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The French Cystic Fibrosis Data Registry

Annual Data report 2008

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2011

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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) in the blood 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 mucovicidose*. 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 Réunion 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 anonymised data.

Unless otherwise indicated, the results presented hereafter relate to the population seen during the year 2008 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.

1 – Patients seen during the year - Centres participating in the registry

A total of 5,357 patients were seen by the centres who contributed data to the registry in 2008.(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 22 additional patients who were not seen by them during the year but whose vital status was known on 31 December (13 were alive and 9 had died). The registry thus included a potential total of 5,379 patients in 2008, which represents, by our estimates, around 90% of the population with cystic fibrosis in France.

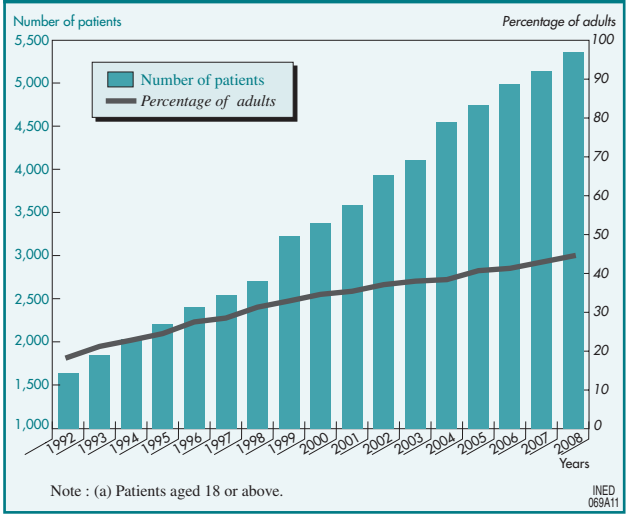
Registration status as a patient with chronic illness/cystic fibrosis under the French social security system (referred to as ALD 18 status) is known for only 814 patients (15.2% of the total), as this variable was included in the registry questionnaire only very recently. Among patients whose status is known, 783 have ALD 18 status, representing 96.2% of the total.

These figures, along with the total number of patients in the registry, compare against a total of 5,268 patients registered with ALD 18 status on 31 December 2008 under the general social security regime (for wage employees) which covers 56.5 million persons (around 88% of the French population enumerated by INSEE).(2)

The majority of the patients in the registry (97.3%) were followed by cystic fibrosis care centres, hereafter referred to by their French acronym CRCM (*centre de ressources et de compétences de la mucoviscidose*), and 2.5% by local centres (Table 1). The average number of patients per type of centre is very variable: above 96 in the CRCM, no more than 15 in the local centres, and 3 in other centres (centres outside the CRCM network or transplant centres). In terms of age, some adult patients are still followed by the paediatric CRCM (where the highest observed age is 48 years) and some young patients are followed by adult CRCM (lowest observed age 12 years).

The annual number of patients included in the registry, whether new or already registered, has risen steadily since 1992 (Figure 1), with a 4.2% increase in 2008 over 2007 (5,140 patients). The proportion of adults (patients aged 18 or above) has also increased: they represented 42.9% of the total in 2007, and 44.5% in 2008. Among adults, 272 patients were aged 40 and above (5.1% of the population), and 12 were aged between 70 and 78.

Figure 1 – French CF Registry 2008. Number of patients seen during the year and percentage of adults (a): trend since 1992



Note : (a) Patients aged 18 or above.

(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, 65 centres were taken into account from among the total of 72 which contributed to the registry in 2008.

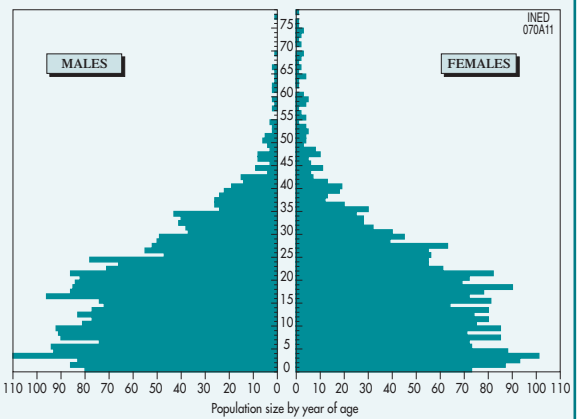
(2) Païta M. and Weill A., 2009, "Les personnes en affection de longue durée au 31 décembre 2008", *Points de repère*, 27, 8 p.

Table 1 – French CF Registry 2008. Characteristics of centres

TYPES OF CENTRE	CHARACTERISTICS						
	Number of centres (a)	Characteristics of patients in centres				Patients' age	
	Total	Total	Proportion (%)	Mean number	Extremes	Mean (years)	Extremes (years)
Paediatric CRCM	19	2,045	38.2	107.6	25 – 282	9.5	0 – 48
Adult CRCM	12	1,428	26.6	119.0	39 – 305	29.5	12 – 76
Paediatric and adult CRCM	18	1,739	32.5	96.6	28 – 205	16.6	0 – 78
Paediatric local centres	10	116 (b)	2.2	11.6	1 – 44	13.5	0 – 42
Adult local centres	1	2	0.0	2.0	2 – 2	23.5	21 – 26
Paediatric and adult local centres	1	15 (c)	0.3	15.0	15 – 15	16.6	6 – 34
Other	4	12 (d)	0.2	3.0	1 – 8	14.1	4 – 34
TOTAL	65	5,357	100.0	82.4	1 – 305	17.3	0 – 78

Notes: (a) After checking for patients in the multiple account category.
(b) Including 23 patients also seen by a CRCM.
(c) Including 3 patients also seen by a CRCM.
(d) Including 3 patients also seen by a CRCM.

Figure 2 – French CF Registry 2008. Population pyramid of patients seen during the year



Note: 153 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, 18 children born in 2007 (of which 8 in December) were diagnosed with cystic fibrosis by neonatal screening in 2008. On the 2007 population pyramid, the number of patients aged 0, which stood at 137, could thus have been 137 +18 = 155.

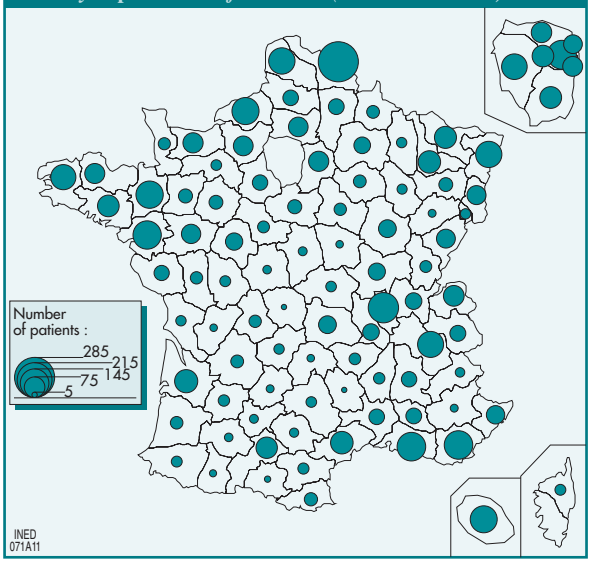
2 – Demographic characteristics

The population is structurally young (Figure 2 and Table 2). The mean age is 17.3 years, the median age is 16.0 years, and 55.5% of the population are under 18 (2,971 patients). The total number of males exceeds that of females: the sex ratio (number of males per 100 females) is 108. This ratio has remained stable over the years, standing at 111 in 2005, 108 in 2006 and 110 in 2007.

Table 2 – French CF Registry 2008. Main characteristics of the population

Characteristics	2008 REGISTRY
OVERALL	
Number of patients	5,357
Number of males per 100 females	108
Children: below age 18 (number and %)	2,971 – 55.5
Adults: age 18 and above (number and %)	2,386 – 44.5
Mean age (in years)	17.3
Median age (in years)	16.0
Extremes of age (in years)	0 – 78
MALES	
Number of patients	2,786
Children: below age 18 (number and %)	1,539 – 55.2
Adults: age 18 and above (number and %)	1,247 – 44.8
Mean age (in years)	17.1
Median age (in years)	16.0
Extremes of age (in years)	0 – 77
FEMALES	
Number of patients	2,571
Children: below age 18 (number and %)	1,432 – 55.7
Adults: age 18 and above (number and %)	1,139 – 44.3
Mean age (in years)	17.4
Median age (in years)	16.0
Extremes of age (in years)	0 – 78

Map 1 – French CF Registry 2008. Distribution of patients by **département** *of residence (absolute numbers)*



The place of residence is known for 5,257 patients in the registry in 2008, representing 98.1% of the population. There are marked differences between the *départements* of metropolitan France (Map 1). The majority of patients (nearly 58%) are concentrated firstly in a north-western arc (Nord-Pas-de-Calais, Normandy, Brittany and 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 8.1 patients per 100,000 inhabitants over the whole territory (metropolitan France and Réunion Island), with marked variations between *départements* (Map 2), the highest densities being seen particularly in the *départements* of Doubs, Territoire de Belfort, Meurthe-et-Moselle, Côtes-d'Armor, Finistère, Ille-et-Vilaine, Haute-Corse, Var and Réunion Island (12 patients or more per 100,000).

Map 2 – French CF Registry 2008.
Prevalence of cystic fibrosis by **département**
(number of patients per 100,000 inhabitants)

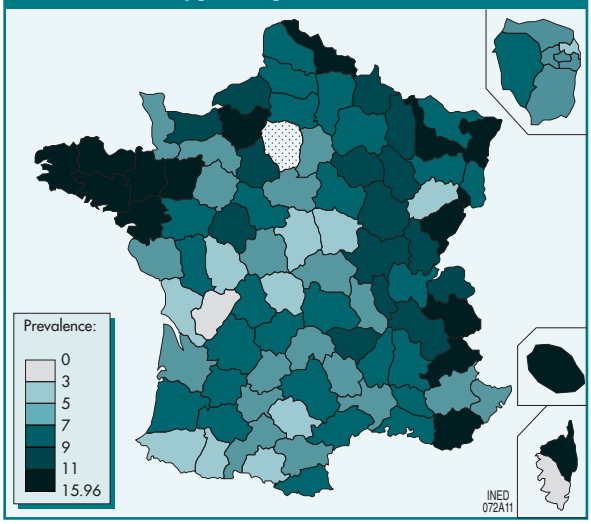
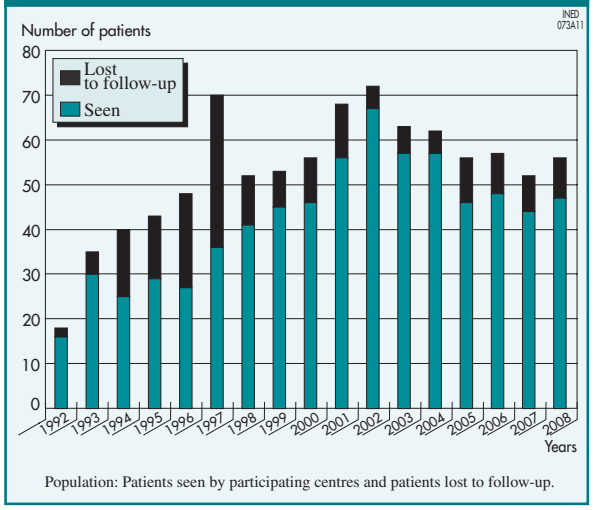


Figure 3 – French CF Registry 2008.
Number of deaths in the year: trend since 1992



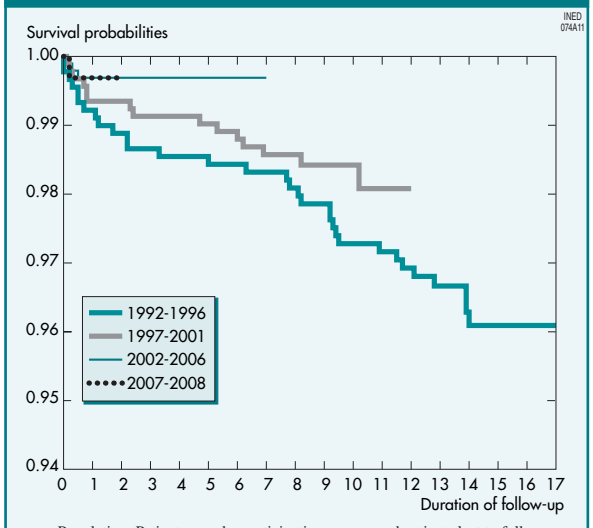
Population: Patients seen by participating centres and patients lost to follow-up.

A total of 56 deaths occurred in 2008 (a crude mortality rate of 10.8 per 1,000): 47 patients of participating centres and 9 patients lost to follow-up. This annual total is similar to that of 2007 (Figure 3). A slight downtrend in deaths has been observed in the last six 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 28.2 years, with the youngest aged below 1 [(3)] and the oldest aged 66. The mean age at death has increased steadily over the last five years.

Length of life is expressed in terms of survival probabilities calculated by survival analysis (Kaplan-Meier method).[(4)] It was calculated for four different birth cohorts (Figure 4): patients born in 1992-1996 (in 2008 this cohort had been followed for a maximum of 17 years), in 1997-2001 (followed for 12 years maximum), in 2002-2006 (followed for 7 years maximum) and in 2007-2008 (followed for 2 years maximum). A total of 3,117 patients were included in the analysis, among whom 51 had died. For a comparable duration of follow-up, the younger the cohort, the higher the survival probability, although only one significant difference is observed: at 7 years of follow-up, between the 1992-1996 cohorts for whom survival probability is 98.31% (95% CI [97.22 – 98.98]) and the 2002-2006 cohorts for whom it is 99.68% (95% CI [99.04 – 99.89]).

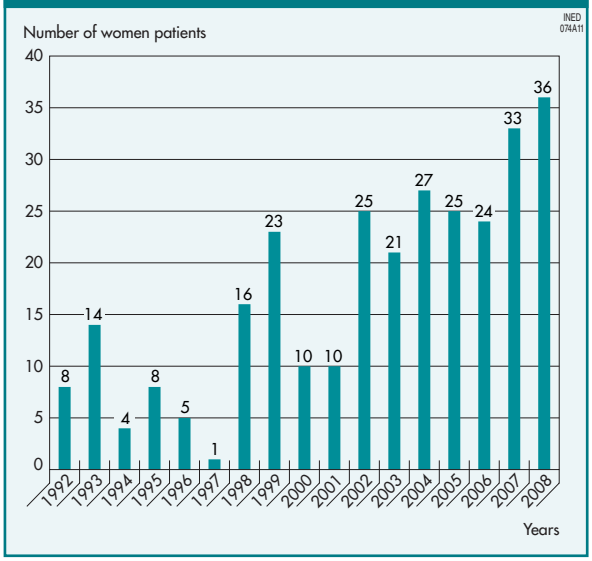
A total of 36 early pregnancies were reported to the registry in 2008 and the mean age of the women concerned was 27.0 years. This number is the highest since the registry first began (in 2008 the conception rate was 29 per 1,000 among female patients aged 15-49), although annual variations are very large (Figure 5).

Figure 4 – French CF Registry 2008.
Survival curves by cohort (Kaplan-Meier method)



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

Figure 5 – Number of women patients reporting early pregnancy during the year: trend since 1992



(3) The death was attributed to preterm birth.

(4) See appendix for additional information on survival analysis.

3 – Diagnosis

A total of 235 new patients were diagnosed in 2008, i.e. 4.4% of the total population (Table 3). By comparison, the numbers of new cases in 2006 and 2007 were 234 (4.7% of the total) and 205 (4.0%), respectively.

A total of 144 patients were diagnosed by neonatal screening (representing 61.3% of new cases in 2008) versus 172 (73.5%) and 118 (57.6%) in 2006 and 2007, respectively.

The number of patients diagnosed by neonatal screening (144) 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 2008. Main characteristics of diagnosis

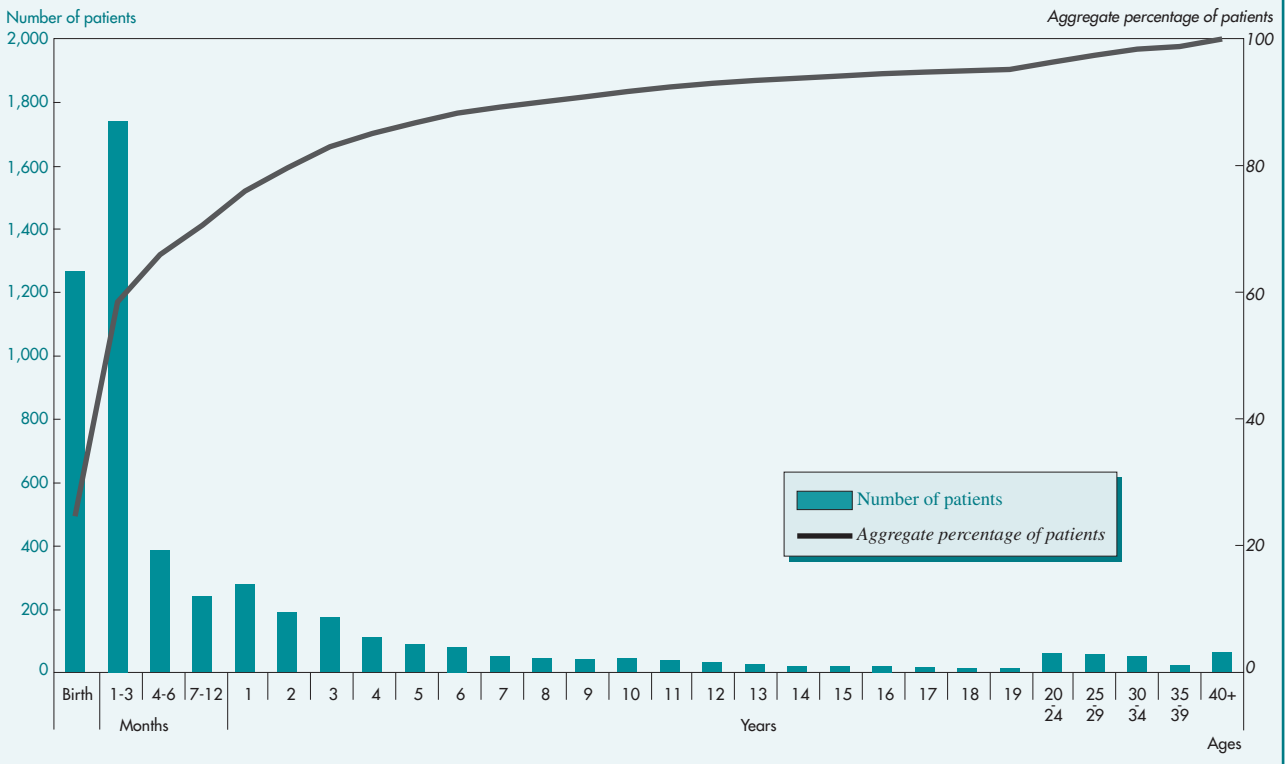
Characteristics	2008 REGISTRY
NEW PATIENTS DIAGNOSED DURING THE YEAR	
All new patients (all diagnostic signs) (a)	
New patients (number and %)	235 – 4.4
Mean age at diagnosis (in months)	60.4
Median age at diagnosis (in months)	1.0
Extremes of age at diagnosis (in years)	0 – 58
Context of diagnosis	
Prenatal diagnosis (number and %)	5 – 2.1
Patients diagnosed on the basis of meconium ileus [MI] (number and %)	26 – 11.1
Patients diagnosed by neonatal screening [excluding patients diagnosed before screening results were known] (number and %)	144 – 61.3
Patients diagnosed through symptoms [other than MI] (number and %)	52 – 22.1
Mean age at diagnosis (in years) of patients diagnosed through symptoms (other than MI)	21.4
ALL PATIENTS	
Patients whose age at diagnosis is known (number and %)	5,145 – 96.0
Mean age at diagnosis (in months)	37.3
Median age at diagnosis (in months)	2.0
Extremes of age at diagnosis (in years)	0 – 74

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

Among the 235 new patients, 153 were born in 2008. The method used to compile this report (patients seen in a care centre in 2008) means that infants born in 2008 and seen for the first time in 2009 are excluded.

Out of the 5,145 patients whose age at diagnosis is known, half were diagnosed with cystic fibrosis before the age of 2 months (Figure 6).

Figure 6 – French CF Registry 2008. Number of patients and aggregate percentage of patients by age at diagnosis



Note: N = 5,145 (number of patients whose age at diagnosis is known).

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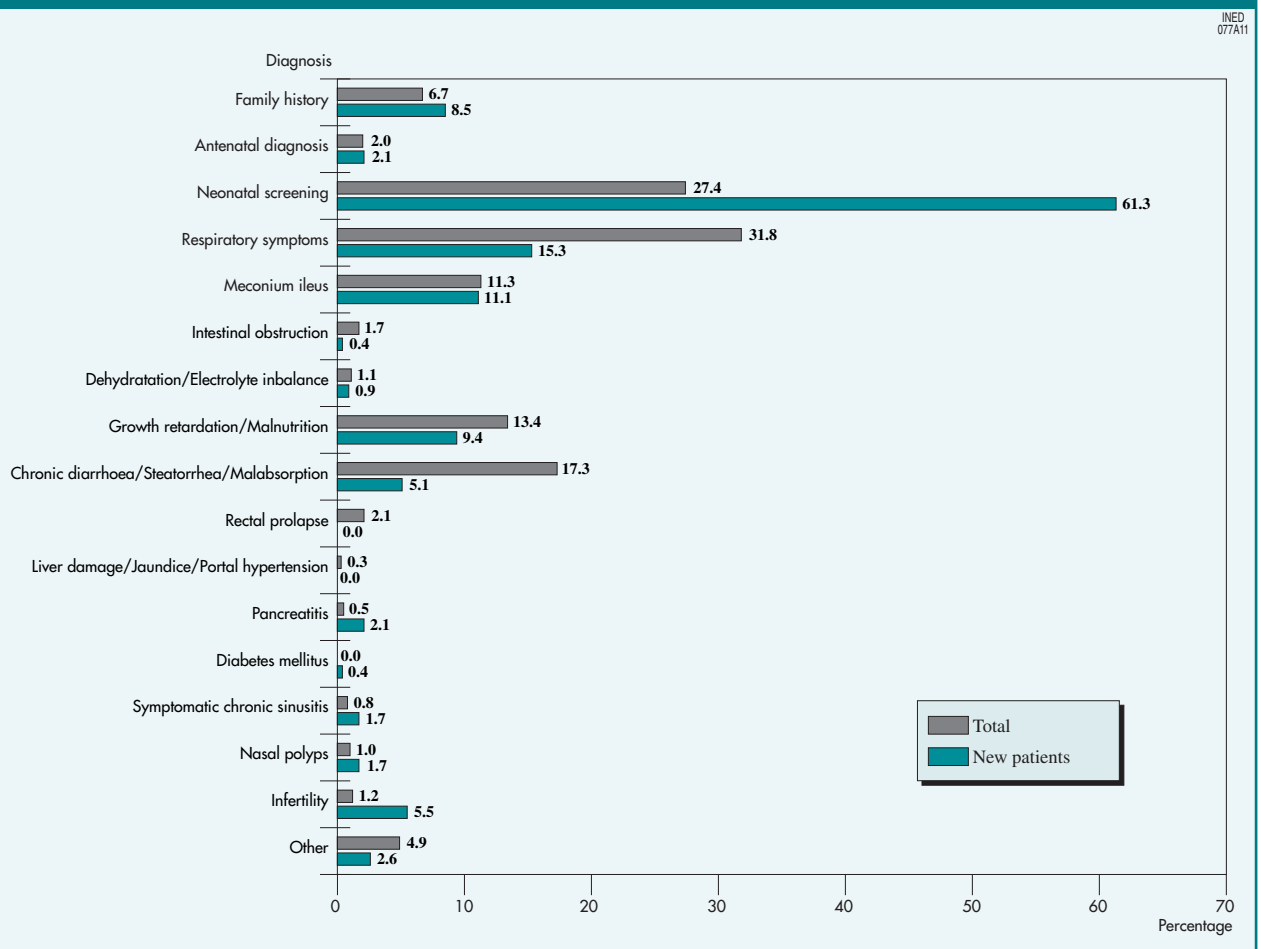
Diagnostic signs are shown in Figure 7. The most frequent for all the patients are respiratory symptoms (31.8%), neonatal screening, which concerns more than a quarter of patients in the registry (27.4%), followed by chronic diarrhoea/steatorrhoea/malabsorption (17.3%), growth retardation/malnutrition (13.4%) and meconium ileus (11.3%). Among the year's 235 new patients, the majority were diagnosed by neonatal screening, as in previous years (61.3%), followed by respiratory difficulties (15.3%), meconium ileus (11.1%) and growth retardation/malnutrition (9.4%).

With regard to the *CFTR* gene, the genotypes of 5,006 patients in the registry had been identified in 2008, representing 93.4% of the population; 3.4% of patients have genotypes with a single identified mutation and the other patients (3.2%) did not undergo genetic analysis or had a genotype consisting of unstudied or as yet unidentified mutations.

Figure 7 – French CF Registry 2008. 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 (43.8% of identified genotypes), and the proportion of F508del/other genotypes is 37.2%. 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 3.8% among new patients diagnosed in 2008.

Table 4 – French CF Registry 2008. Numbers and proportions of genotypes by decreasing frequency

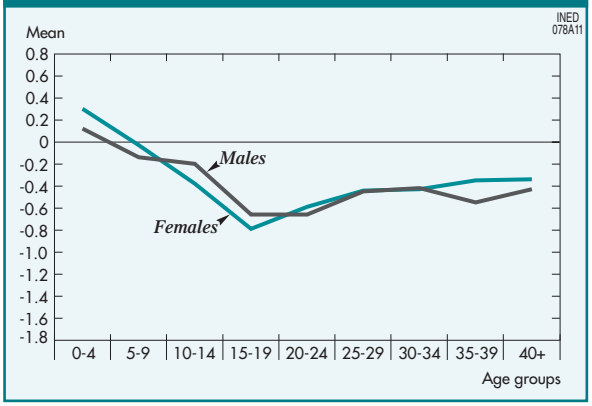
GENOTYPES	Number of patients	Proportion (%)
F508del / F508del	2,345	43.8
F508del / G542X	168	3.1
F508del / N1303K	121	2.3
F508del / 1717-1G->A	90	1.7
F508del / 2789+5G->A	77	1.4
F508del / R117H	73	1.4
F508del / R553X	60	1.1
F508del / G551D	50	0.9
F508del / Y122X	42	0.8
F508del / W1282X	41	0.8
F508del / 3272-26A->G	39	0.7
F508del / 3849+10kbC->T	36	0.7
F508del / I507del	35	0.7
F508del / 2183AA->G	30	0.6
F508del / L206W	29	0.5
F508del / R347P	28	0.5
F508del / Y1092X	25	0.5
F508del / A455E	24	0.4
F508del / R1162X	24	0.4
F508del / 1078delT	21	0.4
F508del / 3659delC	19	0.4
F508del / 711+1G->T	19	0.4
F508del / S1251N	18	0.3
F508del / G85E	17	0.3
N1303K / N1303K	17	0.3
F508del / E60X	16	0.3
F508del / 394delTT	16	0.3
G542X / G542X	16	0.3
F508del / 3120+1G->A	15	0.3
F508del / 1811+1.6kbA->G	14	0.3
Y122X / Y122X	13	0.2
F508del / W846X	13	0.2
F508del / R334W	11	0.2
F508del / 621+1G->T	10	0.2
711+1G->T / 711+1G->T	10	0.2
G542X / 2789+5G->A	8	0.1
G542X / R117H	7	0.1
Other *CFTR* genotypes	1,409	26.3
SUB TOTAL	5,006	93.4
F508del / Unidentified	119	2.2
Other / Unidentified	63	1.2
Unidentified / Unidentified	169	3.2
TOTAL	5,357	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 = 51.24; $p < 10^{-4}$).

Table 5 – French CF Registry 2008. Age of patients by genotype: summary

GENOTYPES			PATIENTS' AGE		
	Number	Proportion (%)	Mean (years)	Median (years)	Max. age (years)
F508del / F508del	2,345	43.8	16.3	16.0	54
F508del / Other	1,995	37.2	16.8	15.0	68
Other / Other	666	12.4	16.8	15.0	76
F508del / Unidentified	119	2.2	25.1	22.0	73
Other / Unidentified	63	1.2	23.9	22.0	66
Unidentified / Unidentified	169	3.2	29.6	26.0	78

Figure 8 – French CF Registry 2008. 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 [5] 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 8). The z-scores are near 0.20 at the age of 0-4 years, and gradually become negative in the period of adolescence (–0.73 on average at age 15-19). Although they subsequently improve, mean z-scores remain negative in adulthood, with values of between –0.66 and –0.34.

(5) The z-score corresponds to the centred reduced anthropometric variable ($z = \frac{measure - mean}{st.dev}$) 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 9 – French CF Registry 2008. Weight z-score (mean by sex and age)

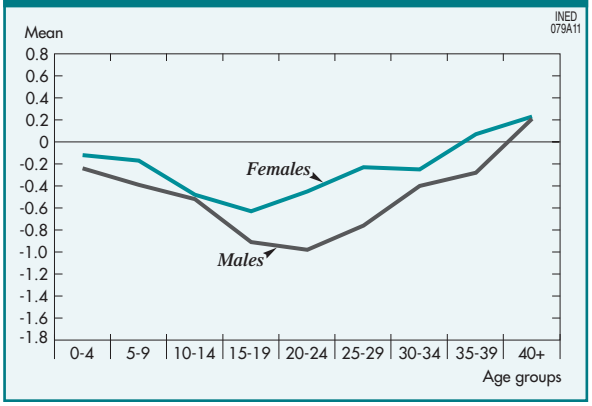
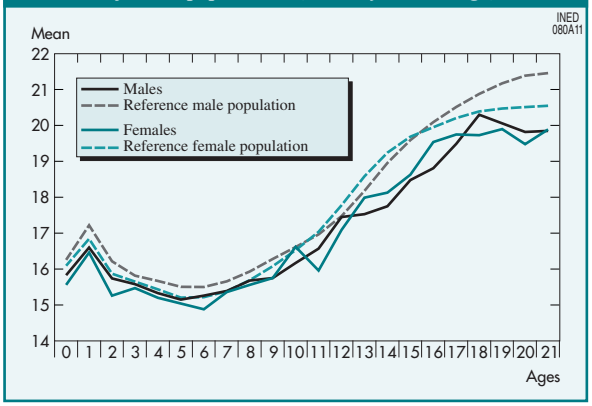


Figure 10 – French CF Registry 2008. Body mass indices (BMI) compared with the BMIs of the male and female reference populations (mean by sex and age)



In terms of weight, the differences between males and females at different ages are quite marked, with females having higher scores (Figure 9). From the first years of life, considerable slowing in weight gain occurs, with z-scores of approximately –0.18 at the ages of 0-4 years. As is the case for height, z-scores decrease from adolescence to early adulthood in males (–0.98 on average at age 20-24), while in females, weight recovery occurs earlier (–0.63 on average at age 15-19, falling to –0.45 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 10). Differences with respect to the reference populations emerge mainly from age 11 among females and from age 13 among males; they then persist, becoming even more pronounced among males. For females, the disparity narrows around age 16-17 before widening again.

Figure 11 – French CF Registry 2008. FVC percent predicted (mean by sex and age)

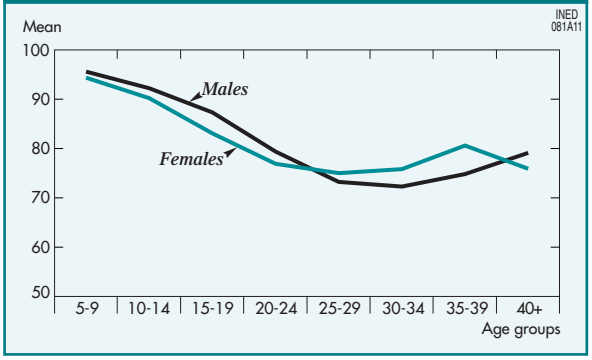
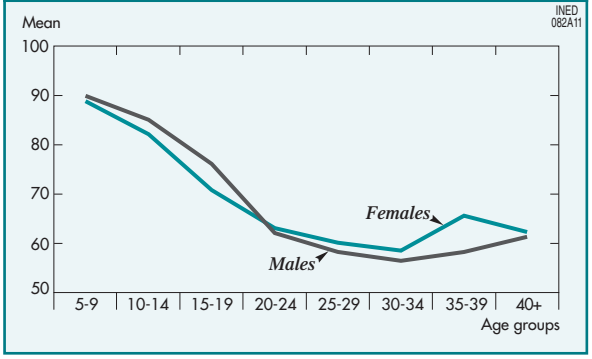


Figure 12 – French CF Registry 2008. FEV_1 percent predicted (mean by sex and age)



5 – Spirometry [6]

In 2008, 90.9% 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 equivalent to that of 2007 (90.6%) and higher than in 2006 (87.2%).

The forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), are expressed as percentages of the predicted values [7]. Starting at levels around 90-95% (Figures 11 and 12), FVC and FEV_1 decrease progressively up to ages 25-34 among men and women (FVC at these ages is around 73% and FEV_1 around 58% of the predicted values). A slight improvement is then observed. **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**.

(6) See appendix for additional information on spirometry.

(7) 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 13 – French CF Registry 2008. FEV_1 percent predicted classes (as a percentage of the total for each population)

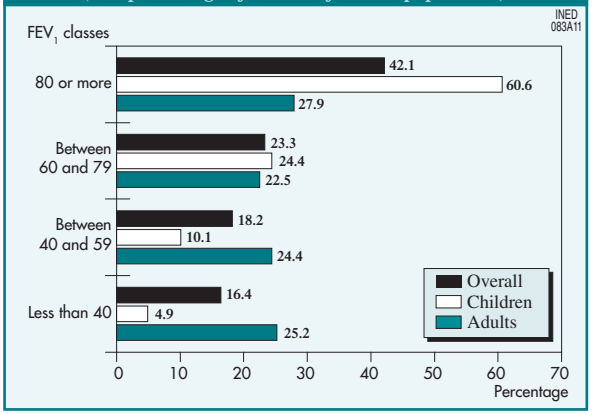
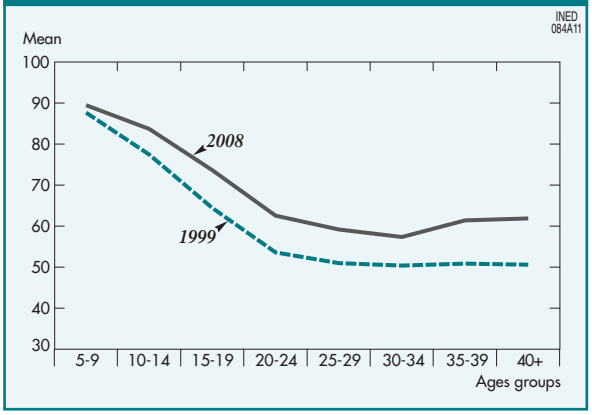


Figure 14 – FEV_1 percent predicted in 2008 compared with 1999 (mean by age)



The FEV_1 values are divided into four «functional» classes corresponding to different degrees of bronchial obstruction (Figure 13). The majority (60.6%) 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, with 25.2% having an FEV_1 below 40% of the predicted normal.

For comparison, the mean FEV_1 values at different ages in 2008 are given with those of 1999 (Figure 14). The two curves have practically identical profiles, but the 2008 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, and probably also to the selection effect of older patients.

6 – Microbiology

In 2008, 92.6% of the patients had at least one sputum culture (Table 6), a proportion that has remained stable (93.5% in 2007 and in 2006). Note that among patients who did not have a sputum culture in the year, almost 35% were transplanted patients.

Table 6 – French CF Registry 2008. Sputum cultures

Patients who had at least 1 sputum culture during the year	NUMBER	PERCENTAGE
Overall	4,961	92.6
Children (below age 18)	2,861	96.3
Adults (age 18 or above)	2,100	88.0

Figure 15 – French CF Registry 2008. Clinically important bacteria (percentage by age)

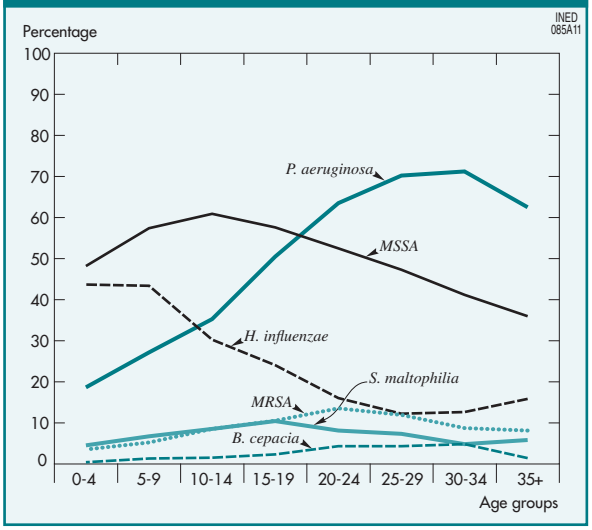


Figure 16 – Bacteria in 2008 compared with 1999 (percentage by age)

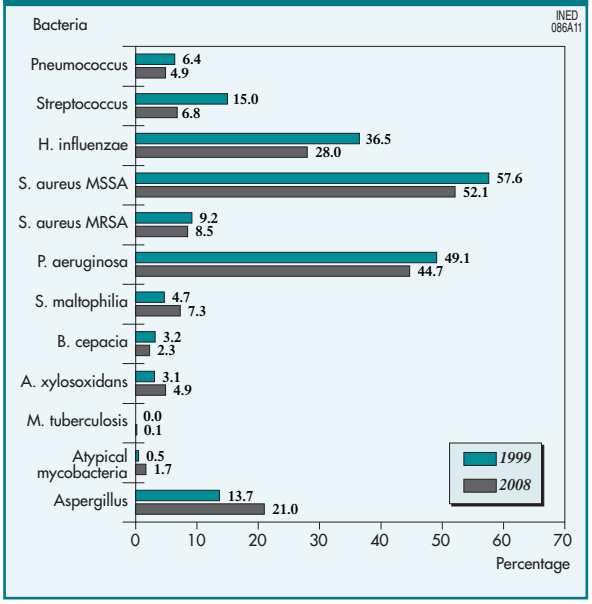


Figure 15 shows the distribution by age of five bacteria considered to be of clinical importance, *Staphylococcus aureus* being divided into MSSA (methicillin-susceptible) and MRSA (methicillin-resistant).

The patients' age distribution profile by bacteria remains practically unchanged with respect to the previous year (2007 data). Some of these micro-organisms are frequently detected at a very young age: at age 0-4 years, *Haemophilus influenzae* is present in 43.7% of patients and MSSA in 48.2% (in 2005, the proportions in both cases were above 50% in this age group). *Pseudomonas aeruginosa*, present in 18.7% of patients aged 0-4, is most frequent (71.2%) in patients aged 30-34. MRSA was detected among 3.6% of the 0-4 age group. The proportion rises to 13.6% among the 20-24 age group (14.3% in this age group in 2007) then falls slightly to around 9% at the highest ages.

Figure 16 gives the variations observed for the organisms documented in 2008 compared with 1999. It shows a number of significant changes. Downward: Streptococci, which fell from 15.0% of all patients who had a sputum culture in 1999 to 6.8% in 2008 ($p < 10^{-9}$), *Haemophilus influenzae* (36.5% to 28.0%; $p < 10^{-9}$), MSSA (57.6% to 52.1%; $p < 10^{-5}$), *Pseudomonas aeruginosa* (49.1% to 44.7%; $p < 10^{-3}$) *Streptococcus pneumoniae* (6.4% to 4.9%; $p < 10^{-2}$), and *Burkholderia cepacia* (3.2% to 2.3%; $p < 0.05$).

Upward: *Aspergillus* (from 13.7% in 1999 to 21.0% in 2008; $p < 10^{-9}$), *Stenotrophomonas maltophilia* (4.7% to 7.3%; $p < 10^{-5}$), atypical mycobacteria (0.5% to 1.7%; $p < 10^{-5}$) and *Achromobacter xylosoxidans* (3.1% to 4.9%; $p < 10^{-3}$).

In addition, out of the 2,218 patients colonised by *Pseudomonas aeruginosa*, chronic colonisation [8] was observed in 54.7% of cases (multi-resistant or otherwise); colonisation with multi-resistant strains [9] (chronic or non-chronic) represented 23.1% of cases. Information was missing for almost 30% of them, however.

(8) 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)

(9) Multi-resistant colonization: resistant to all antibiotics in at least two antibiotic classes

Figure 17 – French CF Registry 2008.
Events occurring during the year:
1 – Respiratory complications (percentage by age)

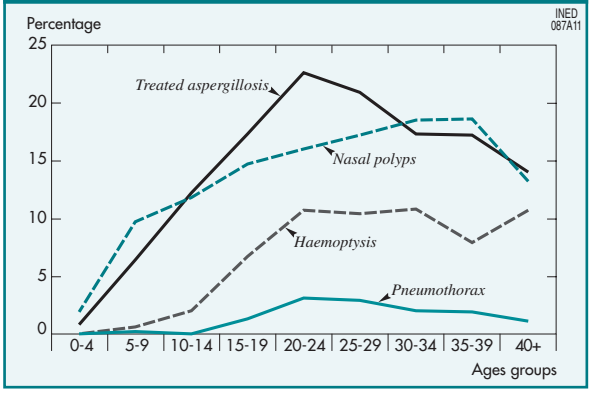
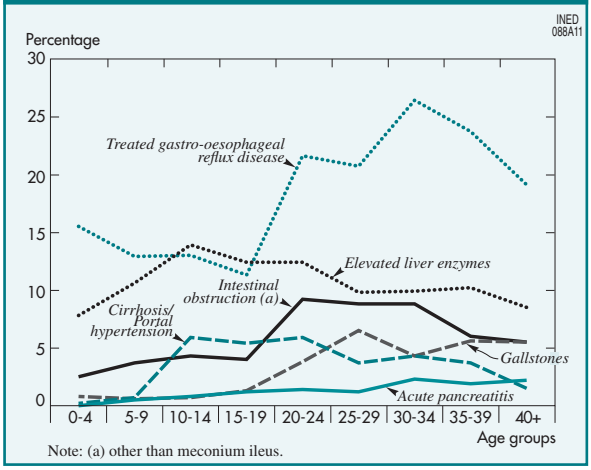


Figure 18 – French CF Registry 2008.
Events occurring during the year:
2 – Gastro-intestinal problems (percentage by age)



Note: (a) other than meconium ileus.

7 – Complications Transplants

Patients with no reported complications represent 7.3% of the total.

The main events recorded during the year 2008 are grouped into broad categories and shown by age in Figures 17 to 20.

In brief, among the youngest patients, the most frequent complications were elevated liver enzymes, treated gastrooesophageal reflux disease and treated aspergillosis (13.9%, 13.0% and 12.2%, respectively, at ages 10-14, for example), and nasal polyps (11.8% at ages 10-14 and 9.7% at ages 5-9). Cirrhosis/Portal hypertension and diabetes (insulin-dependent or otherwise) were also relatively frequent (5.9% and 3.8% respectively at ages 10-14).

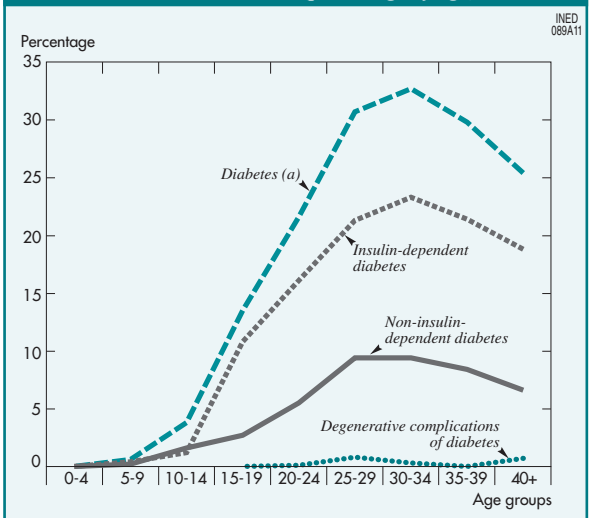
In adult patients, where morbidity is higher, elevated liver enzymes, treated gastro-oesophageal reflux disease and treated aspergillosis were still very frequent (12.4%, 21.6% and 22.6%, respectively, at ages 20-24, for example), and almost one-third (31.2%) of the population aged 25-39 had diabetes. Note also that in adults, the frequency of bone diseases (7.1% at ages 30-34) and arthropathy (7.7% at age 40 and above) was also noticeably high.

Only 27 patients (0.5% of the total), almost all of whom were women, were affected by urinary incontinence. 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 on Figure 18, though 83.0% of patients had pancreatic insufficiency (versus 74.8% in 2007). This proportion remains reasonably stable with age: 79.5% at age 0-4, 90.0% at age 20-24, 84.7% at age 30-34, 65.3% after age 35.

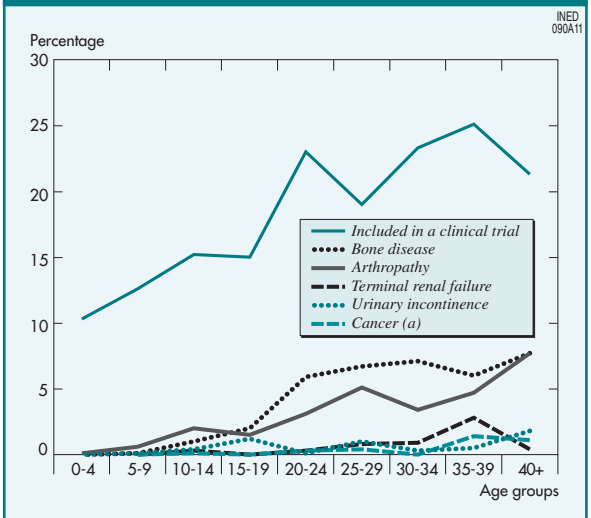
An exceptionally large number of patients were included in clinical trials in 2008: a total of 888 patients of all ages were concerned (16.6% of the population), with more than 10% of children aged 0-4 and 25.1% of patients aged 35-39 taking part.

Figure 19 – French CF Registry 2008.
Events occurring during the year:
3 – Diabetes mellitus (percentage by age)



Note: (a) Total diabetes.

Figure 20 – French CF Registry 2008.
Events occurring during the year:
4 – Other events (percentage by age)



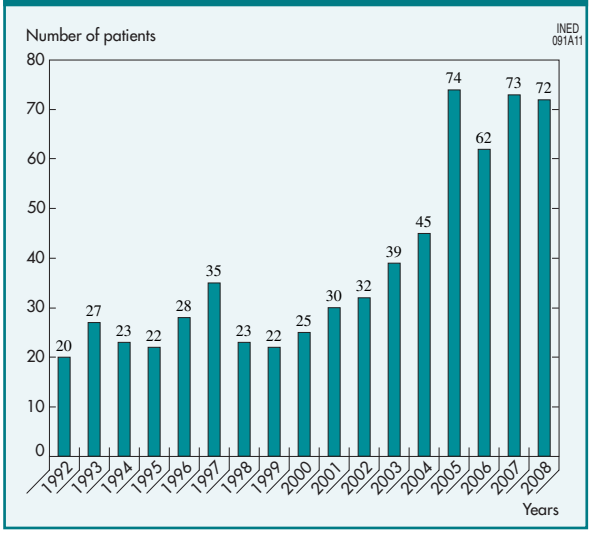
Note: (a) Among patients of all ages, 11 have cancer, of whom 6 are transplanted.

Table 7 – French CF Registry 2008. Transplants:
1 – Main characteristics

Characteristics	2008 REGISTRY	
TRANSPLANTED PATIENTS	**ALL PATIENTS (a)**	**TRANSPLANTED IN 2008 (b)**
Number of patients	353	72
Mean age (in years)	29.6	26.4
Extremes of age (in years)	8 – 53	8 – 45
Bilateral lung transplants (number and %)	282 – 79.9	64 – 88.9
Heart-lung transplants (number and %)	32 – 9.1	4 – 5.6
Liver transplants (number and %)	29 – 8.2	5 – 6.9
Kidney transplants (number and %)	11 – 5.3	3 – 4.2
Other and unidentified transplants (number and %)	13 – 3.7	1 – 1.4
Patients deceased in 2008	20	6
PATIENTS ON THE TRANSPLANT WAITING LIST (C)		
Number of patients	171	
Mean age (in years)	26.1	
Extremes of age (in years)	8 – 50	
New patients registered on the waiting list in 2008 (number and %)	70 – 40.9	
Patients on the waiting list who died in 2008	6	

Notes: (a) All patients transplanted in 2008 or before.
(b) Patients transplanted in 2008 only.
(c) All patients registered on the transplant waiting list in 2008 or before.

Figure 21 – French CF Registry 2008. Transplants:
2 – Annual number of transplanted patients:
trend since 1992



In 2008, 353 patients (6.6% of the population) had received a transplant (Table 7). In around 80% of cases, they were bilateral lung transplants. A total of 72 transplant operations (1.3% of the total population) were performed in 2008 alone, with, as previously, a large majority of bilateral lung transplants. In 2008, a total of 171 patients were on the waiting list (3.2% of the population), of whom 70 were added in 2008. Six patients awaiting a transplant died in 2008, representing 10.7% of deaths in the year.

The number of transplants in 2008 was close to the numbers in 2006 (73 transplants) and in 2005 (74 transplants), the year with the highest number of transplants since the beginning of the registry (Figure 21).

Figure 22 – French CF Registry 2008.
Outpatient and inpatient visits (by age)

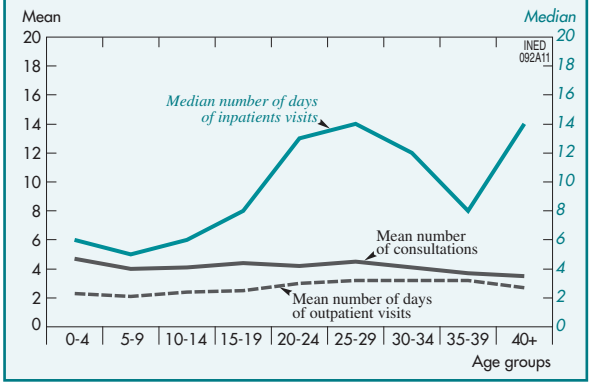


Figure 23 – French CF Registry 2008.
Courses of IV antibiotic treatment:
1 – Patients receiving at least one course of treatment; patients with a TIVAD (by age)

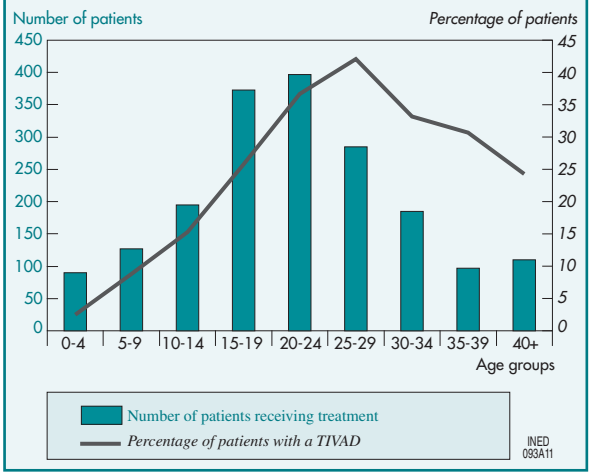
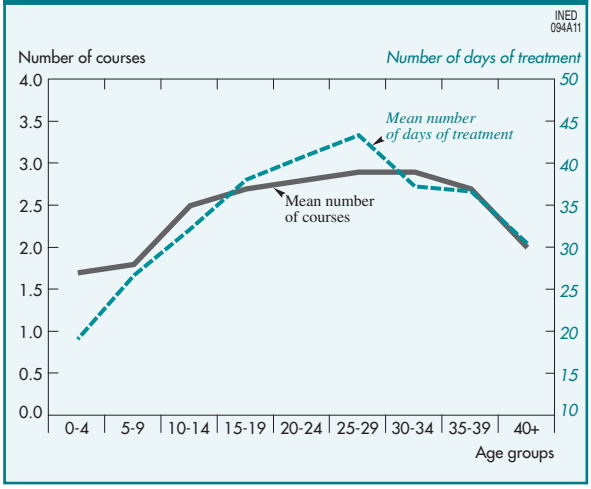


Figure 24 – French CF Registry 2008.
Courses of IV antibiotic treatment:
2 – Mean number of courses and of days of treatment (by age)



8 – Outpatient and inpatient visits Therapeutic management

On average, 4.3 outpatient visits were counted per patient during the year and 2.6 one-day hospital stays. These figures vary only slightly between the different age groups (Figure 22). The proportions of outpatient visits and one-day hospital stays vary considerably between centres, however.

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 22. This median number of days, which was 9.0 for the whole of the population, remains lower for children (5 to 6 days for patients aged under 15) and more variable for adults (8 to 14 days in the years, depending on age).

A total of 1,859 patients received at least one course of intravenous antibiotic treatment in 2008 (i.e. 34.7% of the total population), of which 770 were in the 15-19 and 20-24 age groups. These two age groups accounted for 41.4% of patients receiving courses of treatment (Figure 23).

In all, 21.4% of patients had totally implantable vascular access devices (TIVAD). The proportion increases up to age 30, as shown in Figure 23. 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 2.6 treatment courses, on average, in the year. This average increases steadily with age, rising from 1.7 courses per year among the youngest patients (aged 0-4) to 2.9 courses at age 25-34. Beyond this age, the average drops again to 2 courses per year (Figure 24).

The total number of days of IV treatment in the year spans a broad range, from 1 day to a maximum of 183 days. However, these treatment courses generally take place over a period of 2 weeks (30.7% of patients), one month (19.1% of patients) or 45 days (6.2% of patients). The mean number of days of IV treatment per year is 36.6 for all patients receiving IV treatments, with a highest mean of 43.4 days of treatment at age 25-29 (Figure 24).

Figure 25 – French CF Registry 2008. Therapeutic management: 1 – Respiratory treatment (percentage by age)

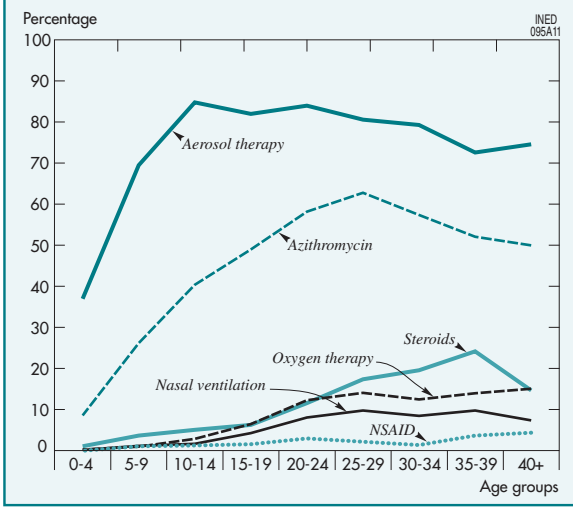


Figure 26 – French CF Registry 2008. Therapeutic management: 2 – Products administered by aerosol therapy (percentage by age)

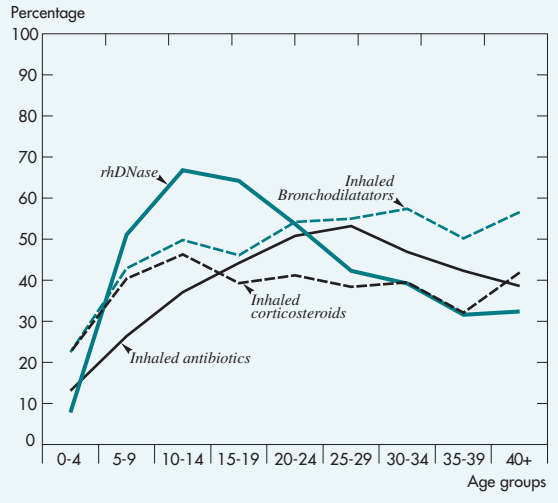
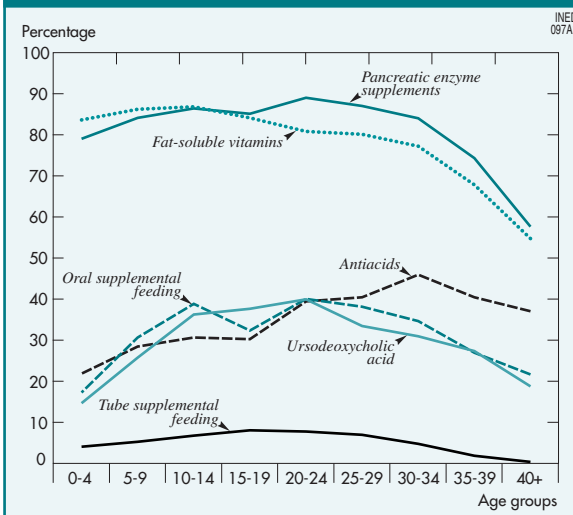


Figure 27 – French CF Registry 2008. Therapeutic management: 3 – Digestive and nutritional treatment (percentage by age)



The main types of therapeutic management, with the exception of IV treatment, are grouped by categories and represented by age in Figures 25 to 27.

Among respiratory treatments, oxygen therapy, non-invasive ventilation and anti-inflammatory drugs (NSAID and steroids) were each administered to less than 8.6% of all patients. Frequencies were much higher for azithromycin (40.8% overall, 49.0% to 52.1% in patients aged 15-39) and for long-term aerosol therapy (72.2% overall and more than 80% in patients aged 10-29).

The products administered by aerosol therapy were most often inhaled bronchodilators (45.6%) and rhDNase (45.1%). Inhaled corticosteroids were administered to 37.7% of patients and antibiotics to 36.8% of patients.

In 37% of cases, aerosol therapy was administered by nebulisation. For close to 41% of patients, nebulisation was associated with a spray or powder; while for 13%, a spray or powder was administered alone (although the mode of administration is not specified in more than 9% of cases).

Regarding digestive and nutritional treatment, pancreatic enzyme supplements were given to 83% 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, 31.5% of patients received long-term oral supplemental feeding and 5.8% long-term tube supplemental feeding. Among the latter, 69.2% received feeding by gastrostomy and 25.6% by nasogastric tube. In addition, 29.9% of patients took ursodeoxycholic acid, 32.7% took antacids (H2 blockers or Proton Pomp Inhibitors) and almost 81.4% took fat soluble vitamins.

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 2008:
– 1/ the FEV_1 of all patients was compared to that of patients who had not received a heart-lung or bilateral lung transplant (Figure 28). The two curves 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, with a difference of almost 3 percentage points. 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.**
– 2/ the FEV_1 percent predicted values calculated using the Knudson reference equations was compared with the values obtained using the Wang-Hankinson equations [10] (Figure 29). The FEV_1 percent predicted values calculated using the two methods are very similar up to age 14; but from age 15, the Wang-Hankison equations give FEV_1 values which are systematically lower – by between 2.6 and 2.7 percentages points – than those obtained with the Knudson equations.

Figure 28 – French CF Registry 2008. FEV_1 percent predicted Comparison between total population and patients who had not received a lung transplant

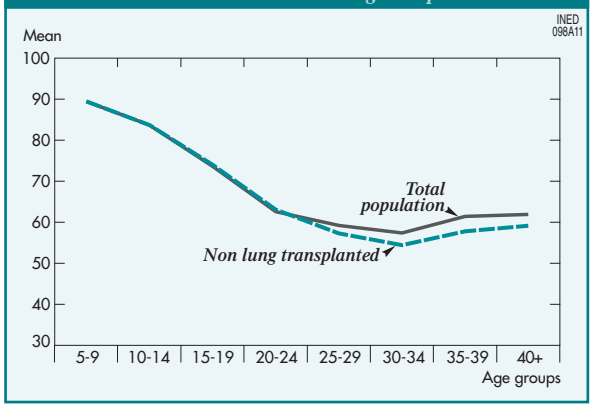
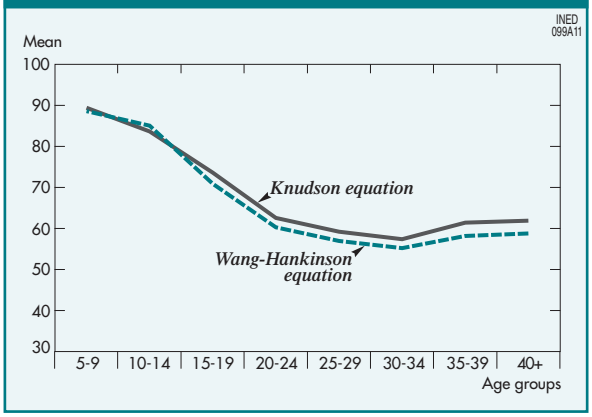


Figure 29 – French CF Registry 2008. FEV_1 percent predicted Comparison between Knudson and Wang-Hankinson methods

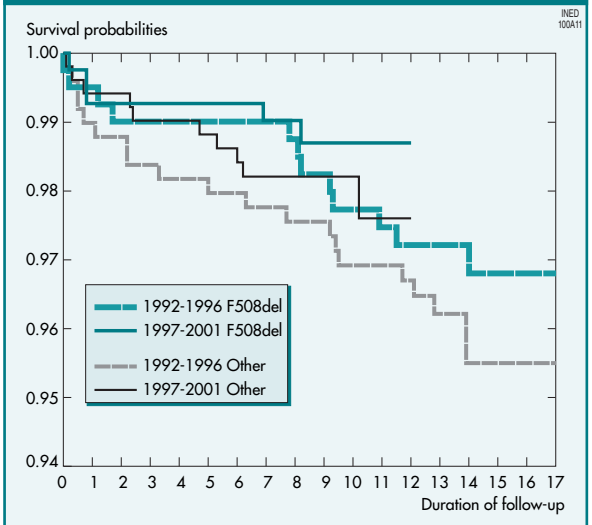


(10) In line with the recommendations to the CFF National Patient Registry, we referred to Wang *et al*. for males aged 6-17 and females aged 6-15; we referred to Hankinson *et al*. for males aged 18+ and for females aged 16+ .

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.

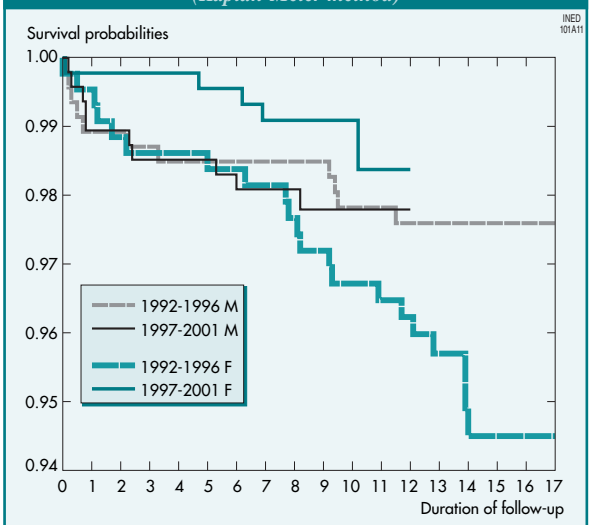
Hankinson J. L., Odencrantz J. R. and Fedan K. B., 1999, "Spirometric reference values from a sample of the general US population", *Am J Respir Crit Care Med*, 159, pp. 179-187.

Figure 30 – French CF Registry 2008.
Survival curves by birth cohort and genotype
(Kaplan-Meier method)



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

Figure 31 – French CF Registry 2008.
Survival curves by birth cohort and sex
(Kaplan-Meier method)



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

9.2 – Additional information on survival analysis

Additional survival analysis was performed for the two oldest cohorts, those of patients born in 1992-1996 and in 1997-2001, to obtain sufficiently long follow-up periods. The analyses were performed in two stages:

– 1/ for each cohort, patients were divided into two subgroups according to genotype (Figure 30): first, homozygotes for the F508del mutation (labelled "1992-1996 F508del", for example, in the first cohort), and second, patients with a quite different genotype, including composite heterozygotes for F508del (labelled "1992-1996 Other" in the first cohort). The proportion of F508del homozygous genotypes is 45.0% in the 1992-1996 cohort and 44.5% in the 1997-2001 cohort. For a given birth cohort, the survival of F508del homozygous patients appears to be better than that of patients with a different genotype, although the differences observed are not significant.

– 2/ each cohort was divided into two sub-groups by sex (Figure 31) and labelled, for the first cohort, for example, "1992-1996 M" or "1992-1996 F". 51.7% of patients in the 1992-1996 cohort are male and 51.2% in the 1997-2001 cohort. In the 1992-1996 cohort, survival of males appears to be better than that of females (except in the first years of life), and the opposite is observed for the 1997-2001 cohort, although the differences observed are not significant, even for the 1992-1996 cohort for which the difference appears quite marked after 17 years of follow-up: the survival probability for males is 97.58% (CI 95% [95.68; 98.65]), and for females it is 94.47% (CI 95% [91.56; 96.40]).

9.3 – Summary of data

	2008	2007 (for comparaison)
Patients seen during the year and centres participating in the registry		
- Patients seen in the year (number):	5,357	5,140
- Centres (number):	65	67
Paediatric CRCM	19	19
Adult CRCM	12	12
Paediatric and Adult CRCM	18	18
Demographic characteristics		
- Male patients (%)	52.0	52.3
- Patient age in years (mean)	17.3	16.8
- Patient age in years (median)	16.0	15.0
- Patient age in years (extremes)	0 – 78	0 – 77
- Patients aged 18 and above (%)	44.5	42.9
- Early pregnancies in the year (number)	36	33
- Conception rate among women aged 15-49 (per 1,000)	29.1	28.2
- Age in years of patients reporting an early pregnancy (mean)	27.0	28.6
- Deaths (number)	56	52
of which deaths of patients lost to follow-up	9	8
- Crude death rate (per 1,000)	10.8	10.4
- Age of deceased patients in years (mean)	28.2	27.0
- Age of deceased patients in years (median)	27.5	25.5
Diagnosis and genetics		
- Age at diagnosis in months (median)	2.0	2.0
- New patients diagnosed in the year (number)	235	205
of which diagnosed by newborn screening	144	118
- New patient age at diagnosis in years (extremes)	0 – 58	0 – 65
- Complete genotypes identified (%)	93.4	90.2
F508del/F508del	43.8	43.1
F508del/Other	37.2	36.0
Other/Other	12.4	11.1
F508del / Unidentified	2.2	3.4
Other / Unidentified	1.2	1.5
Unidentified / Unidentified	3.2	4.9
Anthropometry and spirometry		
- Height z-score, patients aged 17 and below (mean)	- 0.17	- 0.21
- Height z-score, patients aged 18 and above (mean)	- 0.54	- 0.54
- Weight z-score, patients aged 17 and below (mean)	- 0.41	- 0.47
- Weight z-score, patients aged 18 and above (mean)	- 0.47	- 0.53
- FEV_1 percent predicted, Knudson method, patients aged 17 and below (mean)	83.53	84.73
- FEV_1 percent predicted, Knudson method, patients aged 18 and above (mean)	61.90	61.29

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	2008	2007 (for comparaison)
Microbiology		
- Patients who had at least 1 sputum culture during the year (%)	92.6	93.5
H. influenzae	28.0	28.4
MSSA	52.1	50.6
MRSA	8.5	9.9
P. aeruginosa	44.7	45.7
S. maltophilia	7.3	7.5
B. cepacia	2.3	2.4
Aspergillus	21.0	18.2
Complications and transplants		
- Hemoptysis (%)	5.4	5.0
- Cirrhosis/Portal hypertension (%)	3.5	3.5
- Insulin-dependent and non-insulin-dependent diabetes (%)	13.1	12.5
- Transplanted patients (number)	353	307
of which transplanted in the year	72	73
- Patients on the transplant waiting list (number)	171	145
of which registered in the year	70	83
deceased before receiving a transplant	6	8
Therapeutic management		
- Courses of IV antibiotic treatment (%)	34.7	35.7
- Oxygen therapy (%)	6.7	6.0
- Non-invasive ventilation (%)	4.4	4.4
- Azithromycin (%)	40.8	38.7
- Inhaled antibiotics (%)	36.8	37.8
- rhDNase (%)	45.1	42.3
- Inhaled bronchodilatators (%)	45.6	43.1
- Inhaled corticosteroids (%)	37.7	35.3
- Pancreatic enzyme supplements (%)	83.0	79.9