order to assess the activity of a fluoroquinolone such as ciprofloxacin (CIP). Almost all of the strains (95%) are susceptible to CIP *(figures 13 and 16)*. However, NAL-resistant strains *(figures 15 and 18)* are much less susceptible to CIP (trimodal distribution of inhibition zone diameters: 6mm, 10-12mm, 25-30mm) than NAL-susceptible strains (unimodal distribution: 31-36mm) and this is true whatever the type of sample considered. Finally, half of the NAL-R strains are CIP-resistant. The observed diameter distributions are similar to those found in 1999 *(3)*.

Figure 19 shows that, for strains isolated in private laboratories, the behaviour of *Pseudomonas aeruginosa* with respect to ticarcillin is trimodal: susceptible (mode: 25mm), moderately resistant (distribution of diameters ranging from 12 to 17mm) and high level of resistance (diameter: 6mm). The intermediate population is difficult to separate from the susceptible one.

Figure 20 shows the behaviour of *P. aeruginosa* with respect to ceftazidime. There are two populations: a susceptible one, with a mode of 28mm, and an intermediate or mildly resistant one, with a mode of 16mm. *Figure 21* shows that the behaviour of *P. aeruginosa* with respect to ciprofloxacin is highly heterogeneous.

Figure 22 shows that, for strains isolated in private laboratories, the behaviour of *Enterococcus faecalis* with respect to ampicillin is very homogeneous, with a single susceptible population *(mode: 25mm)*.

Figure 23 shows that the behaviour of *E. faecalis* with respect to gentamicin 500 is bimodal: a susceptible population (mode: 24mm) and a population that is resistant at a very high level (mode: 6mm).

Figure 24 shows the behaviour of *S. pneumoniae* with respect to the three main beta-lactams: penicillin G, ampicillin and cefotaxime. The distribution is bimodal for these three beta-lactams. The mode of the susceptible population is identical for the three drugs (< 0.01mg/L) but that of the nonsusceptible population depends on the drug considered: 0.5mg/L for cefotaxime and 1mg/L for penicillin G and ampicillin.

Figure 25 shows the behaviour of *S. pneumoniae* with respect to fluoroquinolones. The distribution is unimodal for tested drugs, levofloxacin and moxifloxacin, with a mode at 0.25mg/L for moxifloxacin but 1mg/L for levofloxacin. There are three strains with a levofloxacin MIC > 4mg/L. In two of these three stains, moxifloxacin MIC exceeds 2mg/L and one strain has a MIC of 2mg/L.

Figures 26 to 28 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), the behaviour is heterogeneous and roughly trimodal with a susceptible population, a population of intermediate susceptibility or barely resistant and a highly resistant population. For spiramycin, the main population is spread on both sides of the two critical diameters, while for the other two antibiotics, this main population is more clearly defined by one of the two critical diameters.

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

Staphylococcus aureus

Methicillin-resistance in *Staphylococcus aureus* (MRSA) will be discussed in more detail below (appendix 4, multidrug-resistant bacteria). In the hospital setting *(tables 8-10)*, only 9% of the strains are susceptible to penicillin G, and 35% are MRSA. Two thirds of the strains are susceptible to kanamycin (and therefore to amikacin) and tobramycin, while 96% are susceptible to gentamicin. The latter proportion is higher than in 1999. As in 1999 *(3)*, two thirds of the strains are susceptible to erythromycin and fluoroquinolones, and over 90% are resistant to pristinamycin, fusidic acid, sulfamethoxazole+trimethoprim and rifampicine. Strains not susceptible to glycopeptides are very rare (< 0.5%).

MRSA are much less often susceptible to aminoglycosides than MSSA (15% versus 95% to kanamycin-amikacin, 16% versus 97% to tobramycin, 91% versus 99% to gentamicin), to erythromycin (35% versus 79%) and to fluoroquinolones (6% versus 91%).

Enterococcus sp

Enterococcus faecalis (tables 11 and 12) was much more often isolated than *Enterococcus faecium* in hospital laboratories: 760 strains of *E. faecalis* were isolated in 2002 in the hospitals of the REUSSIR Network, while during the same period, only 43 strains of *E. faecium* were isolated in the same network. *E. faecalis* remains much more often susceptible to penicillin A (100%) than *E. faecium* (58%). The same was true for furanes (98% versus 23%). Resistance to glycopeptides was rare in France (< 1%) in 2002 in both species. This was not the case in other European countries participating to the EARSS network since, for example, the rate of resistance to vancomycin in *E. faecium* was 21% in Italy and 19% in Spain during the same period *(4)*.

Streptococcus pneumoniae

Streptococcus pneumoniae (table 57) was more often susceptible to cefotaxime (> 80%) and amoxicillin (69%) than to penicillin G (47%). This species was also more often susceptible to cotrimoxazole (59%) than to erythromycin (41%). The frequency of susceptibility to fluoroquinolones remained very high (> 99%).

Streptococcus pyogenes and *Streptococcus agalactiae*

Resistance to macrolides was very high in *Streptococcus pyogenes (5)*. In 2002, from 62% to 80% of the strains were susceptible to erythromycin according to the network and the type of patients considered *(tables 38 and 58)*, while the proportion of susceptible strains exceeded 90% in 1996 *(figure 29)*. However, all of the strains remained susceptible to penicillin A and pristinamycin. The value of erythromycin as an alternative to penicillin G in the treatment of pharyngitis was highly reduced and alternative drugs are urgently required *(5)*.

Such a reduction in macrolides susceptibility was also observed in *Streptococcus agalactiae*, although the period of surveillance is shorter. In 2002, only 75% of the strains were susceptible to erythromycin compared to >80% in 2000 (*table 33*, REUSSIR Network). This decrease has to be confirmed by other networks and during the coming years. In the laboratory network

connected to the NRC for streptococci, the rate of resistance to erythromycin of this species was 17% in 2003, slightly under the one observed in 2002 by the REUSSIR Network *(6)*. However, the origin of the strains differs since those of the REUSSIR Network were issued from all types of clinical samples while the NRC only considered vaginal samples taken at the end of pregnancy.

Enterobacteria

Tables 13 to 21 show major differences in the proportion of susceptibility to antimicrobials among Enterobacteriaceae:

– For species belonging to the first group *(Escherichia coli, Proteus mirabilis)*, i.e. species naturally susceptible to amoxicillin (AMX), only 55% of *E. coli* strains were susceptible to this antibiotic. Amoxicillin-clavulanate (AMC) restored the activity in slightly more than 10% of *E. coli* strains, 66% of the strains being susceptible to this antibiotic. Almost 80% of *P. mirabilis* strains were susceptible to AMC.

– For species belonging to the second group *(Klebsiella pneumoniae, Klebsiella oxytoca)*, i.e. species naturally resistant to amino- and carboxypenicillins, and for *Proteus vulgaris*, one of the very rare species of the third group where natural beta-lactamase was inhibited by clavulanate, over 80% of the strains were susceptible to AMC.

– Frequency of susceptibility to cefotaxime was higher for group 1 enterobacteria (≥ 99%) compared with that for group 2 species (95-98%) and especially group 3 strains, that were naturally resistant to aminopenicillins and first generation cephalosporins (48-98%), e.g. *Enterobacter cloacae* (73%), *Enterobacter aerogenes* (48%), *Citrobacter freundii* (74%) and *Serratia marcescens* (86%).

– Frequency of susceptibility to fluoroquinolones, including ciprofloxacin, was higher for group 1 and group 2 enterobacteria (85-96%) compared with that of group 3 (44-83%), in particular *E. aerogenes* (45%), *S. marcescens* (83%) and *C. freundii* (77%). When comparing the different compounds, there was clearly a difference in pefloxacin, ofloxacin and ciprofloxacin activities, the latter being the most active drug. In some cases, it should be noted that there was a higher proportion of strains that were susceptible to ofloxacin than ciprofloxacin. This is due to the fact than susceptibility to ofloxacin has not been determined for all of the strains.

– Frequency of susceptibility to gentamicin was higher for group 1 and group 2 enterobacteria (93-97%) than for group 3 (85-99%).

– Frequency of susceptibility to amikacine was the lowest for *E. aerogenes* (61%) compared to other species (> 95%).

Other species

Pseudomonas aeruginosa and *Acinetobacter baumannii* are species almost exclusively isolated in the hospital setting. Both species are naturally resistant to aminopenicillin, first and second generation cephalosporins and classical quinolones, and both often have acquired resistance to other antimicrobials *(tables 22 and 44 to 47)*:

– large spectrum penicillins: *P. aeruginosa* was a little more often susceptible to piperacillin than to ticarcillin (79 versus 65%) while it was the opposite for *Acinetobacter* spp (40 versus 60% in 2002);
– penicillin+beta-lactamase inhibitor associations: piperacillin-tazobactam had a similar activity to ticarcillin-clavulanate against *Acinetobacter* (63-70% of susceptible strains in 2002) but was slightly more active against *P. aeruginosa* (82 versus 64%);
– imipenem: 100% of *Acinetobacter* strains, but only 83% of *P. aeruginosa* were susceptible to imipenem;
– aminoglycosides: for both species, 68-85% of the strains were susceptible to tobramycin or amikacin, but less than 55% to gentamicin.

Almost all of *P. aeruginosa* strains remained susceptible to colistin, an antibiotic that is increasingly used against multiresistant gram-negative bacteria.

Stratified analysis

The interest of stratified analysis by parameters available in the laboratory (type of patient, type of sample, etc.) is underlined in ONERBA's recommendations *(1)* and in European recommendations for monitoring antimicrobial resistance *(7)*.

Tables 24 to 26 give examples for strains isolated from urines. Globally, no difference was found in the susceptibility of *E. coli* strains isolated from urines and that of strains obtained from all clinical samples. The same observation is made for *P. aeruginosa* strains, except for susceptibility to ciprofloxacin, which is 60% for strains isolated in urines and 69% for all strains. On the opposite, *S. aureus* strains isolated in urines from hospitalised patients were more often resistant to methicillin than the entire population of *S. aureus* strains (60% of MRSA versus 35%).

Tables 48 to 56 give examples of susceptibility after stratifying ambulatory patients by outpatient clinics or patients seen in emergency departments. Globally, for the main three species considered *(S. aureus, E. coli, P. aeru-*

ginosa), strains isolated from outpatients were more frequently susceptible to antimicrobials than those from the emergency wards. It is the case for *S. aureus* and susceptibility to methicillin (82% versus 73%), *E. coli* and fluoroquinolones (93% versus 92%), and *P. aeruginosa* and ciprofloxacine (78% versus 64%). This may be due to a higher frequency of a past history of hospitalisation in patients seen in emergency wards.

Trends in susceptibility

The interest of monitoring statistics of resistance on a regular basis and over time is illustrated in *tables 27 to 56*. However, since only a 3-year period was available, statistical analysis of trends has not been carried out.

– For methicillin-susceptible *S. aureus* (MSSA), there was a tendency toward a more frequent susceptibility to penicillin G and a reduction in the susceptibility to fluoroquinolones over the three years (2000-2002).

– For *E. faecalis*, percentages of susceptibility were globally identical from 2000 to 2002 for ampicillin, while there was a tendency toward a reduction in the susceptibility (low level resistance) for gentamicin and kanamycin. Percentages of susceptibility to other antimicrobials remained stable.

– For *E. faecium*, there seems to be an increase in the percentage of strains susceptible to ampicillin from 2000 to 2002. However, the total number of strains tested was low.

– For enterobacteria, percentages of susceptibility to most antimicrobials were globally stable, but some differences should be noted between species or antimicrobials.
✓ For *E. coli*, the frequency of susceptibility to ciprofloxacin decreased from 95% to 93% between 2000 to 2002. The same observation was done for susceptibility to mecillinam (74% versus 71%).
✓ For *E. cloacae*, susceptibilities to third generation cephalosporins, quinolones and aminoglycosides has dropped over the 3-year period. This is probably due to the increase in the proportion of ESBL in this species *(table 119)*.
✓ The frequency of susceptibility to classical quinolones and fluoroquinolones has increased in *S. marcescens* (ciprofloxacine 75% versus 83%) while the susceptibility to beta-lactams has remained the same.

– For *P. aeruginosa*, percentages of susceptibility have globally remained the same from 2000 to 2002 for most antimicrobials.

– However, there is a reduction in *A. baumannii* susceptibility to ticarcillin (71% versus 60%), ceftazidime (50% versus 32%) and ciprofloxacin (47% versus 34%).

2.3 *Statistics of antimicrobial resistance in well-defined infections or in specific epidemiological situations (type 3 information)*

Examples of statistics of resistance established by several networks for documented infections and in specific epidemiological situations (nosocomial/community, type of infection, etc.) are provided in *tables 60 to 113*.

Bacteraemia: evolution of the susceptibility to antimicrobials

Table 61 shows that, between 1997 and 2002, the susceptibility of *E. coli* isolated from blood cultures has remained stable with respect to most antimicrobials except for ciprofloxacin (98% to 94%). Stratification by amoxicillin susceptibility (AMX) shows that strains resistant to AMX are slightly less frequently susceptible to aminoglycosides, and ciprofloxacin, compared to strains susceptible to AMX *(table 63)*. In addition, a higher reduction in the frequency of susceptibility to ciprofloxacin is observed in strains resistant to AMX (96% to 91%) than in strains susceptible to AMX (100% to 97%).

The observed trend is reversed for *K. pneumoniae (table 62, figure 32)*. The frequency of susceptibility to ciprofloxacin goes form 86% to 98% from 1996 to 2002, probably due to a reduction in ESBL-producing *K. pneumoniae (table 116 and 119)*. This hypothesis is reinforced by the increase in the frequency of susceptibility of this species to cefotaxime *(table 62)*.

Comparisons of the frequency of susceptibility of strains isolated from bacteraemia with those isolated from urine samples *(tables 68 to 73 and 45 to 47)* show that:

– For *S. aureus*, the frequency of susceptibility to methicillin was higher for strains isolated from bacteraemia than for those isolated from urines. It was expected, since a high proportion of *S. aureus* bacteraemia is community-acquired, while community-acquired urinary infections with *S. aureus* are not commonly observed.

– For *E. coli*, percentages of susceptibility were globally similar for strains isolated from blood cultures and those isolated from urines. This is related to the very frequent urinary origin of *E. coli* bacteraemia.

– For *P. aeruginosa*, strains isolated from bacteraemia were more often susceptible to antimicrobials than strains isolated from urines.

CHAPTER VI

Bacteraemia in the hospital setting: links between the nosocomial/ community origin and antimicrobials susceptibility

The distribution of microorganisms isolated in community and nosocomial bacteraemia differed markedly *(tables 74, 85, 88)*: *S. aureus* accounts for over 20% of species isolated in nosocomial bacteraemia but for about 10% of community bacteraemia. On the opposite, *E. coli* accounted for almost 50% of the microorganisms isolated in community bacteraemia and for about 20% in nosocomial bacteraemia. *P. aeruginosa* and fungi were almost exclusively isolated from nosocomial bacteraemia and *Salmonella sp* from community bacteraemia.

For *S. aureus* bacteraemia, it is well known that a nosocomial acquisition involves a much higher risk of resistance to beta-lactams (MRSA) than acquisition in the community *(tables 75, 86 and 90)*. Hospital-acquired MSSA did not seem to be more resistant to aminoglycosides, macrolides, rifampicine, fluoroquinolones and fusidic acid than community-acquired MSSA *(tables 76, 89)*. However and as expected, MSSA strains were much more often susceptible to these antibiotics (86-99%) than MRSA strains (10-86%), as shown in *tables 76, 89 and 90.*

The susceptibility of enterobacteria isolated from community-acquired bacteraemia to the main antimicrobials used in the treatment of severe infections (third-generation cephalosporins, aminoglycosides, fluoroquinolones) remained very high (95-100%). The susceptibility of enterobacteria from hospital-acquired bacteraemia was only about 90% (87-95%), thereby exposing patients to a risk of treatment failure in case of probabilistic monotherapy with these antibiotics *(tables 79, 86, 93 to 98).* Such differences were primarily related to differences in susceptibility within the same species when comparing community and nosocomial strains. For example, it was the case for *E. coli (tables 79, 86, 94)* whether strains were isolated from urines or not *(table 82)*, susceptible or not to amoxicillin *(table 80)*, or to nalidixic acid *(table 81)*. Such differences can also be observed for *P. mirabilis (table 95)* or *K. pneumoniae (table 97)*. In addition, differences in susceptibility were also related to a much higher proportion of species with a high frequency of resistance (*Enterobacter*, *Serratia*, etc.) in nosocomial rather than in community bacteraemia *(table 93)*.

Of interest, strains isolated in children were globally more susceptible to antimicrobials than those isolated in adults *(table 83)*. In addition, strains isolated in medical, surgical or paediatrics wards were globally more susceptible than those isolated in oncology-haematology or in rehabilitation or long-term care units *(table 84)*.

Infections in the community

Streptococcus pneumoniae and *Haemophilus influenzae*

The analysis of *S. pneumoniae* antibiotic resistance as a function of age and type of sample is given in *tables 100 to 109*. Strains isolated from children blood cultures (< 16years) were not more often resistant to betalactams, fluoroquinolones, macrolides or cyclines than strains isolated from adult blood cultures. However, strains isolated from children's meningitis were more often resistant to penicillin G than those isolated in adults (46.7% versus 58.4%; p = 0.05). Although strains of children's meningitis were more often resistant to amoxicillin than those of adults (72.9% versus 78.5%), the difference was not statistically significant (p = 0.25). There was no difference between resistance rates to cefotaxime for strains isolated from children or adult meningitis.

Strains isolated from acute otitis media (AOM) were less frequently susceptible to antibiotics than strains isolated from meningitis. This was the case for penicillin G (26.5% versus 46.7%; p < 0.01), cefotaxime (72.4% versus 88.8%; p < 0.01), erythromycin (20.4% versus 43.9%; p < 0.01) and cotrimoxazole (46.9% versus 58.9%; p = 0.05).

Such a higher resistance in AOM was also found for *H. influenzae*, with a percentage of resistance to amoxicillin of 43% in strains isolated from conjonctivitis and 34% in strains isolated from otitis, but this difference was not statistically significant (p = 0.23).

Mycobacterium tuberculosis

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

Table 111 shows that the percentages of strains susceptible to isoniazid, rifampicine and ethambutol, three of the four antibiotics of the standard treatment regimen, was almost 95% for new patients (so-called "primary" or "initial" resistance), but 77% in previously-treated patients (so-called "secondary" or "acquired" resistance). Resistance was more frequent for isoniazid (5.0% primary resistance and 18.0% secondary resistance) than for rifampicine. The only region where resistant strains were more frequent was the Paris region *(table 112)*, although the proportion of resistant strains may be more frequent in some other regions, due to the low number of strains isolated. Rates of primary and secondary resistance to first line drugs did not statistically differ from those of 2001.

Streptococcus uberis in cattle

Strains of *Streptococcus uberis* isolated in bovine mammitis *(table 113)* were much more often resistant to macrolides (susceptibility < 40%) than human *Streptococcus* species.

Comment
It is important to remind that global resistance statistics (type 2 information) originate in part from difficult cases, relapses, therapeutic failures, nosocomial and iatrogenic infections. Therefore, such statistics provide a skewed picture that bias toward higher resistance rates in community infections and may lead to overconsumption of some antimicrobials. For example, since urine analysis is not recommended for uncomplicated urinary tract infections in the young woman, it is probable that the use of this test is more common in case of therapeutic failure or relapse, two factors that may be related to the frequency of antimicrobial resistance. For this reason, it is necessary to pay attention to the methodological characteristics of resistance studies before drawing up recommendations concerning probabilistic antibiotic treatments. Therefore, in study dealing with prevalence of antimicrobial resistance, it is advised to identify clearly the epidemiological context (nosocomial/community; past history of antibiotic treatment) and situations in which strains are collected in order to be able to effectively use resistance statistics.

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

MRSA at the hospital

As we have seen above, the overall percentage of MRSA within the *S. aureus* species was fairly homogenous in French hospitals: about 35% in 2002 for all types of hospitals and for all types of clinical sample *(tables 8, 114, 120)*. However, this percentage ranged from 29% to 35% for short-stay hospitals and from 62% to 66% for rehabilitation and long-term care hospitals (LTC). The percentage of MRSA remained stable for all hospitals in the C-CLIN Paris-Nord Network between 1998 and 2002, but sharply declined in short-stay hospitals in the Assistance Publique-Hôpitaux de Paris (AP-HP Network) during the same period of time. Indeed, it dropped from 39% in 1993 to 29% in 2002 *(figure 35)*. This decrease was even greater when only data from the AP-HP intensive care units are analysed. The percentage of MRSA decreased from 55% to 29% during the same period *(table 114 and figure 36)*.

However, the percentage of MRSA in LTC hospitals increased from 54% to 62% during the ten years of monitoring *(table 114 and figure 36)*.

It is necessary to keep in mind that MRSA rates result from a mixture of nosocomial and community infections (especially for the denominator). When only nosocomial infections are taken into account, percentages are much higher, ranging from 40% to 60% MRSA *(tables 75, 87)*. The high percentage of MRSA in urines, close to 60%, is also due to the fact that *S. aureus* urinary infections are almost always nosocomial, and related to urinary catheters (in this case, the denominator includes fewer community MSSA).

Extended-spectrum beta-lactamase (ESBL) in the hospital

Klebsiella pneumoniae was almost the only ESBL-producing species at the beginning of the ESBL phenomenon in 1984-85 *(14)*. It is now seldom isolated when compared with *Enterobacter aerogenes* or *Escherichia coli* *(tables 116, 119, 122)*. The increasing place of *E. coli* among the ESBL-producing species is confirmed by the 2003 and 2004 results (refer to the next reports) and may foresee a risk of dissemination in the community, if not already done. Specific surveys conducted on a regular basis are therefore required to assess the extent of this phenomenon.

In parallel to the decrease in ESBL-producing *K. pneumoniae*, it should be noted that this species is now more often susceptible to aminoglycosides (amikacin: 38% in 1993 versus 56% in 2002), classical quinolones and fluoroquinolones (ciprofloxacin: 38% versus 50%) *(table 117 and figure 39)*.

Other multidrug-resistance in the community

Multidrug-resistance also concerns bacteria isolated in the community. This is the case for *Mycobacterium tuberculosis*, in which multidrug-resistance, defined by resistance to both isoniazid and rifampicine (the two major antituberculosis drugs) is rare (< 1%) in France. However, in 2002, this proportion increased to more than 1% (1.4%) for the first time in 10 years, i.e. about a 50% increase *(table 23)*. This increase was then confirmed in 2003 *(8)*. A detailed analysis of cases of tuberculosis reported in 2002 by the NRC demonstrated that, in 2002, patients were younger and more often born abroad than those reported in the previous years *(8)*. There was a significant increase in the number of patients coming from sub-Saharan Africa and Eastern Europe.

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