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

1 Comments

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

Data in humans

Figures 1.76, 1.77, 1.85 and 1.86 compare the activity of amoxicillin+clavulanate (AMC) to amoxicillin alone (AMX) against *Escherichia coli*. The behaviour of this species with respect to AMX (figure 1.76) is bimodal, with a susceptible subpopulation (mode, 24-26 mm) and a clearly resistant one (mode, 6 mm) widely separated by the two critical values. The behaviour of *E. coli* toward AMC shows a rather unimodal distribution (mode, 21mm), spread over a wide zone on either side of « D » (21 mm), the upper critical diameter (figures 1.77 and 1.86). Stratification on AMX susceptibility (susceptible strains (S) *versus* non-susceptible strains, i.e. intermediate susceptibility and resistant, R), clearly shows two distinct subpopulations (figures 1.85 and 1.86). The behaviour of AMX-S strains toward AMC is comparable to the one toward AMC, with a unimodal distribution (mode 24-26 mm). On the other hand, for AMX-R strains, the distribution of AMC diameters is highly heterogeneous. AMC only restored susceptibility (diameter ≥ 21 mm) in a very small proportion of AMX-R strains (about one third), suggesting a high level of amoxicillin resistance. The proportion of ESBL-producing *E. coli* strains that were susceptible to AMC is even smaller, with a majority of the strains in the intermediate category (figure 1.11). However, it is interesting to note that the majority of these strains remains susceptible to the piperacillin-tazobactam association, with a very widespread distribution of diameters (figure 1.13) [1, 2].

Figure 1.78 shows that the behaviour of *E. coli* toward cefotaxime is highly homogeneous, most strains being very susceptible (inhibition diameter ≥ 35 mm). As observed in previous years, a small proportion of strains is highly resistant, possibly due to the presence of strains producing ESBL of CTX-M type [3,4]. This hypothesis is confirmed by figure 1.15, which clearly shows that ESBL-producing *E. coli* are in majority highly resistant to cefotaxime, while strains with a lower level of resistance present a distribution of diameters that is highly heterogeneous, with even a few rare strains that remain susceptible.

Figure 1.79 presents the behaviour of *E. coli* toward imipenem. The distribution is unimodal (mode, 31 mm), although there is a peak at 35 mm relative to the upper detection limit of some automated cameras. It is noteworthy that ESBL-prducing strains present a very similar distribution of inhibition diameters (figure 1.20).

Figure 1.80 shows that the behaviour of *E. coli* toward nalidixic acid (NAL) is bimodal, with a susceptible subpopulation presenting a 25 mm modal inhibition diameter and a resistant subpopulation (mode, 6 mm) that is constantly increasing since 2005 and that is exceeding 25% in 2009. Figure 1.82 shows the behaviour of the same *E. coli* strains toward ciprofloxacin (CIP). Three populations can be delineated. The subpopulation of highly resistant to CIP is slightly increasing compared to 2007 (12%). All isolates susceptible to nalidixic acid (figure 1.83) are also fully susceptible to CIP. However, the repartition of inhibition diameters is bimodal (modes, 26-34 mm and > 34 mm), suggesting the presence of an acquired resistance mechanism in the subpopulation that is less susceptible. Strains that are intermediate or resistant to nalidixic acid (figure 1.84) are distributed in three subpopulations (modes: 6 mm, 8-15 mm, 24-32 mm). More than half of the NAL-R strains is also resistant to CIP [1].

Figure 1.87 shows that the behaviour of *E. coli* toward cotrimoxazole is trimodal, with a susceptible subpopulation (mode, 28 mm), a highly resistant subpopulation (mode 6 mm), and an intermediate subpopulation located exactly between « d » and « D ». No variation was observed since 2007.

Figure 1.81 presents the behaviour of *E. coli* toward gentamicin. The repartition is trimodal, with a majority of strains that are susceptible (mode, 25 mm), a second subpopulation spread between resistant and intermediate strains (mode, 8-14 mm), and a third one comprising highly resistant strains (mode, 6 mm). This highly resistant population (2% of the strains) is stable compared to 2007 data (1.8%).

Data from food animals

Figures 1.88 and 1.89 show that *E. coli* isolated from bovines frequently present resistances to amoxicilline, associated or not to clavulanic acid. Resistance to third generation cephalosporins is detected by ceftiofur, a C3G specifically used in veterinary medicine (figure 1.90). The resistance to C3G is still limited, but these data, as well as those from previous years, confirm that cattle constitute a reservoir of either ESBL-producing strains (principally from the CTX-M group, [5,6]), or strains over-expressing a chromosomic or plasmidic AmpC (CMY-2). Even though the use of ceftiofur remains the most probable cause for the selection of C3G-resistant strains, others factors might have a role in co-selection [7]. Indeed, figures 1.91 and 1.92 show that about 20% of the *E. coli* strains harbor a phenotypic resistance to gentamicin, and 80% to enrofloxacin (a veterinary fluoroquinolone), which can be used in empiric treatments and consequently promote the dissemination of C3G resistance determinants.

Figures 1.93 to 1.96 show that about 10% of the *S. uberis* bovine strains, which are nearly exclusively isolated from mammary gland infections, are resistant to erythromycin, lincomycin, spiramycin and tetracyclines. These resistances remain low and stable over the years, even if they concern antibiotics that are widely used in the treatment of bovine mastitis.

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

Staphylococcus aureus

Tables 2.24, 2.25, 2.26, 2.33 and 2.34 show susceptibility rates of *S. aureus*.

In the MedQual network of private laboratories (Table 2.33 and 2.34), around 16% of *S. aureus* isolated in the community are resistant to methicillin (MRSA). This does not mean that these strains are community-acquired MRSA as previous history of patients is not recorded herein. Most of *S. aureus* strains (98%) are gentamicin-susceptible, and 89 % are kanamycin and tobramycin-susceptible. Of interest, 80% of the strains are susceptible to erythromycin in 2009 and 92% to fusidic acid. Only 80% of the strains are susceptible to fluoroquinolones, suggesting that at least 4% of methicillin susceptible strains are fluoroquinolone-resistant.

In the REUSSIR network of hospital laboratories 25% are resistant to methicillin (MRSA). The susceptibility to fusidic acid are higher than in the MedQual network (92,5%) (Table 2.24).

Enterobacteria

Tables 2.1 to 2.12 and table 2.35 and 2.36 show susceptibility rates of enterobacterial species isolated in Human.

- to amoxicillin (AMX) : 50,4% and 57% 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 2.35 and 2.36).
- to the amoxicillin-clavulanic acid combination: 67,2% of *E. coli* strains are susceptible to this antibiotic when considering the REUSSIR network (Table 2.1) and 72% for the MedQual network (Table 2.36), resulting in 15 % more susceptible strains than for AMX in both networks ; 78% among *P. mirabilis* (Table 2.9), 82% among *K. pneumoniae* (Table 2.7) and 77% among *K. oxytoca* (Table 2.6).
- to cefotaxime for group 1 and 2 enterobacteria (susceptibility rates between 92% and 97%) compared to group 3 enterobacteria that naturally produce AmpC enzyme (susceptible rates 59% to 94%). Of note, the least susceptible species is *E. aerogenes* that display a susceptibility rate of only 59% (Table 2.4);
- to fluoroquinolones for group 1 and 2 enterobacteria (77% to 95%) compared to group 3 enterobacteria (26% to 88%). Some species remain susceptible (86% of susceptibility for *E. coli* in REUSSIR and MedQual network, 97% for *P. vulgaris*), while others are less susceptible (78% of susceptible for *P. mirabilis*, 80% for *E. cloacae*, 79% for *M. morganii*, 78,7% for *C. freundii*), and finally some species are rarely susceptible (69% of susceptible for *E. aerogenes*, 26,5% for *P. stuartii*).

Pseudomonas aeruginosa

This species is almost strictly hospital acquired, and is naturally resistant to aminopenicillin, 1st and 2nd generation cephalosporins, and classical quinolones. In In the REUSSIR network of hospital laboratories 78% of susceptibility for *P. aeruginosa* to ceftazidime, 84% to imipenem and only 72% to ciprofloxacin (Table 2.22).

In Microbiologist network from Pas de Calais, only 78% of *P. aeruginosa* are susceptible to ceftazidime, 79% to imipenem and 66% to ciprofloxacin (Table 2.37).

Trends in susceptibility (Tables 2.13 to 2.21, 2.23, 2.27 to 2.29, 2.37 to 2.41)

S.aureus

S.aureus susceptibility to methicillin was higher in 2008, climbing from 64% in 2000 to 74% in 2008 in the REUSSIR network (Table 2.27) and from 68% to 72% in the ATB CCLIN Paris-Nord (Table 2.41). The susceptibility rate was also higher for lincomycin (71% in 2000, 83% in 2008), and fluoroquinolones (62,5% in 2000 71% in 2008) (Table 2.27).

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 86% in 2008. In addition, no strain resistant to cefotaxime was recorded in 2000 when 5% of isolates are resistant to this antibiotic in 2008 in the REUSSIR network (Table 2.13) and 6,4% in the ATB C-CLIN Paris-Nord network (Table 2.38).

E. aerogenes

E. aerogenes susceptibility rates to cefotaxime and fluoroquinolones (Table 2.15) increased from 35% in 2000 to 59% in 2008 for cefotaxime, from 36% to 69% for fluoroquinolones, respectively.

E. cloacae

In the REUSSIR network, *E. cloacae* susceptibility to third generation cephalosporins has decreased from 2000 (78%) to 2008 (66%) (Table 2.16). Fluoroquinolones susceptibility decreased (87% in 2000 to 80% in 2008). In addition, there was a slight decrease in cotrimoxazole susceptibility (93% in 2000 to 85% in 2008).

In the ATB C-CLIN Paris-Nord network, *E. cloacae* susceptibility to cefotaxime has decreased from 20002 (71,4%) to 2008 (60,4%) (Table 2.39).

K. pneumoniae

K. pneumoniae susceptibility to most antibiotics did not vary much between 2000 and 2007 (Table 2.18).

P. mirabilis

As for *E. cloacae*, there is a slight decrease in fluoroquinolones (87% in 2000 to 79% in 2008) and cotrimoxazole susceptibility (81% in 2000 to 71% in 2008) (Table 2.19).

S. marcescens

In contrast to *E. cloacae, S. marcescens* susceptibility to third generation cephalosporins has increased by 12% from 2000 (82%) to 2008 (94%) (Table 2.21). Fluoroquinolones susceptibility increased also (75% in 2000 to 88% in 2008). In addition, there was a light increase in cotrimoxazole susceptibility (79% in 2000 to 93% in 2008).

P. aeruginosa

There was no significant trend in *P. aeruginosa* susceptibility to ß-lactams from 2000 (Table 2.23). In the ATB C-CLIN Paris-Nord network, only 63% of *P. aeruginosa* are susceptible to Ticarcillin in 2003 and 55,6% in 2009 (Table 2.40). On the opposite, there was an upward trend in susceptibility to fluoroquinolones (65,3% in 2003 to 71% in 2009). In the microbiologist Pas-de-Calais network, 64% of *P. aeruginosa* are susceptible to fluoroquinolones in 2009 (Table 2.37).

Trends in susceptibility in strains isolated from animals

Comparison of the data gathered from 2003 to 2007 (Table 2.45) shows a constant and very low level of susceptibility of cattle *E. coli* to amoxicillin (25.2%), which is only partially restored by clavulanic acid (49.3% of susceptible cattle isolates in 2009). Susceptibility to third generation cephalosporins is slowly decreasing over the years (98.4% in 2005 *versus* 94.8% in 2009), confirming that a special attention must be paid to this animal ESBL reservoir. Susceptibility to fluoroquinolones remains constant and stable as well, with about 70 to 80% of susceptible strains, a level, which is below the one observed in pigs and poultry. Low levels of susceptibility to streptomycin (23.4 %) and tetracycline (21.9 %) are also to note.

Amongst *E. coli* strains isolated from poultry and swine (Tables 2.42 to 2.44) between 37.3% and 44% are susceptible to amoxicillin in 2009. More than 95% of strains are susceptible to ceftiofur for pig and turkey but this proportion decreases to 87.8% for chicken. Between 2003 and 2009, a decrease of the proportion of susceptible *E. coli* to ceftiofur or fluoroquinolones is noted for these three animal species. For pig, unlike chicken and turkey, this decrease is also observed for gentamicin. Percentages of cotrimoxazole-susceptible *E. coli* are significantly different between poultry (66.7% to 73.2%) and pig (33.5%) ($p < 0.01$) in 2009, with an increase of proportion of susceptible *E. coli* between 2003 and 2009 for chicken and turkey. Less than 16% of *E. coli* isolated from poultry and pig are susceptible to tetracycline.

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

Bacteraemia and urinary tract infections: trends in antibiotic susceptibility

The analysis of the distribution of bacteria implicated in nosocomial and community-acquired bacteraemia shows that the Gram negative species, previously majority among community-acquired bacteraemia since 2001, are as well the first ones among nosocomial bacteraemia since 2005 in several but not all networks (Table 3.9, Table 3.4 and Table 3.46). In one network, the proportion of community-acquired bacteraemia due to *E. coli* decreased significantly since 2000 (37.5% in 2009 vs 52.8% in 2001) whereas this proportion was stable in the hospital acquired-setting (Table 3.9). Concerning the Gram positive bacteria, the related proportion of community-acquired bacteraemia increased since 2001 (40.8% in 2009 vs 27.8% in 2001); the streptococcal genus is a particularly good example of this trend which was not identified among hospital-acquired bacteraemia (Table 3.9).

Among *S. aureus*, the percentage of methicillin susceptible strains still raised, particularly among hospital-acquired isolates (Table 3.10 and Table 3.45); according to the different networks, the percentage of MRSA varied from 69% to 76% in hospitals and from 79.1% to 86.1% in the community-acquired setting. The full gentamicin susceptibility is now established for MSSA (100% gentamicin susceptible strains) and MRSA (99%) (Table 3.5 and Table 3.1, Figure 3.1). In the last ten years, this almost complete disappearance of gentamicin resistant MRSA and the decreasing proportion of MRSA among *S. aureus* were the most noteworthy epidemiological variation occurring in this specie. During the last decade, the antibiotic susceptibility of *E. coli*, the main bacterial specie responsible for community-acquired and nosocomial infections, decreases markedly especially for some first-line agents. Indeed the amoxicillin susceptibility rate exhibits a 13% decrease between 1996 and 2009; less than one in two *E. coli* strains are now fully susceptible to this compound (Table 3.6). Similarly the percentage of ciprofloxacin susceptible strains reaches 85% in 2009, which leads to a 13% decrease comparing to 1996 (Table 3.6 and Table 3.49). This trend is also identified for nalidixic acid: in 2009 less than 80% of the strains are fully susceptible to this compound, comparing to 90% in 2000 (Table 3.6 and Table 3.49). Hospital-acquired isolates are more prone to show such decreased antibiotic susceptibility than community-acquired ones (Tables 3.16 b and c). Nevertheless among isolates coming from community acquired- urinary tract infection only 80% and 84.8% were susceptible to nalidixic acid and ciprofloxacin, respectively (Table 3.49). This trend of decreasing fluoroquinolones susceptibility was also identified among *E. cloacae* (two thirds of ciprofloxacin susceptible strains) and *K. pneumoniae* (Table 3.19 and Table 3.7). Stratification on amoxicillin susceptibility shows that amoxicillin-resistant *E. coli* are less frequently susceptible to ciprofloxacin than the susceptible strains (Table 3.8). In 2009 the percentage of extended-spectrum ß-lactamase producing strains reaches 5.3% among *E. coli*, that corresponded to a 3 fold increase comparing to 1996 (1.6%) (Table 3.6). Among isolates coming from community acquired-urinary tract infection the percentage of ESBL producing strains doubled between 2008 and 2009 (0.98% *vs* 1.83%, Table 3.49). In one network the rate of cefotaxim susceptible *E. coli* among hospital-acquired bacteraemia was only 81.7% (Tables 3.16 b and c). In 2009 a trend to increase of ESBL harbouring strains is identified among *K. pneumoniae*: the proportion of ESBL producing strains in 2009 was ten fold higher than in 2001 (15.1% *vs* 1.5%, Table 3.20). Whatever the implicated mechanism, less than 1 in 2 *E. cloacae* isolates was susceptible to cefotaxim in 2009 (Table 3.7).

During the same period a similar trend was not identified among *P. mirabilis* strains. In summary, the *E. coli* antimicrobial susceptibility, and particularly fluoroquinolones and cefotaxim ones, dramatically decreased in the hospital and community settings; these trends are particularly alarming.

Streptococcus pneumoniae

Between 2001 and 2009, the proportion of invasive strains (isolated from meningitis or bacteraemia), susceptible to beta-lactams or macrolides significantly increased among both children (<16 years) and adults ($p<10^{-3}$) (Table 3.31 to 3.32, Figure 3.21 to 3.22). When considering fluoroquinolone resistance, proportion remained stable between 2001 and 2009 (Table 3.32, Figure 3.22).

Analysis of *S. pneumoniae* resistance according to age and type of sample is presented in Table 3.23 to Table 3.34. In 2009, among both adults and children, the proportion of strains with reduced susceptibility to penicillin, amoxicillin and cefotaxime were respectively about 27%, 15% and 8% of invasive strains (isolated from meningitis or bacteraemia). No strain resistant to amoxicillin or cefotaxime has been isolated from invasive infections in children. In adults, one strain isolated from meningitis was resistant to cefotaxime, and seven strains isolated from bacteraemia were resistant to amoxicillin. Despite the increase in the proportion of susceptible strains to macrolides since 2001, strains resistant to erythromycin still represent nearly 30% of invasive pneumococcal strains in 2009 (28% in adults, 24% in children). The proportion of strains that have acquired a mechanism of resistance to fluoroquinolones (<1%) has not increased since 2001, those strains remaining more frequently observed in bacteraemia in adults.

For strains isolated from acute otitis media (AOM) in children, the proportion of strains non-susceptible to beta-lactams (penicillin, 62%; amoxicillin, 39%; cefotaxime, 25%), macrolides (59%) or cotrimoxazole (49%) was significantly higher than in invasive strains ($p<10^{-3}$). This is explained by the fact that in France, the tympanocentesis are essentially performed in case of failure of treatment of the AOM.

Mycobacterium tuberculosis

The frequency of resistance of *M. tuberculosis* to first-line drugs (isoniazide, rifampicin, ethambutol) is showed in table 3.44.

Among patients without history of treatment or new patients (primary resistance or initial resistance) accounting for a majority of cases (84% of all cases), the percentage of strains susceptible to all three antituberculosis drugs is 93.5%, i.e. very similar to the percentage observed since 2006. This proportion is far lower in case of previous history of treatment (secondary resistance or acquired resistance). Indeed, only 82.1% of strains isolated from these patients are susceptible to the three drugs. As in the previous years, the most frequent resistance is isoniazide resistance (6.1% among new patients and 17.0% among previously treated patients). Primary resistance to rifampicin remains stable around 1%, and all rifampicin-resistant strains are multidrug-resistant strains (resistant to isoniazide+rifampicin). Secondary resistance to rifampicin is more than ten times more frequent (13.2%) than primary resistance.

Documented infections in animals

Neonatal diarrhoae in calves constitute the major pathological setting for antimicrobial use in cattle. The main target species is *E. coli* (Table 3.35), which presents a particularly low and constant percentage of susceptibility to amoxicillin over the years (13.1% in 2005, 15.6% in 2009). Resistances to third generation cephalosporins (4.9% in 2009) and fluoroquinolones (23.9% to 32.7% depending on the molecule) are identified in cattle as well.

Bacterial respiratory infections in cattle are mainly due to the two species *Pasteurella multocida* and *Mannheimia haemolytica*, which present very high susceptibility levels to all antimicrobials (Table 3.36 and Table 3.37).

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

Methicillin-resistant *Staphylococcus aureus* (MRSA)

The overall proportion of MRSA among *S. aureus* is very homogenous in French hospitals: between 22 and 31% for most hospitals in 2009, regardless of the type of clinical sample (Tables 4.1 to 4.4). However, this proportion varies depending on the type of hospitalisation: between 19 and 26% in acute care, and between 54 and 58% in chronic or long-term facilities. The proportion of MRSA remained stable (around 40%) in the Paris and North region of the nosocomial network (C-CLIN) between 1998 and 2004 and decreased afterwards (Table 4.1). This decreased was more noticeable in acute-care facilities of the « Assistance Publique-Hôpitaux de Paris » network. Indeed, MRSA proportions dropped from 39% in 1993 to 19% in 2009 (Table 4.2 and Figure 4.3). This decrease was even more drastic in Intensive Care Units of the AP-HP network, where MRSA proportions dropped from 55% in 1993 to 16% in 2009 (Figure 4.4). In the other networks, MRSA trends are encouraging, with a slight decreased MRSA proportions among *S. aureus*, although observed decreases are less pronounced. Of note, this downward trend is observed in an international, and particularly European context of quasi-generalized rise of this indicator [9].

Most MRSA strains (between 90 and 94%) are gentamicin-susceptible, and the proportion of tobramycin-susceptible strains increased steadily since 2000, reaching 54% in 2009 in the Paris and North region of the nosocomial network (C-CLIN) (Tables 4.6 to 4.8). Between 54 and 59% of MRSA strains are erythromycin-susceptible. MRSA susceptibility to other antimicrobials such as fusidic acid, rifampicin, pristinamycin and cotrimoxazole is high, exceeding 90%. On the opposite, resistance to fluoroquinolones remains high, above 90%.

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

In the past few years, the distribution of enterobacterial species producing extended-spectrum ß-lactamases has changed considerably, showing an increase in *Escherichia coli* species and a concomitant decrease in *Enterobacter aerogenes* and *Klebsiella pneumoniae*, depending on the network (Tables 4.11 to 4.20 and Figures 4.8 to 4.10). In 2009, in the AP-HP network, 50% of ESBL strains belong to *E. coli* species while it was only 10% in 1995. This trend is also observed in all regions of France, with a slight time lag. In the Paris and North region of the nosocomial network (C-CLIN), 62% of ESBL-producing strains belong to *E. coli* species (6% in 2000) and 6% to *Enterobacter aerogenes* species (56% in 2000). In 2008, in the South-West region of nosocomial network (C-CLIN), the proportion of ESBL-producing strains reaches 4,5% (1,9% in 2005) (Table 4.23). It occurs as a result of the spread of CTX-M producing strains. Risk of dissemination in the community and the situation observed in neighbouring countries such as Spain and the United Kingdom [10] must prompt us to the greatest vigilance concerning these MDR strains that require specific monitoring and control procedures.

In 2009, 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 (C-CLIN). Overall, ESBL-positive strains remain highly resistant to all antimicrobials except carbapenems (Tables 4.19 to 4.22 and Figure 4.11).

Other multidrug-resistant bacteria

The proportion of strains of *Pseudomonas aeruginosa* multi-resistant defined as the number of strains resistant to ticarcillin, ceftazidime and imipenem varies between 8 and 10% between 2008 and 2009 as assessed by the network of microbiologists of the North region (Table 4.27).

Multidrug-resistance among *Acinetobacter baumannii*, as defined by resistance to all beta-lactams except imipenem, decreased between 2004 and 2009 (Table 4.28) around 40%. Among these resistant strains, 10% were also resistant to imipenem. Multidrug-resistant isolates are mainly isolated in ICUs (Table 4.29) and are observed in all departments under surveillance by the South-West network (Table 4.30).

In *Mycobacterium tuberculosis*, the proportion of multidrug resistant strains (combined resistance to isoniazid and rifampicin) among all strains isolated in 2008 and 2009 (Table 4.31) reached back over 1% (1.2%) after a drop under this threshold in 2007 (0.9%). However, there is no statistically significant difference among this proportion during the last five years.