VAINCRE LA MUCOVISCIDOSE

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The French Cystic Fibrosis Data Registry

Annual Data report 2007

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2010

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Cystic fibrosis

Cystic fibrosis is a hereditary disease with autosomal recessive transmission: only subjects who have inherited two mutations – one from the father, the other from the mother – are affected.

The gene responsible for the disease was identified in 1989. It is located on the long arm of chromosome 7 (7q31) and codes for the CFTR protein, a protein involved in the regulation of chloride ion transport across the cell membrane. To date, more than 1,600 mutations have been identified, the most common (encountered in 80% of patients) is the F508del mutation.

Before setting up systematic neonatal screening, the most common context for diagnosis was as follows: alerted by clinical symptoms (steatorrhoea, bronchial obstruction, recurrent respiratory infection), the physician carries out a sweat test. An elevated sweat chloride concentration confirms the diagnosis, and this is followed by molecular analysis of the *CFTR* gene and determination of the disease causing mutations.

Newborn screening is systematic in France since 2002. This decision was taken by the Ministry of Health, which entrusted the task to the French association for screening and prevention of disabilities in children (*AFDPHE - Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant*). The screening technique uses measurement of immunoreactive trypsin (IRT) at age 3 days and detection of *CFTR* mutations. The IRT protein is more abundant when there is pancreatic abnormality during foetal life or in the first few months of life. Measuring IRT concentrations enables 95-98% of newborn children with cystic fibrosis to be detected, though the test is not sufficiently specific (it picks out some children who do not have cystic fibrosis) and is therefore linked with a molecular analysis.
After looking for the main *CFTR* mutations (F508del and about thirty others), three situations can arise:
– two mutations are identified. The newborn baby and its parents are asked to visit a cystic fibrosis care centre (*CRCM - centre de ressources et de compétences de la mucoviscidose*) to confirm the diagnosis based on a clinical assessment and a positive sweat test, and to initiate the necessary treatment and monitoring.
– a single mutation is identified (the probability of not identifying a second mutation is around 15%). The sweat test must be carried out in a specialised centre. If the test is positive, the child is treated in the same way as the previous group. If the test results are negative, information concerning the heterozygous nature of the newborn will be given to the parents during genetic counselling.
– although the IRT level is high, no mutation is found. The risk that the child has cystic fibrosis is, in this case, below 1%. A second blotting paper sample test is carried out at age 21 days. If a raised IRT level persists at D21, the child is referred to a specialised centre for an additional assessment (sweat test).

On the pathological level, functional abnormalities occur in affected subjects in the digestive tract, the respiratory tract, the sweat glands and the genital tract. This wide range of abnormalities is associated with a broad spectrum of clinical expression, both regarding the age when the first symptoms appear and their subsequent evolution. The severity of respiratory symptoms affects life expectancy in the majority of cases.

Lifelong treatment is time consuming, demanding and aimed at symptomatic relief. It is essentially based on respiratory management (physiotherapy, antibiotic treatment, oxygen therapy, lung transplant for end stage disease) and digestive and nutritional management (pancreatic enzyme supplements and a hypercaloric diet).

The French Cystic Fibrosis Data Registry

The medical council of the association *Vaincre la Mucoviscidose*, set up a national cystic fibrosis observatory, the *Observatoire national de la mucovicidose*, (ONM) in 1992 with the following objectives:
— improve knowledge concerning the medical and social characteristics of the population with cystic fibrosis and the impact of therapeutics;
– gain a better understanding of the socioeconomic cost of this disease with a view to obtaining sufficient resources to cover constantly growing needs;
– improve information available to help both parents and patients in their personal choices, and associations and other institutional partners in strategic decisions.

A further objective that of covering the entire population of patients in France, has now been added. To this end, the association has transformed the ONM into a national cystic fibrosis registry, the *Registre français de la mucoviscidose*. This initiative was approved in July 2006 by the committee for protection of personal data in medical research (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, CCTIRS*) and in March 2007 by the data protection agency (*Commission nationale de l'informatique et des libertés, CNIL*). At the end of 2008 (with effect from 1 January 2009), the registry was certified by the national committee of rare disease registries (*Comité National des Registres Maladies Rares*), an organ of the Institut de Veille Sanitaire (InVS) and of the *Institut National de la Santé et de la Recherche Médicale* (INSERM).

The population is composed of people with cystic fibrosis followed in care centres associated with the registry in France (metropolitan France and Reunion Island). Data are collected once a year by means of a questionnaire transmitted using Web, paper questionnaires or exports from electronic patient files. The information requested refers to the preceding year and includes semi-anonymous patient identification, diagnosis, medical follow-up, treatments used, anthropometric data, respiratory function, bacteriological data, evolution of the condition and social and family situation. Statistical analysis is performed on anonymized data.

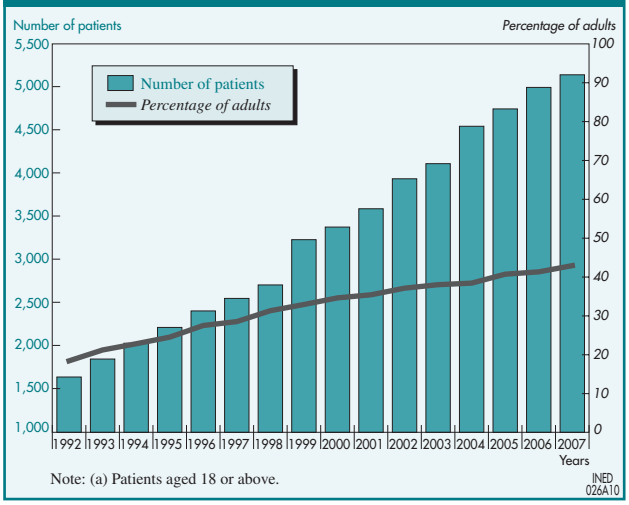
Unless otherwise indicated, the results presented hereafter relate to the population seen during the year 2007 and were produced by cross-sectional analysis of data. Data on patients seen during the year in at least two centres were processed separately. Patients in this category (said to have multiple accounts) were counted only once and allocated to the centre they visited most often during the year.

Preliminary notes

This report on 2007 data includes a number of changes.
– In order to provide comprehensive mortality statistics, annual data include not only the deaths of patients seen by the participating centres, but also deaths of patients lost to follow-up when the event was recorded.
– Survival analysis to measure length of life between birth and death has been temporarily suspended pending the resolution of certain methodological questions (cohort recruitment method).
– Molecular biology statistics are now calculated using the entire registry population, and not only the patients whom complete genotypes have been identified.

1 – Participating centres – Patients seen during the year

Figure 1 – Number of patients seen during the year and percentage of adults (a): trend since 1992



Note: (a) Patients aged 18 or above.

A total of 5,140 patients were seen by the centres who contributed data to the registry in 2007 (1). This report is based on the data of these patients, whose demographic and clinical characteristics are described in detail by the centres. Alongside this total, the participating centres recorded information on 19 additional patients who were not seen by them during the year but whose vital status was known on 31 December (11 were alive and 8 had died). The registry thus included a potential total of 5,159 patients in 2007, which represents, by our estimates, almost 90% of the population with cystic fibrosis in France (2).

The majority of the patients in the registry (96.1%) were followed by cystic fibrosis care centres, hereafter referred to by their French acronym CRCM (*centre de resources et de compétences de la mucovicidose*), and 3.7% by local centres (Table 1). The average number of patients per type of centre is very variable: above 91 in the CRCMs, no more than 15 in the local centres, and below 3 in other centres (centres outside the CRCM network or transplant centres).

The annual number of patients included in the registry, whether new or already registered, has risen steadily since 1992 (Figure 1), with a 2.9% increase between 2006 and 2007 (4,994 patients). The proportion of adults (patients aged 18 or above) has also increased: they represented 41.3% of patients in 2006 and 42.9% in 2007. Among them, 226 patients were aged 40 and above (4.4% of the population), 10 were aged between 70 and 77.

Table 1 – The French CF Registry 2007. Characteristics of centres

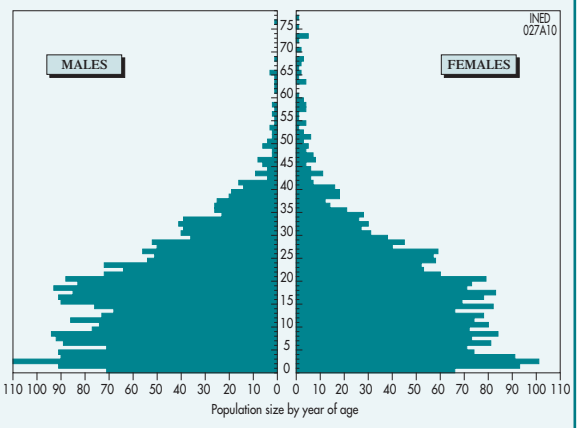
TYPES OF CENTRE	CHARACTERISTICS						
	Number of centres	Characteristics of patients in centres				Patients' age	
	Total	Total	Proportion (%)	Mean number	Extremes	Mean (years)	Extremes (years)
Paediatric CRCM	19	1,969	38.3	103.6	27 – 271	9.3	0 – 47
Adult CRCM	12	1,333	25.9	111.1	33 – 292	28.9	8 – 75
Paediatric and adult CRCM	18	1,639	31.9	91.1	26 – 193	16.2	0 – 77
Paediatric local centres	12	159 (a)	3.1	13.3	4 – 43	13.3	0 – 59
Paediatric and adult local centres	2	30 (b)	0.6	15.0	13 – 17	19.8	5 – 50
Other	4	10 (c)	0.2	2.5	1 – 4	15.9	6 – 33
TOTAL	67	5,140	100.0	76.7	1 – 292	16.8	0 – 77

Notes: (a) Including 41 patients also seen by a CRCM.
(b) Including 4 patients also seen by a CRCM.
(a) Including 4 patients also seen by a CRCM.

(1) Statistics established after checking for patients in the multiple account category. This category includes all patients seen in at least two centres during the course of the year, with patients being allocated to the centre they visited most often. As a result of this procedure, 67 centres were taken into account from among the total of 74 which contributed to the registry in 2007.

(2) This figure can be compared with the number of patients reported in ALD 18 by the CNAM (Païta M. and Weill A., 2008, "Les personnes en affection de longue durée au 31 décembre 2007", *Points de repère*, 20, 8 p.) On December 31, 2007, the general health insurance scheme, which covers 56.5 million persons, had records of 4,995 cystic fibrosis patients.

Figure 2 – – French CF Registry 2007.
Population pyramid of patients seen during the year



Note: 137 patients are aged below 1 (0 years completed age). Entry into the registry is delayed in the first year of life as a certain number of infants diagnosed through neonatal screening in a given year are not registered until the following year. For reference, 16 children born in 2006 (of which 9 in December) were diagnosed with cystic fibrosis by neonatal screening in 2007. On the 2006 population pyramid, the number of patients aged 0 could thus have been 149 + 16 = 165

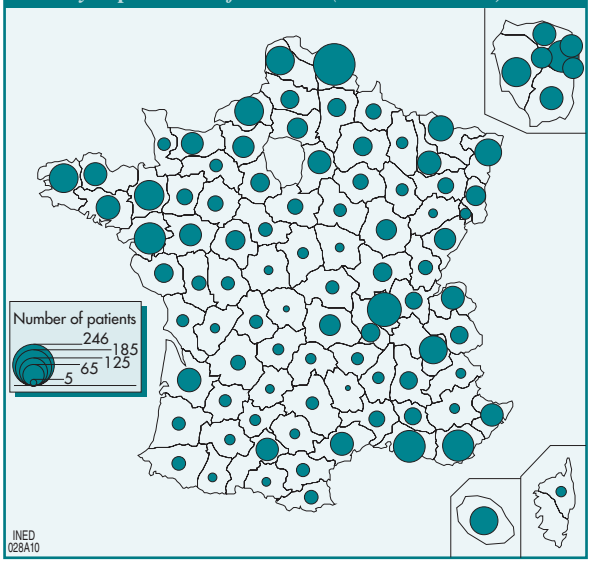
2 – Demographic characteristics

The population is structurally young (Figure 2 and Table 2). The mean age is 16.8 years, the median age is 15.0 years, and 57.1% of the population are under 18 (2,935 patients). The total number of males exceeds that of females: the sex ratio (number of males per 100 females) is 110. This ratio has remained stable over the years, standing at 109 in 2004, 111 in 2005 and 109 in 2006.

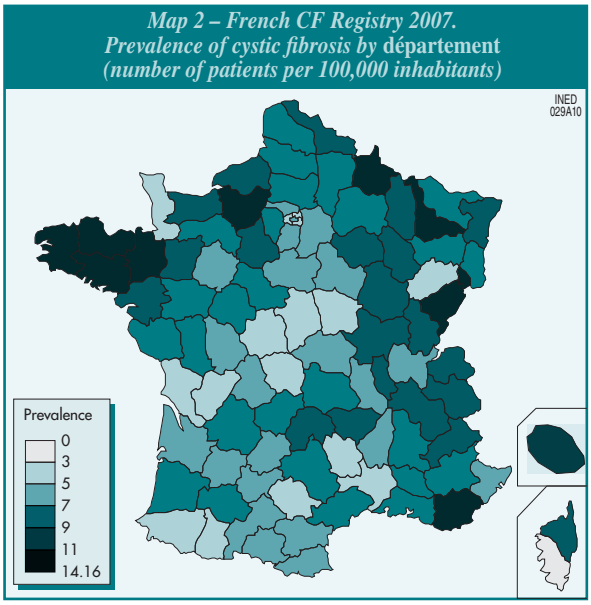
Table 2 – French CF Registry 2007. Main characteristics of the population

CHARACTERISTICS	FRENCH CF REGISTRY 2007
OVERALL	
Number of patients	5,140
Number of males per 100 females	110
Children: below age 18 (number and %)	2,935 – 57.1
Adults: age 18 and above (number and %)	2,205 – 42.9
Mean age (in years)	16.8
Median age (in years)	15.0
Extremes of age (in years)	0 – 77
MALES	
Number of patients	2,686
Children: below age 18 (number and %)	1,519 – 56.6
Adults: age 18 and above (number and %)	1,167 – 43.4
Mean age (in years)	16.7
Median age (in years)	15.5
Extremes of age (in years)	0 – 76
FEMALES	
Number of patients	2,454
Children: below age 18 (number and %)	1,416 – 57.7
Adults: age 18 and above (number and %)	1,038 – 42.3
Mean age (in years)	16.9
Median age (in years)	15.0
Extremes of age (in years)	0 – 77

Map 1 – French CF Registry 2007. Distribution of patients by **département** *of residence (absolute numbers)*



Map 2 – French CF Registry 2007. Prevalence of cystic fibrosis by **département** *(number of patients per 100,000 inhabitants)*

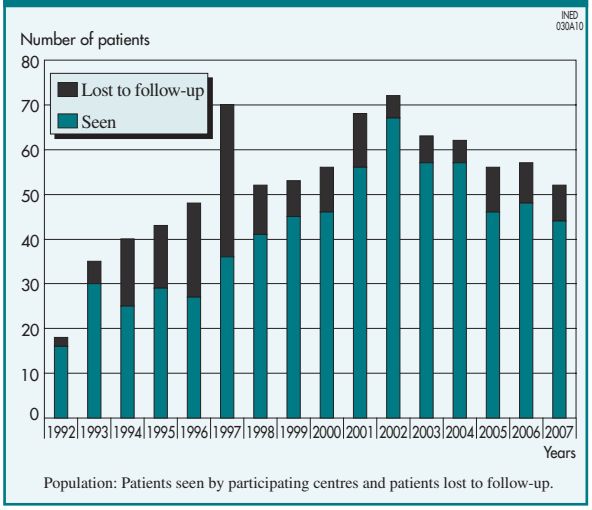


The geographical distribution of the patients (Map 1) shows no notable change with respect to previous years. There are marked differences between the *départements* of metropolitan France. The majority of patients (nearly 58%) are concentrated firstly in a north-western arc (Nord-Pas-de-Calais, Normandy, Brittany and the Pays de la Loire), and secondly in an eastern arc (Lorraine, Alsace, Franche-Comté, Rhône-Alpes and Provence-Alpes-Côte d'Azur). The mean prevalence is 7.8 patients per 100,000 inhabitants over the whole territory (metropolitan France and Reunion Island), with marked variations between *départements* (Map 2), the highest densities being seen particularly in the *départements* of Ille-et-Vilaine, Côtes-d'Armor and Finistère, Var and Reunion Island (12 patients or more per 100,000), and in Morbihan, Territoire de Belfort and Doubs, Meurthe-et-Moselle, Ardennes and Eure (11 patients per 100,000).

A total of 52 deaths occurred in 2007: 44 patients of participating centres and 8 patients lost to follow-up. This annual total is similar to that of 2006 (Figure 3). A slight downtrend in deaths has been observed in the last three years, following the steady rise over the period 1998-2001 between the peaks of 1997 (70 deaths) and 2002 (72 deaths). The mean age of patients who died in 2007 was 27.0 years, with the youngest aged 10 and the oldest aged 70.

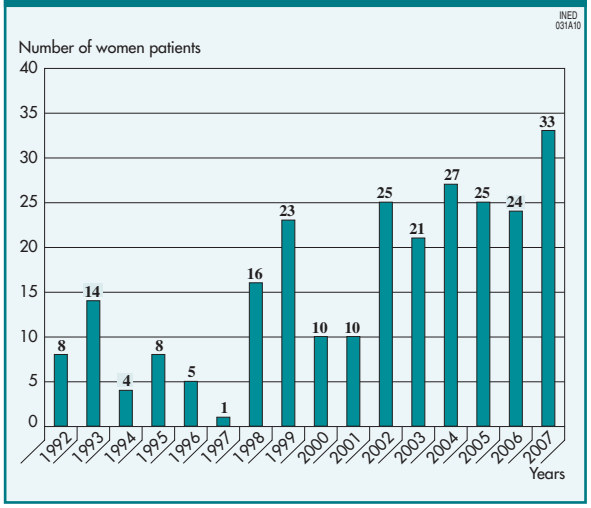
A total of 33 early pregnancies were reported to the registry in 2007, this number is the highest since the registry first began, although annual variations are very large (Figure 4). The mean age of the women was 28.6 years.

Figure 3 – Number of deaths in the year: trend since 1992



Population: Patients seen by participating centres and patients lost to follow-up.

Figure 4 – Number of women patients reporting early pregnancy during the year: trend since 1992



3 – Diagnosis

A total of 205 new patients were diagnosed in 2007, i.e. 4.0% of the total population (Table 3). By comparison, the numbers of new cases in 2005 and 2006 were 245 (5.2% of the total) and 234 (4.7%), respectively.

A total of 118 patients were diagnosed by neonatal screening (representing 57.6% of new cases), versus 149 (60.8%) and 172 (73.5%) in 2005 and 2006 respectively.

The number of patients diagnosed by neonatal screening (118) given in this report is not the actual total for France, but represents the patients for whom screening resulted in diagnosis. Patients who were diagnosed with cystic fibrosis before the screening result was known are not included in the total.

Table 3 – French CF Registry 2007. Main characteristics of diagnosis

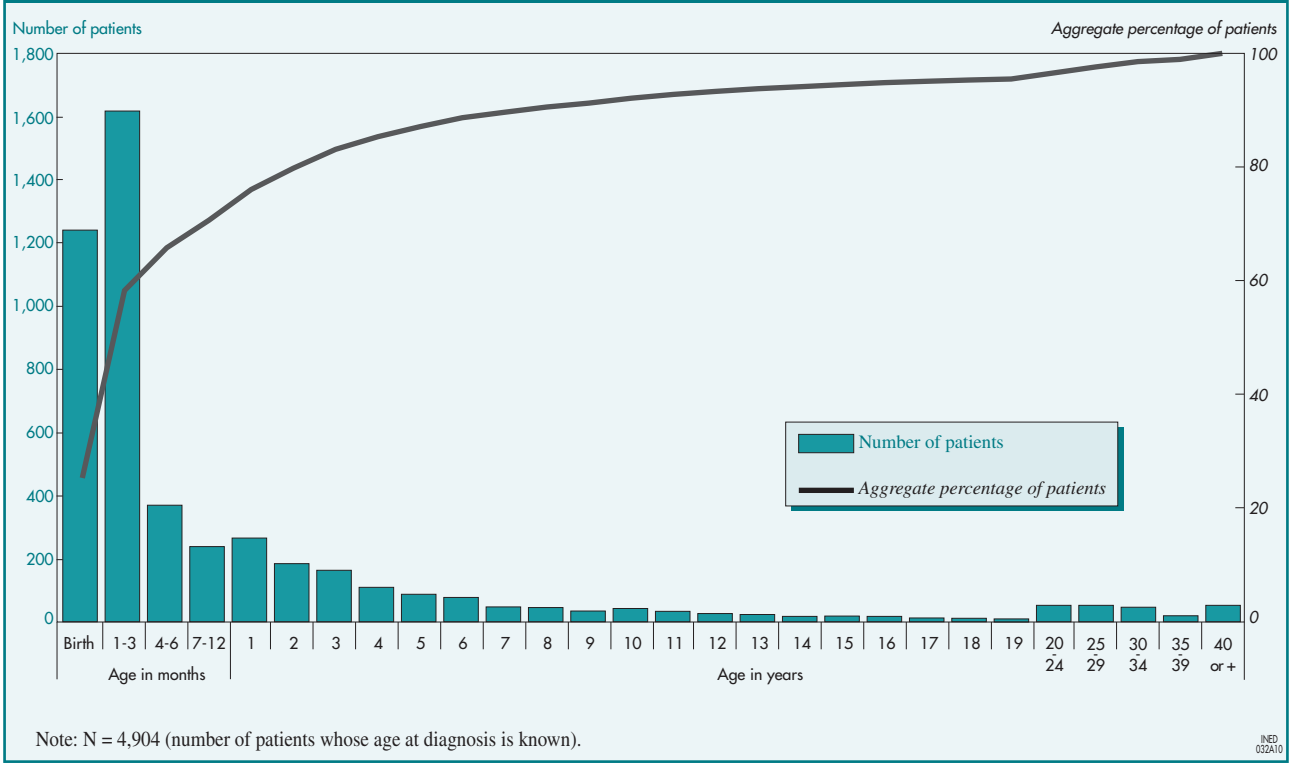
CHARACTERISTICS	2007 REGISTRY
NEW PATIENTS DIAGNOSED DURING THE YEAR	
All new patients (all diagnostic signs) (a)	
Number of patients	205
Mean age at diagnosis (in months)	49.6
Median age at diagnosis (in months)	1.0
Extremes of age at diagnosis (in years)	0 – 65
Context of diagnosis	
Number of prenatal diagnoses	7
Number of patients diagnosed on the basis of meconium ileus (MI)	21
Patients diagnosed by neonatal screening (excluding patients diagnosed before screening results were known)	118
Patients diagnosed through symptoms [other than MI]	52
Mean age at diagnosis (in years) of patients diagnosed through symptoms (other than MI)	14.4
ALL PATIENTS	
Number of patients whose age at diagnosis is known	4,904
Mean age at diagnosis (in months)	36.0
Median age at diagnosis (in months)	2.0
Extremes of age at diagnosis (in years)	0 – 74

Notes: (a) Including family history and antenatal diagnosis.

Among the 205 new patients, 134 were born in 2007. The method used to compile this report (patients seen in a care centre in 2007) means that infants born in 2007 and seen for the first time in 2008 are excluded.

Out of the 4,904 patients whose age at diagnosis is known, half were diagnosed with cystic fibrosis before the age of 2 months (Figure 5).

Figure 5 – French CF Registry 2007. Number of patients and aggregate percentage of patients by age at diagnosis

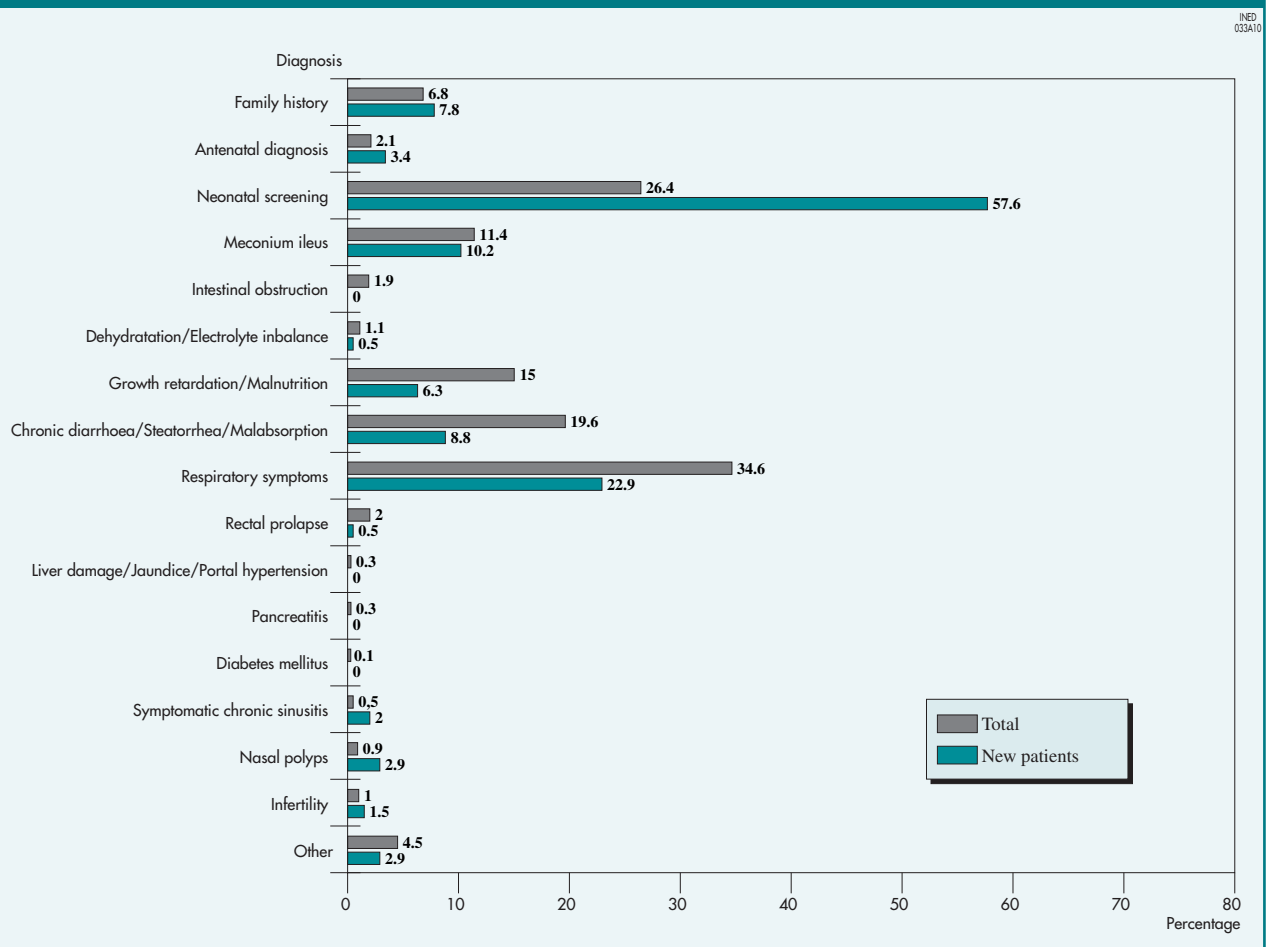


Note: N = 4,904 (number of patients whose age at diagnosis is known).

Diagnostic signs are shown in Figure 6. The most frequent for all the patients are respiratory symptoms (34.6%), neonatal screening, which concerns more than a quarter of patients in the registry (26.4%), followed by chronic diarrhoea/steatorrhoea/malabsorption (19.6%), growth retardation/malnutrition (15.0%) and meconium ileus (11.4%). Among the year's 205 new patients, the majority were diagnosed by neonatal screening, as in previous years (57.6%), followed by respiratory difficulties (22.9%), meconium ileus (10.2%) and the group of signs represented by chronic diarrhoea/steatorrhoea/malabsorption (8.8%).

With regard to the *CFTR* gene, the genotypes of 4,634 patients in the registry had been identified in 2007, representing 90.2% of the population; 4.9% of patients have genotypes with a single identified mutation and the other patients (also 4.9%) did not undergo genotypic analysis or had a genotype consisting of unstudied mutations or studied but as yet unidentified mutations.

Figure 6 – French CF Registry 2007. Diagnostic signs (as a percentage of the total for each population)



Note: The sum of percentages is above 100 because several diagnostic signs may be observed.

The most frequent genotype (Table 4) is F508del/F508del (43.1% of identified genotypes), and the proportion of F508del/other genotypes is 36.0%. The systematic newborn screening has increased the frequency of specific genotypes such as F508del/R117H, whose frequency is 1.4% in the total population and 4.4% among new patients diagnosed in 2007.

Table 4 – French CF Registry 2007. Numbers and proportions of genotypes by decreasing frequency

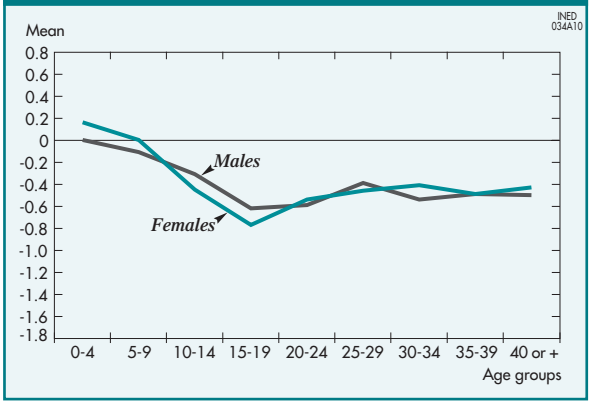
GENOTYPES	Number of patients	Proportion (%)
F508del / F508del	2,215	43.1
F508del / G542X	151	2.9
F508del / N1303K	116	2.3
F508del / 1717-1G->A	84	1.6
F508del / R117H	74	1.4
F508del / 2789+5G->A	69	1.3
F508del / R553X	57	1.1
F508del / G551D	49	1.0
F508del / Y122X	40	0.8
F508del / 3272-26A->G	38	0.7
F508del / W1282X	36	0.7
F508del / 3849+10kbC->T	33	0.6
F508del / I507del	32	0.6
F508del / 2183AA->G	30	0.6
F508del / R347P	28	0.5
F508del / 1078delT	23	0.4
F508del / A455E	23	0.4
F508del / R1162X	22	0.4
F508del / L206W	21	0.4
F508del / 3659delC	20	0.4
F508del / 711+1G->T	18	0.4
F508del / S1251N	18	0.4
F508del / E60X	17	0.3
F508del / 1811+1.6kbA->G	16	0.3
F508del / 3120+1G->A	16	0.3
F508del / Y1092X	16	0.3
N1303K / N1303K	16	0.3
F508del / 394delTT	15	0.3
F508del / G85E	14	0.3
G542X / G542X	14	0.3
Y122X / Y122X	13	0.3
F508del / W846X	11	0.2
F508del / 621+1G->T	10	0.2
F508del / R334W	10	0.2
711+1G->T / 711+1G->T	7	0.1
R117H / R117H	7	0.1
G542X / 2789+5G->A	5	0.1
G542X / N1303K	5	0.1
Other *CFTR* genotypes	1,245	24.2
SUB TOTAL	4,634	90.2
F508del / Unidentified	175	3.4
Other / Unidentified	77	1.5
Unidentified / Unidentified	254	4.9
TOTAL	5,140	100.0

Table 5 shows, for the total population, the age characteristics of patients by genotype identification status and presence or absence of the F508del mutation. Patients with at least one unidentified allele are significantly older, on average, than those whose genotype is fully identified (F test = 50.63; $p < 10^{-4}$)

Table 5 – French CF Registry 2007. Age of patients by genotype: summary

GENOTYPES			PATIENTS' AGE		
	Number	Proportion (%)	Mean (years)	Median (years)	Max. age (years)
F508del / F508del	2,215	43.1	15.7	15.0	53
F508del / Other	1,851	36.0	16.3	14.0	73
Other / Other	568	11.1	15.7	14.0	68
F508del / Unidentified	175	3.4	22.2	20.0	70
Other / Unidentified	77	1.5	22.4	20.0	75
Unidentified / Unidentified	254	4.9	26.7	24.0	77

Figure 7 – French CF Registry 2007. Height z-scores (mean by sex and age)



4 – Anthropometry

Important: in the following analysis (sections concerning anthropometry, spirometry, microbiology, morbidity, consultations and hospitalisations, therapeutic management) the figures do not represent trends but provide a cross-sectional overview of the characteristics of different patient groups at different ages.

Anthropometric data are expressed as z-scores [3] (with reference to the mean for the French population) with, in addition, the body mass index measured as weight (in kg) divided by height squared (in metres).

Height data by age are fairly similar in males and females (Figure 7). The z-scores are near 0 at the age of 0-4 years, and gradually become negative in the period of adolescence (–0.70 on average at age 15-19). Although they subsequently improve, mean z-scores remain negative in adulthood, with values of between –0.54 and –0.39.

(3) The z-score corresponds to the centred reduced anthropometric variable ($Z = \frac{mesure - mean}{st.dev}$) rendered independent of sex and age, the mean and the standard deviation being taken from the French reference population of the same sex and age as the subject. This score measures the difference with population norms and a negative score means growth retardation.

Figure 8 – French CF Registry 2007. Weight z-score (mean by sex and age)

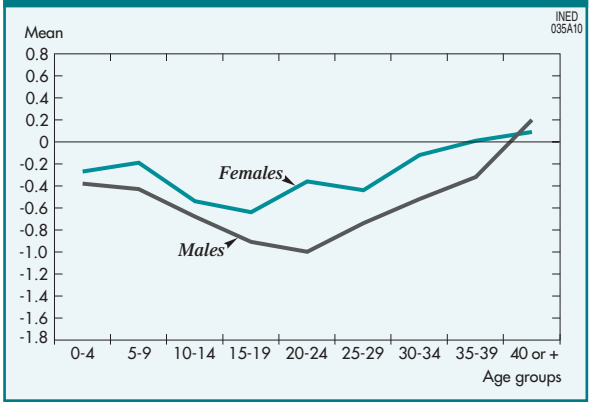
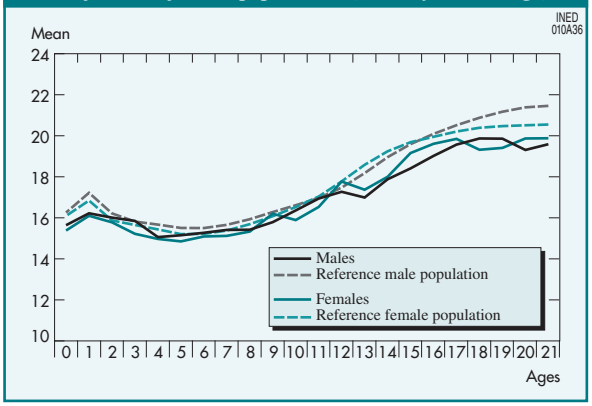


Figure 9 – French CF Registry 2007. Body mass indices (BMI) compared with the BMIs of the male and female reference populations (mean by sex and age)



In terms of weight, the differences between males and females at different ages are quite marked, with females having higher scores (Figure 8). From the first years of life, considerable slowing in weight gain occurs, with z-scores of approximately –0.33 at the ages of 0-4 years. As is the case for height, z-scores decrease from adolescence to early adulthood in males (–1.00 on average at age 20-24), while in females (–0.64 on average at age 15-19), weight recovery occurs earlier (–0.36 on average at age 20-24). The weight z-scores then improve markedly, with men even catching up with women beyond age 40. **However, adult patient data are probably affected by selection bias due to the higher mortality of more severely affected patients**.

The patients' poor weight gain is also shown on the curves of body mass index (BMI) by age (Figure 9). Differences with respect to the reference populations emerge mainly from age 13 and then persist, becoming even more pronounced among men. Among women, these differences become smaller at around age 16 before widening again.

Figure 10 – French CF Registry 2007. FVC percent predicted (mean by sex and age)

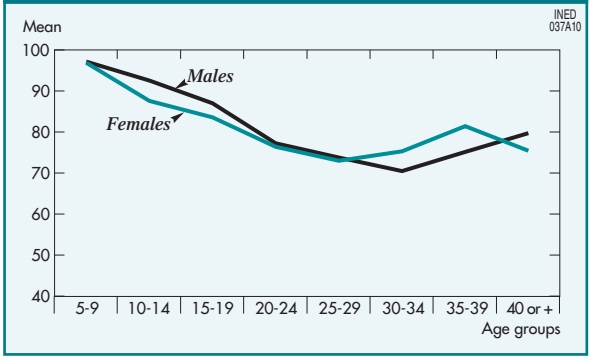
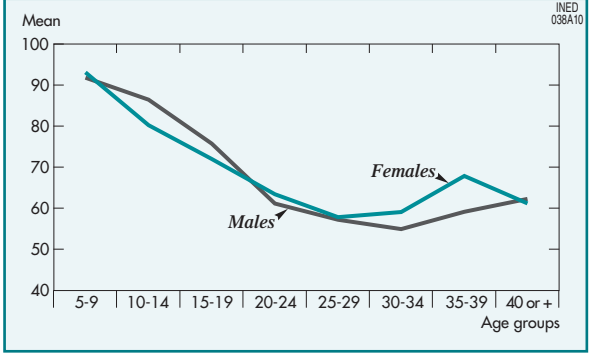


Figure 11 – French CF Registry 2007. FEV_1 percent predicted (mean by sex and age)



5 – Spirometry

In 2007, 90.6% of patients aged 6 or above underwent at least one spirometry test (respiratory function tests require subject participation, and children under this age cannot always do what is asked). The proportion was higher than in 2006 (87.2% in 2006) but lower than in 2005 (91.4% in 2005).

The forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), expressed as percentages of the predicted values [4] (Figures 10 and 11) decrease progressively up to ages 25-29 among women, and up to ages 30-34 among men (FVC at these ages is around 71% and FEV_1 around 56% of the predicted values). A slight improvement is then observed among both men and women. **This effect, as already noted for anthropometry, is very probably due to selection bias resulting from the higher mortality of more severely affected CF patients.**

(4) Knudson R. J., Lebowitz M. D., Holberg C. J. and Burrows B., 1983, "Changes in the normal maximal expiratory flow-volume curve with growth and aging", *Am Rev Respir Dis*, 127, pp. 725-734.

Figure 12 – French CF Registry 2007. FEV_1 percent predicted classes (as a percentage of the total for each population)

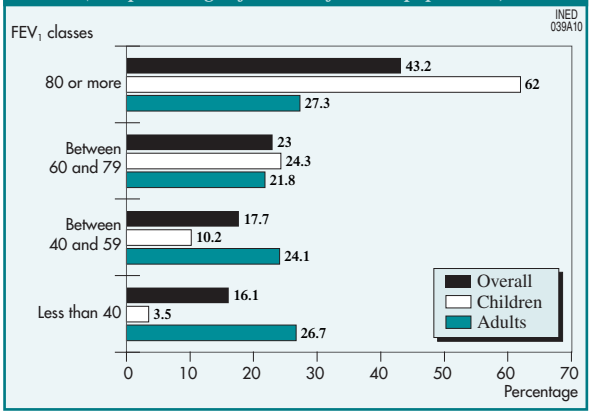
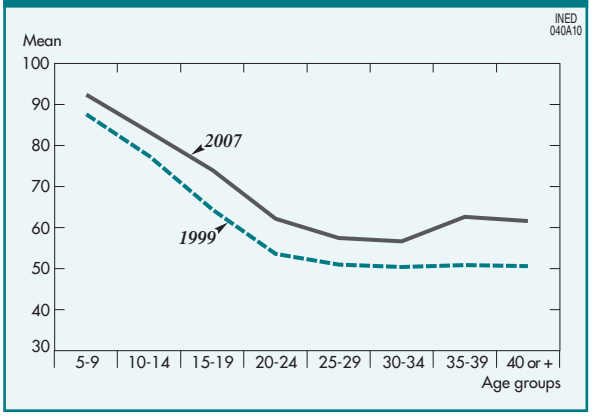


Figure 13 – FEV_1 percent predicted in 2007 compared with 1999 (mean by age)



The FEV_1 values are divided into four «functional» classes corresponding to different degrees of bronchial obstruction (Figure 12). The majority (62%) of the paediatric population (patients below age 18) have an FEV_1 of 80% or more of the predicted value. Adults (patients aged 18 and above) are quite equally distributed between these four classes, though 26.7% of them have an FEV_1 below 40% of the predicted normal.

For comparison, the mean FEV_1 values at different ages in 2007 are given with those of 1999 (Figure 13). The two curves have practically identical profiles, but the 2007 means are always higher than those of 1999. The difference is generally around 8 percentage points, except among the over-35s, for whom the improvement is even greater. This improvement is linked to the large proportion of transplant patients among patients aged 35 and above, plus the selection effect of older patients

6 – Microbiology

In 2007, 93.5% of the patients had at least one sputum culture (Table 6), a proportion that has remained very stable (93.5% in 2006 and 93.2% in 2005). Note that among patients who did not have a sputum culture in the year, almost 29% were transplanted patients.

Table 6 – French CF Registry 2007. Sputum cultures

Patients who had at least 1 sputum culture during the year	NUMBER	PERCENTAGE
Overall	4,806	93.5
Children (below age 18)	2,794	95.2
Adults (age 18 or above)	2,012	91.2

Figure 14 – French CF Registry 2007. Clinically important bacteria (percentage by age)

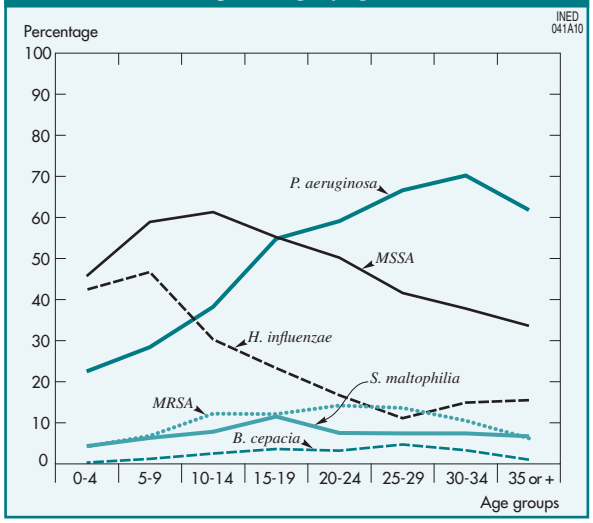


Figure 15 – Organisms in 2007 compared with organisms in 1999 (percentage by year)

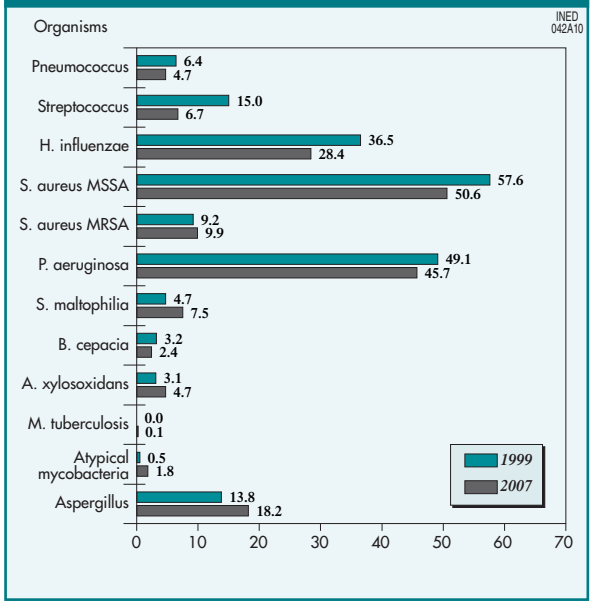


Figure 14 shows the distribution by age of five bacteria considered to be of clinical importance, *Staphylococcus aureus* being divided into MSSA (meticillin-susceptible) and MRSA (meticillin-resistant).

The patients' age distribution profile by bacteria remains practically unchanged with respect to the previous year (2006 data). Some of these micro-organisms are frequently detected at a very young age: at age 0-4 years, *Haemophilus influenzae* is present in 42.5% of patients and MSSA in 45.8%. In this age group, the presence of these two bacteria has been decreasing steadily over the last three years (the proportion was above 50% in 2005). *Pseudomonas aeruginosa*, present in 22.6% of patients aged 0-4, is most frequent (70.3%) in patients aged 30-34. MRSA was detected among 4.3% of the 0-4 age group. The proportion rises to 14.3% among the 20-24 age group (11.6% in this age group in 2006) then falls slightly to just above 10.6% up to age 34.

Figure 15 gives the variations observed for the organisms documented in 2007 compared with 1999. It shows a number of important changes. Downward: Streptococci, which fell from 15.0% of all patients who had a sputum culture in 1999 to 6.7% in 2007 ($p < 10^{-9}$), *Haemophilus influenzae* which fell from 36.5% in 1999 to 28.4% in 2007 ($p < 10^{-9}$), MSSA which fell from 57.6% in 1999 to 50.6% in 2007 ($p < 10^{-8}$), *Streptococcus pneumoniae* (6.4% to 4.7%; $p < 10^{-2}$), *Pseudomonas aeruginosa* (49.1% to 45.7%) and *Burkholderia cepacia* (3.2% to 2.4%) whose difference remains significant at the 5% level.

Upward: *Aspergillus* (from 13.8% to 18.2%; $p < 10^{-6}$), *Stenotrophomonas maltophilia* (from 4.7% to 7.5%; $p < 10^{-5}$), *Achromobacter Xylosoxidans* (from 3.1% to 4.7%; $p < 10^{-3}$) and atypical mycobacteria (from 0.5% to 1.8%; $p < 10^{-6}$).

In addition, out of the 2,198 patients colonized by *Pseudomonas aeruginosa*, chronic colonization [5] was observed in 53.4% of cases (multi-resistant or otherwise); colonization with multi-resistant strains [6] (chronic or non-chronic) represented 19% of cases. Information was missing for 29.6% of them.

(5) Chronic colonization: more than 50% of positive test results in the last 12 months (with at least 4 tests during this period) and/or significant increase in anti-PA antibodies (according to the laboratory).
(6) Multi-resistant colonization: resistant to all antibiotics in at least two antibiotic classes.

Figure 16 – French CF Registry 2007.
Events occurring during the year:
1 – Respiratory complications (percentage by age)

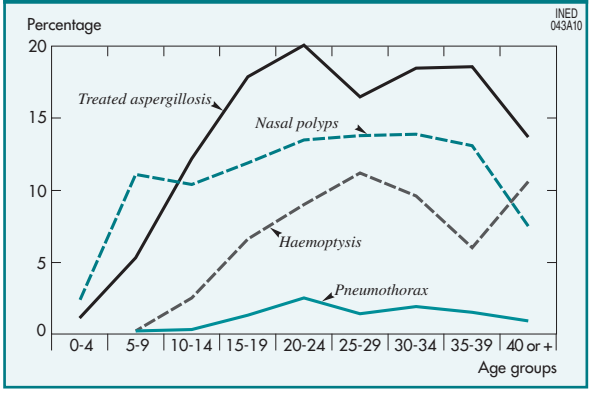
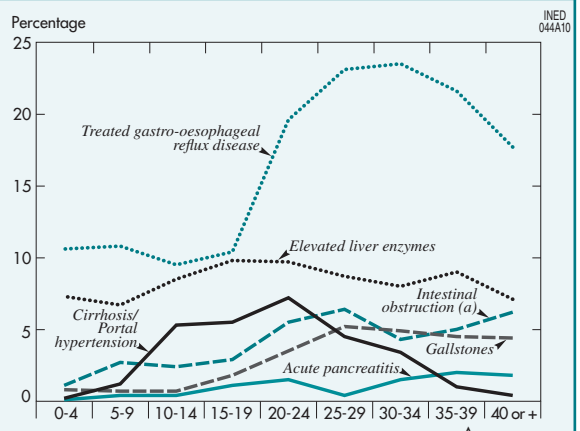
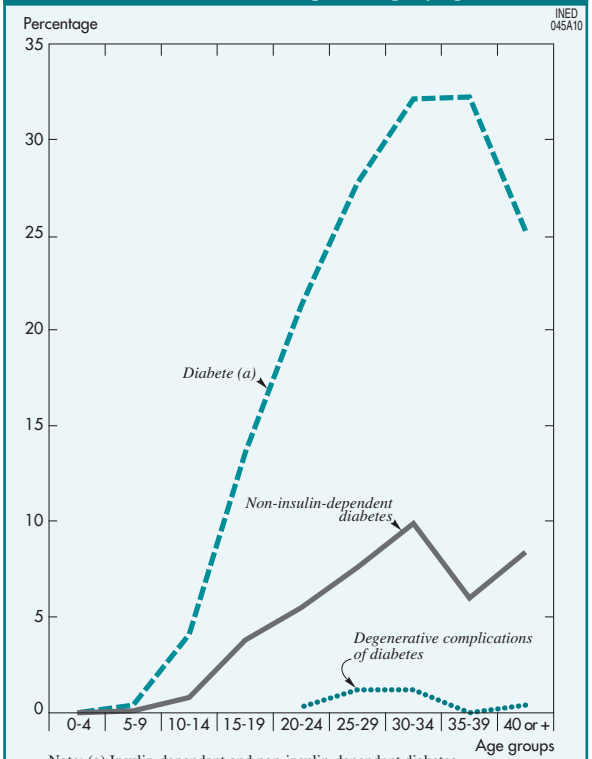


Figure 17 – French CF Registry 2007.
Events occurring during the year:
2 – Gastro-intestinal problems (percentage by age)



Note: (a) other than meconium ileus.

Figure 18 – French CF Registry 2007.
Events occurring during the year:
3 – Diabetes mellitus (percentage by age)



Note: (a) Insulin-dependent and non-insulin-dependent diabetes.

7 – Complications – Transplants

Patients with no reported complications represent 8.2% of the total.

The main events recorded during the year 2007 are grouped into broad categories and shown by age in Figures 16 to 19.

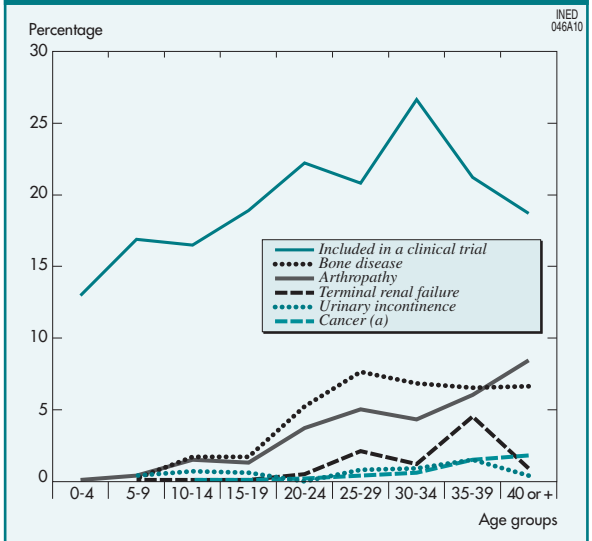
In brief, among the youngest patients, the most frequent complications were treated aspergillosis and nasal polyps (12.2% and 10.4% respectively at age 10-14 for example), treated gastrooesophageal reflux disease and elevated liver enzymes (10.8% and 6.7% respectively at age 5-9). Cirrhosis/ portal hypertension and diabetes (insulin-dependent or otherwise) were also relatively frequent (5.3% and 4.1% respectively at age 10-14).

In adult patients, where morbidity is higher, treated aspergillosis and nasal polyps were still very frequent (20.1% and 13.5% respectively at age 20-24 for example), treated gastro-oesophageal reflux disease affected 23.5% of the 30-34 age group, and almost one-third of the population had diabetes (32.2% at age 30-39). Note also that in adults, the frequency of bone diseases (7.6% at age 25-29) and arthropathy (8.4% at age 40 and above) was also noticeably high.

Only 24 patients (of which 22 are women) were affected by urinary incontinence (0.5% of the total). However, this number is probably under-estimated since urinary incontinence is rarely reported spontaneously.

For reasons of scale, abnormal exocrine pancreatic function is not shown, though 74.8% of patients had pancreatic insufficiency (almost 7 percentage points less than in 2006). This proportion remains reasonably stable with age: 74.8% at age 0-4, 79.3% at age 20-24, 77.5% at age 30-34, 67.3% after age 35.

Figure 19 – French CF Registry 2007.
Events occurring during the year:
4 – Other events (percentage by age)



Note: (a) Among patients of all ages, 14 have cancer, of whom 6 are transplanted.

An exceptionally large number of patients were included in clinical trials in 2007: a total of 939 patients of all ages were concerned (18.3% of the population), notably 13% of children aged 0-4 and 26.5% of patients aged 30-34.

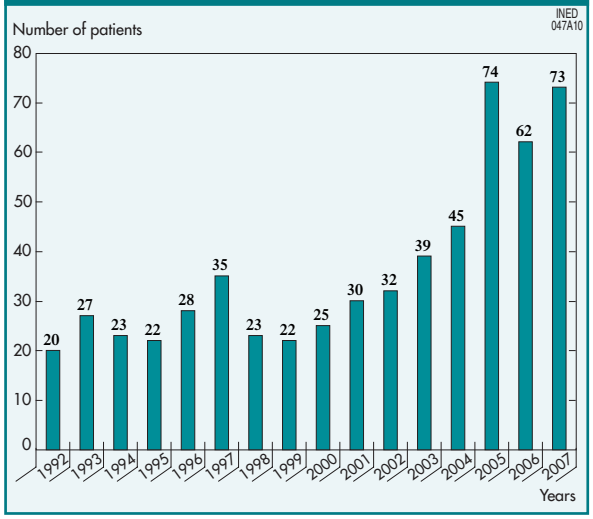
In 2007, 307 patients (6% of the population) had received a transplant (Table 7). In around 80% of cases, they were bilateral lung transplants. A total of 73 transplant operations (1.4% of the total population) were performed in 2007 alone, with, as previously, a large majority of bilateral lung transplants. In 2007, a total of 145 patients were on the waiting list (2.8% of the population), of whom 83 were added in 2007. Eight patients awaiting a transplant died in 2007, representing 15.4% of deaths in the year.

Table 7 – French CF Registry 2007. Transplants: 1 – Main characteristics

CHARACTERISTICS	2007 REGISTRY	
TRANSPLANTED PATIENTS	ALL PATIENTS (a)	TRANSPLANTED IN 2007 (b)
Number of patients	307	73
Mean age (in years)	29.2	26.5
Extremes of age (in years)	9 – 54	10 – 54
Bilateral lung transplants (number and %)	245 – 79.8	61 – 83.6
Heart-lung transplants (number and %)	28 – 9.1	1 – 1.4
Liver transplants (number and %)	24 – 7.8	6 – 8.2
Kidney transplants (number and %)	17 – 5.5	7 – 9.6
Other transplants (number and %)	11 – 3.6	2 – 2.7
Patients deceased in 2007	22	9
PATIENTS ON THE TRANSPLANT WAITING LIST (C)		
Number of patients	145	
Mean age (in years)	25.7	
Extremes of age (in years)	7 – 54	
New patients registered on the waiting list in 2007 (number and %)	83 – 57.2	
Patients on the waiting list who died in 2007	8	

Notes: (a) All patients transplanted in 2007 or before.
(b) Patients transplanted in 2007 only.
(c) All patients registered on the transplant waiting list in 2007 or before.

Figure 20 – French CF Registry 2007. Transplants: 2 – Annual number of transplanted patients: trend since 1992



The number of transplants performed in 2007 is close to the 2005's, when the highest number of transplants was performed since the beginning of the registry (Figure 20).

Figure 21 – French CF Registry 2007. Outpatient and inpatient visits (by age)

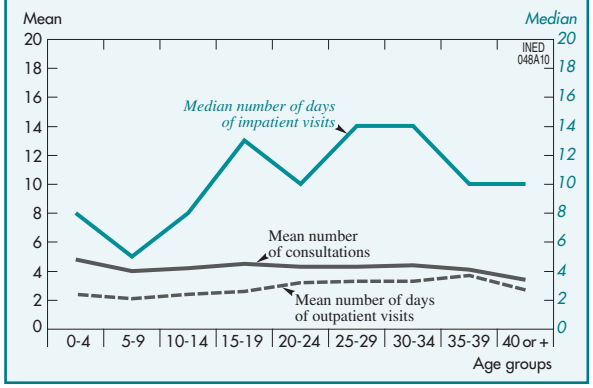
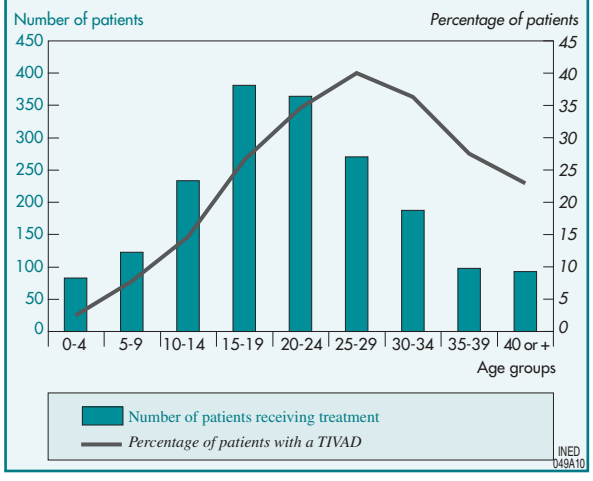


Figure 22 – French CF Registry 2007. Courses of IV antibiotic treatment: 1 – Patients receiving at least one course of treatment; patients with a TIVAD (by age)



8 – Outpatient and inpatient visits – Therapeutic management

On average, 4.3 outpatient visits were counted by patient during the year and 2.7 one-day hospital stays. These figures vary only slightly between the different age groups (Figure 21).

The inpatient length of stay shows widely scattered values. For this reason, it is shown as the median number of days rather that by the mean in Figure 21. This median number of days which was 10.0 for the whole of the population, remains lower for children (8 days for patients aged under 15, dipping to 5 days for patients aged 5-9) and more variable for adults (10.0 to 14.0 days in the years, depending on age).

A total of 1,837 patients received at least one course of intravenous antibiotic treatment in 2007 (i.e. 35.7% of the total population), of which 747 were in the 15-19 and 20-24 age groups. These two age groups accounted for 40.7% of patients receiving courses of treatment (Figure 22).

In all, 20.6% of patients had totally implantable vascular access devices (TIVAD). The proportion increases up to age 30, as shown in Figure 22. The subsequent decrease observed is very probably linked to the selection bias already mentioned (excess mortality of adults with severe forms of the disease).

Patients receiving IV antibiotic treatment had 2.5 treatment courses, on average, in the year. This average increases steadily with age, rising from 1.8 courses per year among the youngest patients (aged 0-4) to 2.8 courses at age 20-29. Beyond age 30, the average decreases again, falling to 2 courses per year (Figure 23).

Figure 23 – French CF Registry 2007. Courses of IV antibiotic treatment: 2 – Mean number of courses and of days of treatment by age

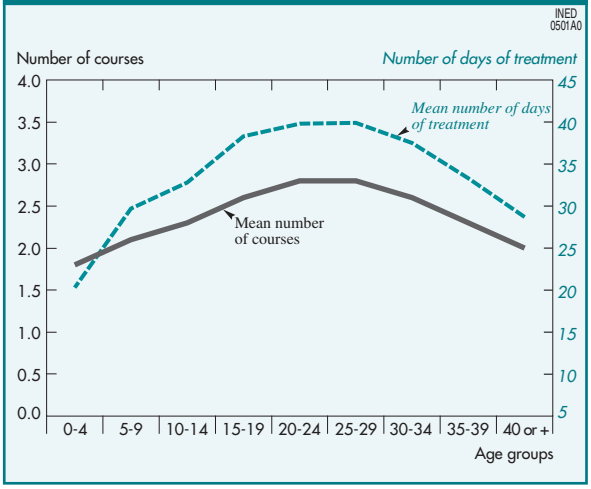


Figure 24 – French CF Registry 2007. Therapeutic management: 1 – Respiratory treatment (percentage by age)

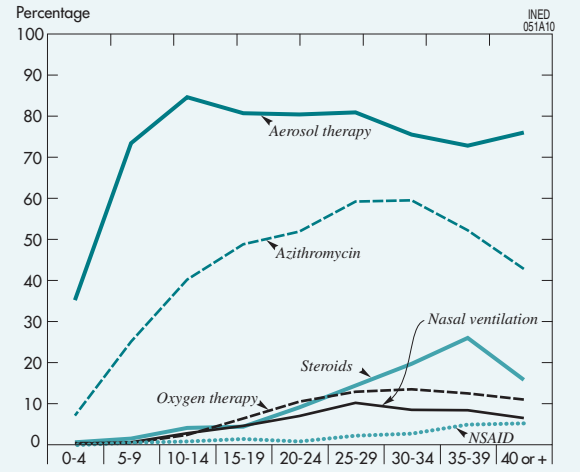
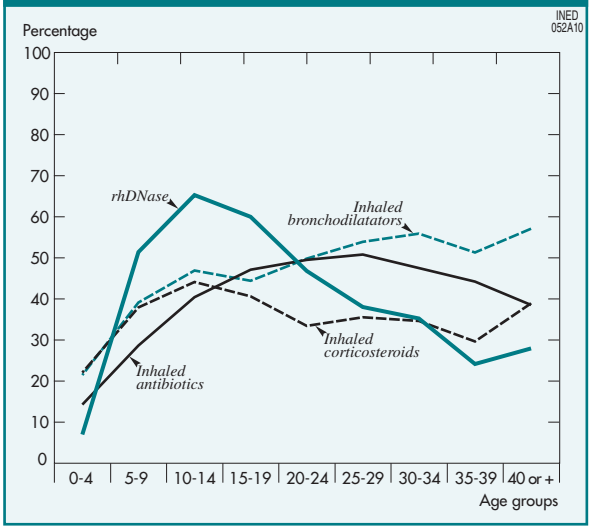


Figure 25 – French CF Registry 2007. Therapeutic management: 2 – Products administered by aerosol therapy (percentage by age)



The total number of days of IV treatment in the year spans a broad range, from 1 day to a maximum of 192 days. However, these treatment courses generally take place over a period of 2 weeks (31.6% of patients), one month (19.4% of patients) or, in some cases, 45 days (7.1% of patients). The mean number of days of IV treatment per year is 36.1 for all patients receiving IV treatments, with a maximum of 40 days of treatment at age 20-29 (Figure 23)

The main types of therapeutic management, with the exception of IV treatment, are grouped by categories and represented by age in Figures 24 to 26.

Among respiratory treatments, oxygen therapy, non-invasive ventilation and anti-inflammatory drugs (NSAID and steroids) were each administered to less than 7.2% of all patients. Frequencies were much higher for azithromycin (38.7% overall, 48.9% to 59.6% in patients aged 15-39) and for long-term aerosol therapy (71.6% overall and more than 80.5% in patients aged 10-29).

The products administered by aerosol therapy were most often inhaled bronchodilators (43.1%) and rhDNase (42.3%). Antibiotics were administered to 37.8% of patients and inhaled corticosteroids to 35.3% of patients.

In 47% of cases, aerosol therapy was administered by nebulization. For close to 37% of patients, nebulization was associated with a spray or powder; while for 14.4%, a spray or powder was administered alone (fewer than 2% did not specify the mode of administration).

Regarding digestive and nutritional treatment, pancreatic enzyme supplements were given to 80% of all patients. **The sharp drop in the number of patients receiving these supplements over the age of 35 is the result of selection bias due to the higher mortality of the more severely affected patients.** Overall, 29.1% of patients received long-term oral supplemental feeding and 5.4% long-term tube supplemental feeding. Among the latter, 68.1% received feeding by gastrostomy and 29.1% by nasogastric tube. In addition, 25.6% of patients took ursodeoxycholic acid, 26.8% took antacids (H2 blockers or Proton Pomp Inhibitors) and almost 70% took fat soluble vitamins.

Figure 26 – French CF Registry 2007. Therapeutic management: 3 – Digestive and nutritional treatment (percentage by age)

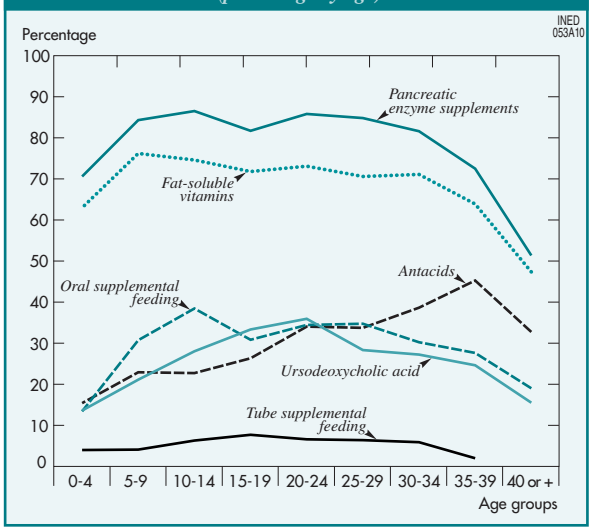


Figure 27 – French CF Registry 2007.
FEV_1 percent predicted. Comparison between total population and non-transplanted patients

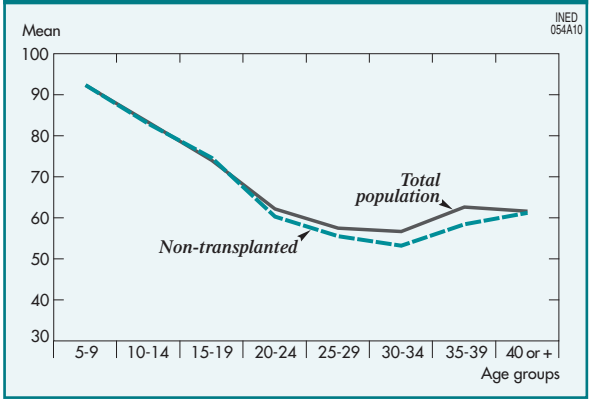
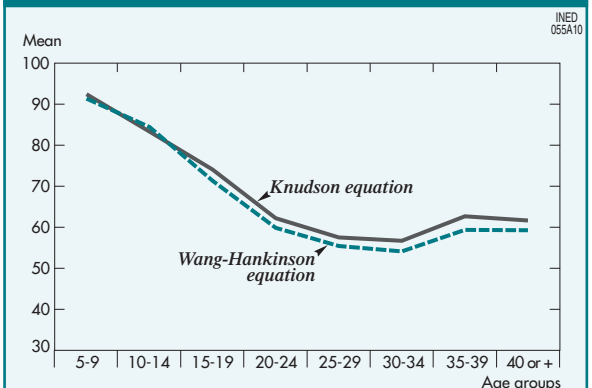


Figure 28 – French CF Registry 2007.
FEV_1 percent predicted
Comparison between Knudson and Wang-Hankinson methods



9 – Appendices

9.1 – Additional information on spirometry

To provide a more comprehensive picture, further comparisons were made using the curves of FEV_1 by age in 2007:
– first, the FEV_1 percent predicted values of all patients were compared with those of patients who had not received a transplant (Figure 27);
– second, the FEV_1 percent predicted values calculated using the Knudson reference equations is compared with the values obtained using the Wang-Hankinson equations [7] (Figure 28).

The two curves (Figure 27) are identical up to age 20-24. After that, and up to age 30-34, the FEV_1 percent predicted of non-transplanted patients drops more sharply than that of the total population. Among older patients (aged 35 or above) an upward trend is observed for both patient categories, **suggesting a selection effect of patients with the mildest forms of CF at these ages.**

9.2 – Summary of data for 2007

– Patients seen in the year (number): 5,140
– Centres (number): 67, of which:
  Paediatric CRCM: 19
  Adult CRCM: 12
  Paediatric and Adult CRCM: 18
– Male patients (%): 52.3
– Patient age in years (mean): 16.8
– Patient age in years (median): 15.0
– Patient age in years (extremes): 0 – 77
– Patients aged 18 or above (%): 42.9
– Age at diagnosis in months (median): 2.0
– New patients diagnosed in the year (number): 205, of which diagnosed by newborn screening: 119
– New patient age at diagnosis in years (extremes): 0 – 65
– Early pregnancies in the year (number): 33
– Conception rate among women aged 15-49 (per 1,000): 28.2

(7) In line with the recommendations to the CFF National Patient Registry, we referred to Wang *et al.* for males aged 6-17 and females aged 6-15; we referred to Hankinson et al. for males aged 18+ and for females aged 16+ .
Wang X., Dockery D. W., Wypij D., Fay M. E. and Ferris B. G., 1993, «Pulmonary function between 6 and 18 years of age», *Pediatric Pulmonology*, 15, pp. 75-88.
Hankinson J. L., Odencrantz J. R. and Fedan K. B., 1999, «Spirometric reference values from a sample of the general US population», *Am J Respir Crit Care Med*, 159, pp. 179-187.

– Age of patients reporting an early pregnancy in years (mean): 28.6
– Deaths (number): 52, of which
  8 patients lost to follow-up
– Crude death rate (per 1,000): 10.4
– Age of deceased patients in years (mean): 27.0
– Age of deceased patients in years (median): 25.5
– Complete genotypes identified (%): 90.2
– Genotypes (%):
  F508del/F508del : 43.1
  F508del/Other : 36.0
  Other/Other: 11.1
– Height z-score (mean):
  patients aged 17 or below: −0.21
  patients aged 18 or above: −0.54
– Weight z-score (mean):
  patients aged 17 or below: −0.47
  patients aged 18 or above: −0.53
– FEV1, percentage of predicted value, Knudson equations (mean):
  patients aged 17 or below: 84.73
  patients aged 18 or above: 61.29
– Patients who had at least 1 sputum culture during the year (%): 93.5
– Positive sputum culture results (%) [8]:
  H. influenzae: 28.4
  MSSA: 50.6
  MRSA: 9.9
  P. aeruginosa: 45.7
  S. maltophilia: 7.5
  B. cepacia: 2.4
  Aspergillus: 18.2
– Complications (%):
  hemoptysis: 5.0
  cirrhosis/portal hypertension: 3.5
  insulin-dependent and non-insulin-dependent diabetes: 12.5
– Therapeutic management (%):
  courses of IV antibiotic treatment: 35.7
  azithromycin: 38.7
  inhaled antibiotics: 37.8
  rhDNase: 42.3
  inhaled bronchodilators: 43.1
  inhaled corticosteroids: 35.3
  pancreatic enzyme supplements 79.9
– Transplanted patients (number): 307, of which
  transplanted in the year: 73
– Patients on the transplant waiting list (number): 145, of which
  added to the list in 2007: 83
  deceased before receiving a transplant: 8

(8) Percentage calculated in relation to patients having at least one sputum culture in the year.