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French Cystic Fibrosis Registry

Annual Data Report 2009

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2012

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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 has been 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 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 2009 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

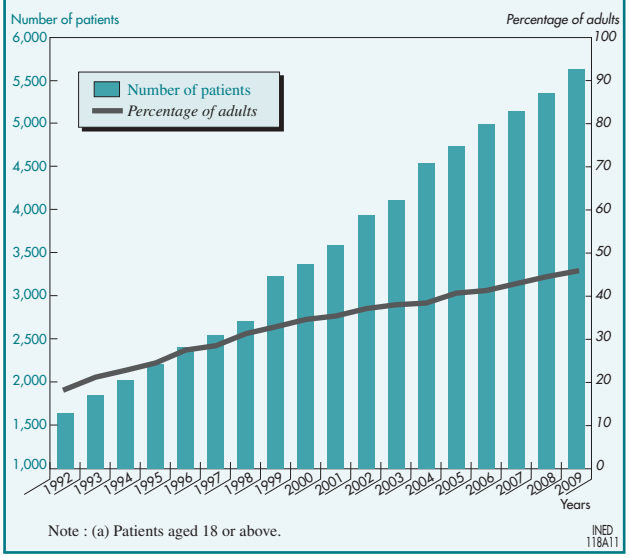
A total of 5,628 patients were seen by the centres who contributed data to the registry in 2009 (1).
This report is based on the data of these patients, whose demographic and clinical characteristics are described in detail by the centres. Alongside this total, the participating centres recorded information on 22 additional patients who were not seen by them during the year but whose vital status was known on 31 December (10 were alive and 12 had died). The registry thus included a potential total of 5,650 patients in 2009, which represents, by our estimates, around 90% of the population with cystic fibrosis in France.

ALD 18 status (i.e. status as a cystic fibrosis patient under the French social security system) is known for only 1,865 patients (33.1% of the total), as this variable was included in the registry questionnaire only very recently. Among these patients, 1,614 have ALD 18 status, representing 86.5% of the total. These figures, along with the total number of patients in the registry, can be compared with the number of patients registered with ALD chronic illness status under the general social security regime (covering wage employees): on December 31, 2009 the general health insurance scheme, which covered 89% of the French population (2), had records of 5,536 patients with ALD 18 status (3).

Practically all of the patients in the registry (97.3%) were followed by cystic fibrosis care centres, hereafter referred to by their French acronym CRCM (*centres de ressources et de compétences de la mucoviscidose*), and 2.5% most frequently by local centres (Table 1). The average number of patients per type of centre is very variable: above 100 in the CRCM, no more than 17 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 age observed age is 49 years) and young patients in the adult CRCM (lowest observed age 13 years).

The annual number of patients included in the registry, whether new or already registered, has risen steadily since 1992 (Figure 1), with a 5.1% increase between 2008 and 2009 (5,357 patients). The proportion of adults (patients aged 18 or above) has also increased: adults represented 44.5% of the total number of patients in 2008 and 45.8% in 2009. Among adults, there were 329 patients aged 40 and above, representing 5.8% of the population. Seventeen patients are aged between 70 and 79.

Figure 1 – French CF Registry 2009. Number of patients seen during the year and percentage of adults (a): trend since 19922



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, 64 centres were taken into account from among the total of 71 which contributed to the registry in 2009.

(2) Figures available online on the Social Security website: http://www.securite-sociale.fr/IMG/pdf/2010_chiffres_cles.pdf

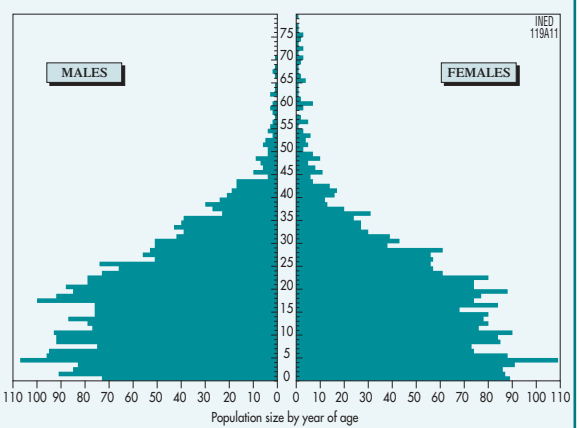
(3) Online on the website: http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/index.php

Table 1 – The French CF Registry 2009. 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	2,124	37.7	111.8	23 – 297	9.4	0 – 49
Adult CRCM	12	1,546	27.5	128.8	42 – 327	29.8	13 – 77
Paediatric and adult CRCM	18	1,808	32.1	100.4	35 – 203	17.3	0 – 79
Paediatric local centres	10	121 (b)	2.1	12.1	2 – 41	14.2	0 – 61
Paediatric and adult local centres	1	17 (c)	0.3	17.0	17 – 17	18.9	7 – 35
Other	4	12 (d)	0.2	3.0	1 – 8	15.1	5 – 35
TOTAL	64	5,628	99.9 (e)	87.9	1 – 327	17.7	0 – 79

Notes: (a) After checking for patients in the multiple account category.
(b) Including 28 patients also seen by a CRCM.
(c) Including 6 patients also seen by a CRCM.
(d) Including 2 patients also seen by a CRCM.
(e) The total does not sum exactly because of rounding.

Figure 2 – French CF Registry 2009. Population pyramid of patients seen during the year



Note: 162 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, 4 children born in 2008 (of whom 3 in December) were diagnosed with cystic fibrosis by neonatal screening in 2009. On the 2008 population pyramid, the number of patients aged 0, which stood at 153, could thus have been 153 + 4 = 157.

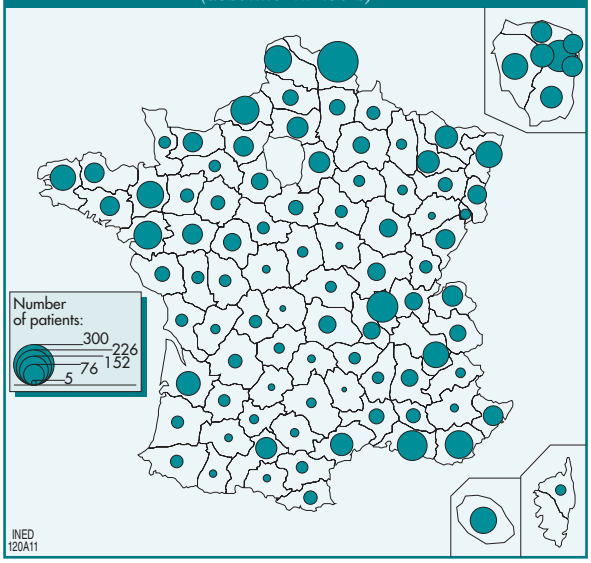
2 – Demographic characteristics

The population is structurally young (Figure 2 and Table 2). The mean age is 17.7 years, the median age is 16.0 years, and 54.2% of the population are under 18 (3,049 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 108 in 2006, 110 in 2007, and 108 in 2008.

Table 2 – French CF Registry 2009. Main characteristics of the population

Characteristics	2009 REGISTRY
OVERALL	
Number of patients	5,628
Number of males per 100 females	108
Children: below age 18 (number and %)	3,049 – 54.2
Adults: age 18 and above (number and %)	2,579 – 45.8
Mean age (in years)	17.7
Median age (in years)	16.0
Extremes of age (in years)	0 – 79
MEN	
Number of patients	2,916
Children: below age 18 (number and %)	1,553 – 53.3
Adults: age 18 and above (number and %)	1,363 – 46.7
Mean age (in years)	17.8
Median age (in years)	17.0
Extremes of age (in years)	0 – 70
WOMEN	
Number of patients	2,712
Children: below age 18 (number and %)	1,496 – 55.2
Adults: age 18 and above (number and %)	1,216 – 44.8
Mean age (in years)	17.6
Median age (in years)	16.0
Extremes of age (in years)	0 – 79

Carte 1 – Cystic Fibrosis Registry 2009. Distribution of patients by département *of residence (absolute numbers)*



The place of residence is known for 5,497 patients in the registry in 2009, representing 97.7% of the population. There are marked differences between the *départements* of metropolitan France (Map 1). The majority of patients (nearly 57%) 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 8.4 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 Finistère, Ille-et-Vilaine, Territoire de Belfort, Var and Réunion Island (13 patients or more per 100,000).

Carte 2 – Cystic Fibrosis Registry 2009.
Cystic fibrosis prevalence by **département**
(number of patients per 100,000 inhabitants)

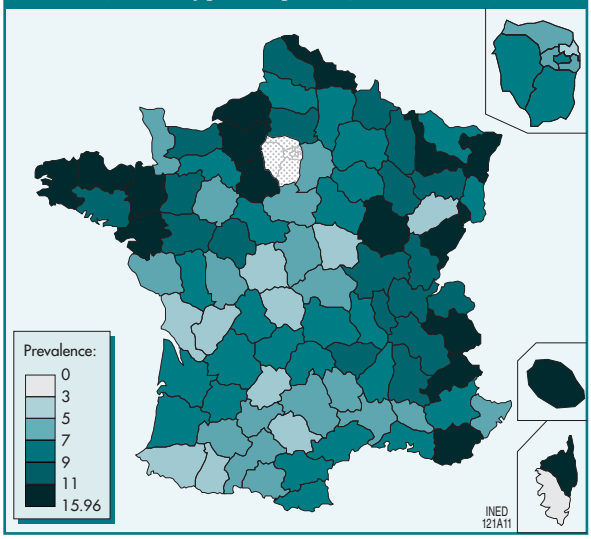
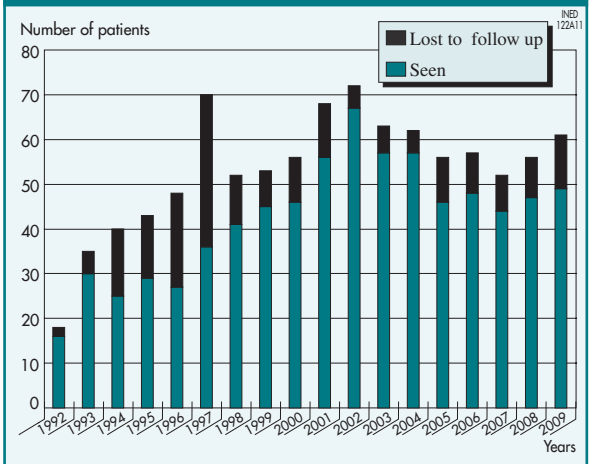
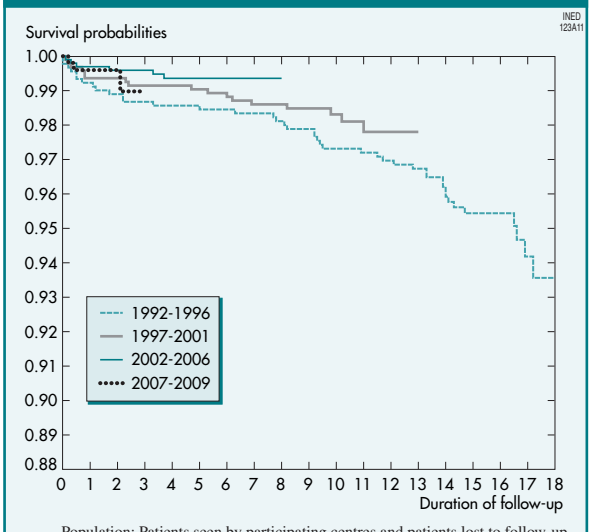


Figure 3 – French CF Registry 2009.
Number of deaths in the year: trend since 1992



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

Figure 4 – French CF Registry 2009.
Survival curves by cohort (Kaplan-Meier method)



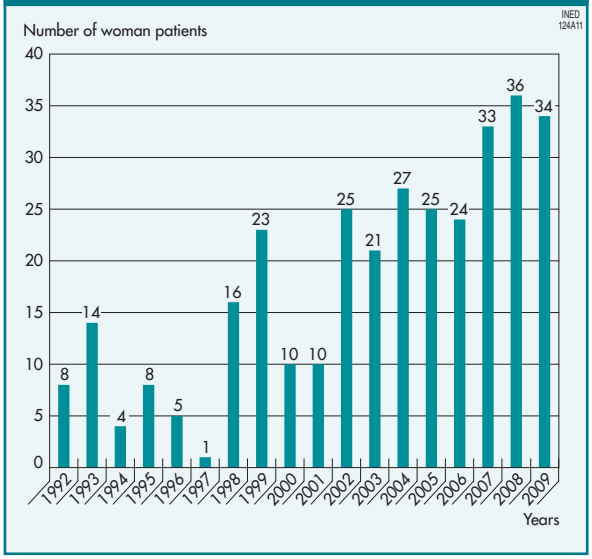
Population: Patients seen by participating centres and patients lost to follow-up.

A total of 61 deaths occurred in 2009 (a crude mortality rate of 11.2 per 1,000): 49 patients of participating centres and 12 patients lost to follow-up (Figure 3). There were 61 deaths in 2009, of whom 24 (39.3%) were transplant patients. The mean age at death was 25.5 years, with the youngest aged below 1 [4] and the oldest aged 73.

Length of life is expressed in terms of survival probabilities calculated by **longitudinal** analysis (Kaplan-Meier method). [5] It was calculated for four different birth cohorts (Figure 4): patients born in 1992-1996 (in 2009 this cohort had been followed for a maximum of 18 years), in 1997-2001 (followed for 13 years maximum), in 2002-2006 (followed for 8 years maximum) and in 2007-2009 (followed for 3 years maximum). A total of 3,356 patients were included in the analysis, among whom 68 had died. For a comparable observation period, the younger the cohort, the higher the survival probability, although no significant difference is observed.

A total of 34 early pregnancies were reported to the registry in 2009 (the conception rate is 25.8 per 1,000 among women patients aged 15-49). The mean age of the women concerned was 28.4 years (in the French population, the mean age of women who gave birth in 2009 was 29.9 years). The number of pregnancies reported in 2009 appears to confirm the sharp rise observed since 2007, although annual variations are very large (Figure 5).

Figure 5 – French CF Registry 2009. Number of women patients reporting early pregnancy during the year: trend since 1992



(4) The death was attributed to a glioma.

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

3 – Diagnosis

A total of 230 new patients were diagnosed in 2009, i.e. 4.1% of the total population (Table 3). By comparison, there were 205 new cases in 2007 (4.0% of the total) and 235 in 2008 (4.4%). [6]

A total of 146 patients were diagnosed by neonatal screening, representing 63.5% of new cases in 2009, versus 118 (57.6% of new cases) in 2007 and 144 (61.3%) in 2008.

The number of patients diagnosed by neonatal screening (146) 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, notably on the basis of meconium ileus, are not included in the total.

Table 3 – French CF Registry 2009. Main characteristics of diagnosis

CHARACTERISTICS	2009 REGISTRY
NEW PATIENTS DIAGNOSED DURING THE YEAR	
All new patients (all diagnostic signs) (a)	
New patients (number and %)	230 – 4.1
Mean age at diagnosis (in months)	73.9
Median age at diagnosis (in months)	1.0
Extremes of age at diagnosis (in years)	0 – 72
Context of diagnosis	
Prenatal diagnosis (number and %)	4 – 1.7
Patients diagnosed on the basis of meconium ileus [MI] (number and %)	12 – 5.2
Patients diagnosed by neonatal screening [excluding patients diagnosed before screening results were known] (number and %)	146 – 63.5
Patients diagnosed through symptoms [other than MI] (number and %)	61 – 26.5
Mean age at diagnosis (in years) of patients diagnosed through symptoms (other than MI)	21.8
ALL PATIENTS	
Patients whose age at diagnosis is known (number and %)	5,355 – 95.1
Mean age at diagnosis (in months)	41.2
Median age at diagnosis (in months)	2.0
Extremes of age at diagnosis (in years)	0 – 74

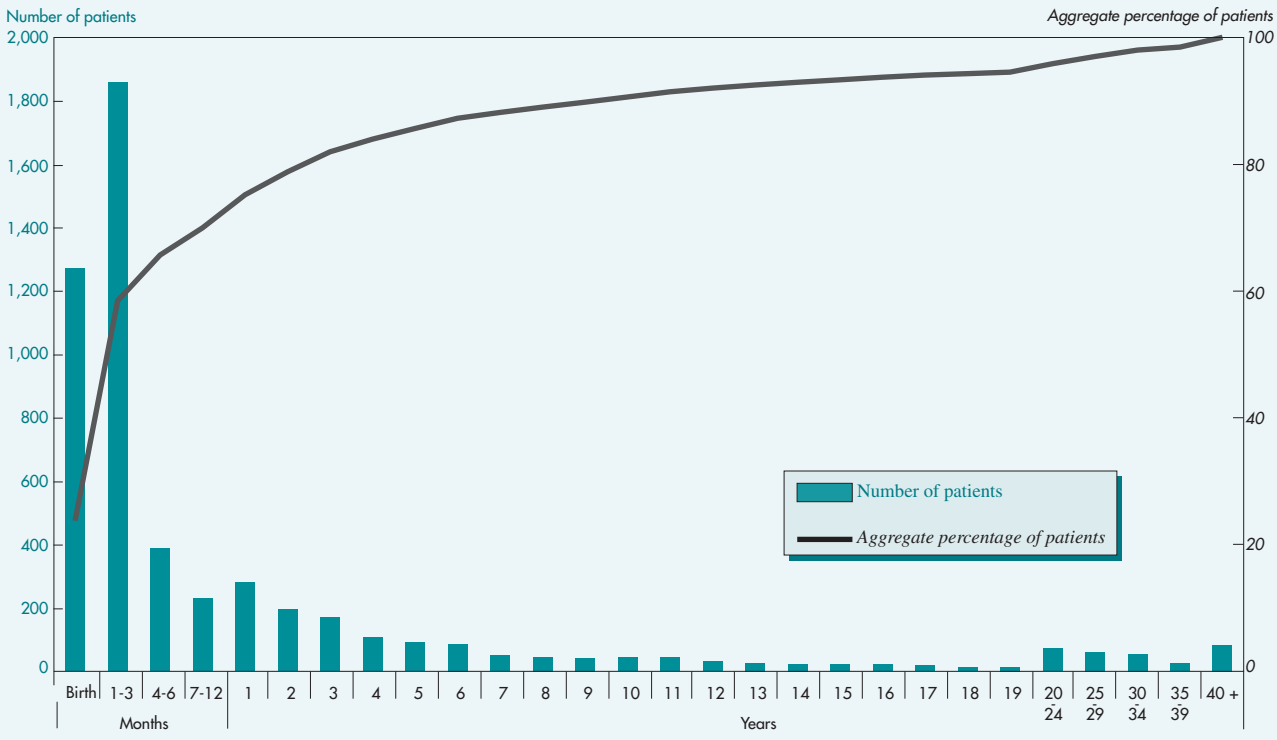
Notes: (a) Including family history and antenatal diagnosis.

(6) Also for comparison, 314 new CF cases were registered with ALD 18 status by the Caisse Nationale de l'assurance maladie des travailleurs salariés in 2009.

Among the 230 new patients, 160 were born in 2009. The method used to compile this report (patients seen in a care centre in 2009) means that infants born in 2009 and seen for the first time in 2010 are excluded.

Out of the 5,355 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 2009. Number of patients and aggregate percentage of patients by age at diagnosis



Note: N = 5,355 (number of patients whose age at diagnosis is known).

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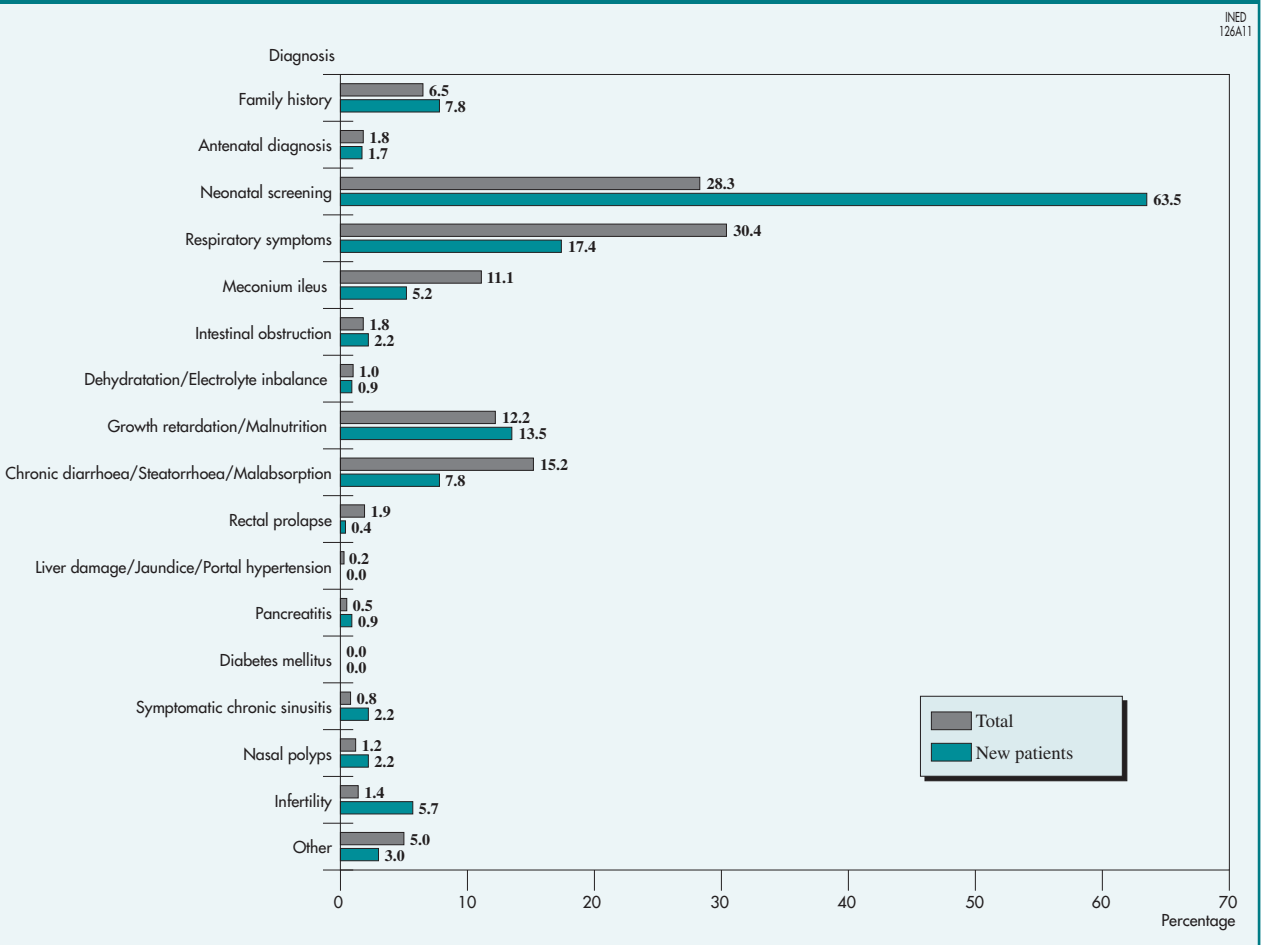
Diagnostic signs are shown in Figure 7. The most frequent for all the patients are respiratory symptoms (30.4%), neonatal screening, which concerns more than a quarter of patients in the registry (28.3%), followed by chronic diarrhoea/steatorrhoea/malabsorption (15.2%), growth retardation/malnutrition (12.2%) and meconium ileus (11.1%). Among the year's 230 new patients, the majority were diagnosed by neonatal screening, as in previous years (63.5%), followed by respiratory difficulties (17.4%), and growth retardation/malnutrition (13.5%).

With regard to the *CFTR* gene, the genotypes of 5,288 patients in the registry had been identified in 2009, representing 93.9% of the population (Table 4). 3.2% of patients have genotypes with a single identified mutation, and the other patients (2.9%) did not undergo genotypic analysis or had a genotype consisting of unstudied or unidentified mutations.

Figure 7 – French CF Registry 2009. 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 is F508del/F508del (43.6% 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 1.5% in the total population and 4.3% among new patients diagnosed in 2009.

Table 4 – Cystic Fibrosis Registry 2009. Numbers and proportions of genotypes in order of decreasing frequency

GENOTYPES	Number of patients	Proportion (%)
F508del / F508del	2,453	43.6
F508del / G542X	176	3.1
F508del / N1303K	127	2.3
F508del / 1717-1G->A	87	1.5
F508del / R117H	84	1.5
F508del / 2789+5G->A	81	1.4
F508del / R553X	62	1.1
F508del / G551D	53	0.9
F508del / W1282X	41	0.7
F508del / Y122X	41	0.7
F508del / I507del	40	0.7
F508del / 3849+10kbC->T	39	0.7
F508del / 3272-26A->G	38	0.7
F508del / R347P	33	0.6
F508del / L206W	30	0.5
F508del / 2183AA->G	29	0.5
F508del / R1162X	27	0.5
F508del / A455E	24	0.4
F508del / 3659delC	22	0.4
F508del / 1078delT	21	0.4
F508del / Y1092X	20	0.4
F508del / 711+1G->T	19	0.3
N1303K / N1303K	19	0.3
G542X / G542X	18	0.3
F508del / S1251N	17	0.3
F508del / E60X	16	0.3
F508del / G85E	16	0.3
F508del / 394delTT	16	0.3
F508del / 1811+1.6kbA->G	16	0.3
F508del / R334W	15	0.3
F508del / W846X	15	0.3
F508del / 3120+1G->A	14	0.2
Y122X / Y122X	13	0.2
F508del / 621+1G->T	11	0.2
711+1G->T / 711+1G->T	8	0.1
G542X / R117H	7	0.1
G542X / 2789+5G->A	7	0.1
3120+1G->A / 3120+1G->A	5	0.1
Other *CFTR* genotypes	1,528	27.1
SUB TOTAL	5,288	93.9
F508del / Unidentified	112	2.0
Other / Unidentified	66	1.2
Unidentified / Unidentified	162	2.9
TOTAL	5,628	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 = 50.06; $p < 10^{-4}$).

Table 5 – French CF Registry 2009. Age of patients by genotype: summary

GENOTYPES	PATIENTS' AGE				
	Number	Proportion (%)	Mean (years)	Median (years)	Max. age (years)
F508del / F508del	2,453	43.6	16.7	16.0	56
F508del / Other	2,095	37.2	17.4	15.0	72
Other / Other	740	13.1	17.5	15.5	77
F508del / Unidentified	112	2.0	25.9	22.0	74
Other / Unidentified	66	1.2	23.3	22.0	65
Unidentified / Unidentified	162	2.9	30.6	27.0	79

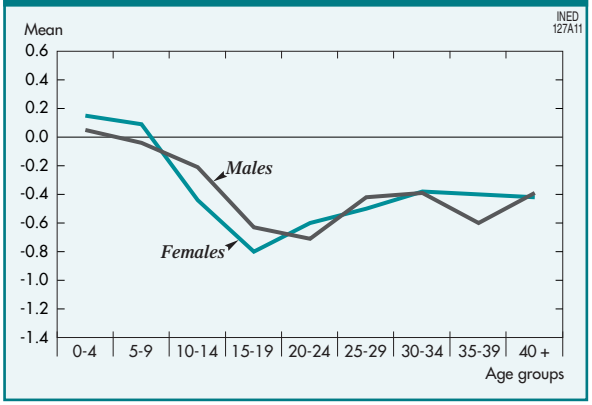
4 – Anthropometry

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 [7] (with reference to the mean for the French population) [8] 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, which are positive at age 0-4 years (0.05 for males, 0.15 for females), gradually become negative in the period of adolescence (–0.63 to –0.80 by sex at age 15-19). Although they subsequently improve, mean z-scores remain negative in adulthood, with values of between –0.60 and –0.38.

Figure 8 – French CF Registry 2009. Height z-scores (mean by sex and age)



(7) The z-score corresponds to the centred reduced anthropometric variable ($Z = \frac{measure - mean}{st.\ dev}$) adjusted for 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.

(8) Sempé M., 1997, *Auxologie – Méthode et séquences*, Méditions, Lyon, 205 p.

Figure 9 – French CF Registry 2009. Weight z-score (mean by sex and age)

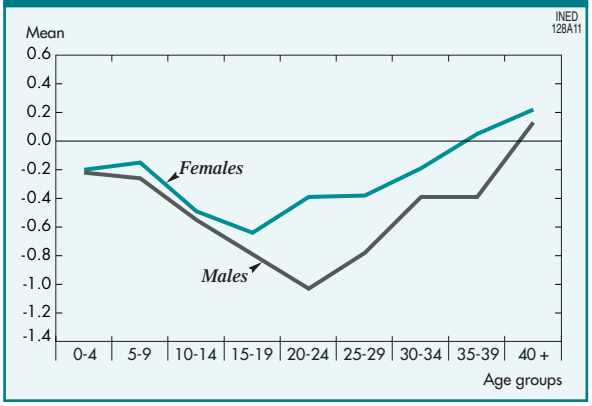


Figure 10 – rench CF Registry 2009. Body mass indices (BMIs) compared with the BMIs of the male and female reference populations (mean by sex and age)

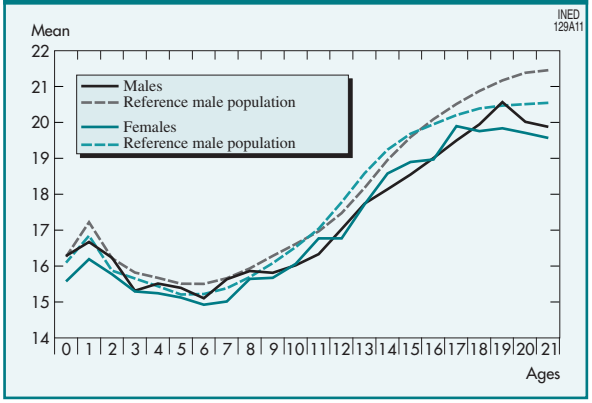


Figure 11 – French CF Registry 2009. FVC percentage of the predicted value (mean by sex and age)

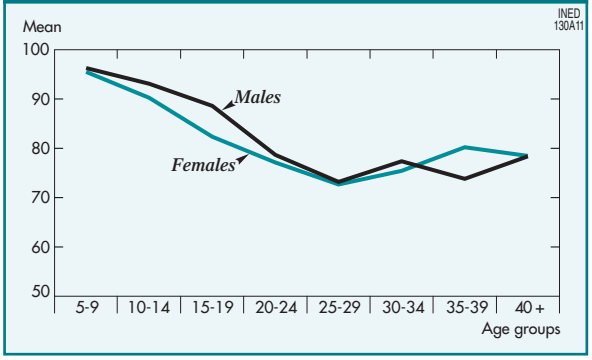
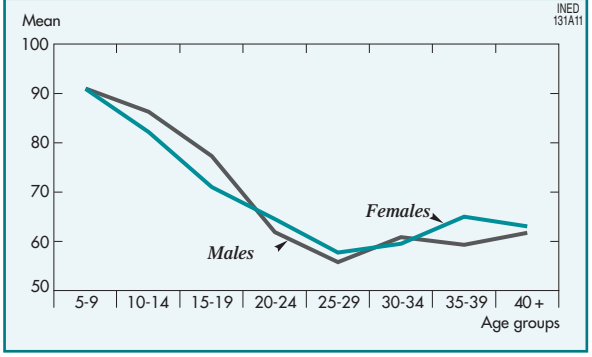


Figure 12 – French CF Registry 2009. FEV_1 percentage of the predicted value (mean by sex and age)



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 –0.21 at the ages of 0-4 years. As is the case for height, z-scores decrease from adolescence to early adulthood in males (–1.03 on average at age 20-24), while in females, weight recovery occurs earlier (–0.64 on average at age 15-19, falling to –0.39 on average at age 20-24). The weight z-scores then improve markedly, although men do not fully catch 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). In both males and females, the difference with respect to the reference population becomes manifest from age 10, and this difference remains or is accentuated from age 15.

5 – Spirometry [9]

In 2009, 88.9% of patients aged 6 or above underwent at least one spirometry test, [10] a slightly lower proportion than in 2008 (90.9%) and in 2007 (90.6%).

The forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), expressed as percentages of predicted normal values. [11] Starting from levels of 90-96%, (Figures 11 and 12), FVC and FEV_1 decrease progressively until ages 25-29 for both male and female patients (the mean FVC at these ages is around 73% and the FEV_1 around 56% of predicted normal). A slight improvement is then observed. This effect, as already noted for anthropometry, is very probably due to the selection bias linked to the higher mortality of the most severely affected patients.

(9) See appendix for additional information on spirometry.

(10) Respiratory function tests require subject participation, and children under this age cannot always do what is asked.

(11) 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 2009. FEV_1 percent predicted classes (as a percentage of the total for each population)

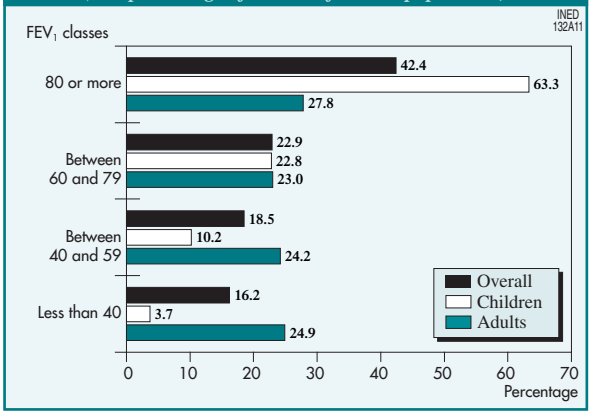
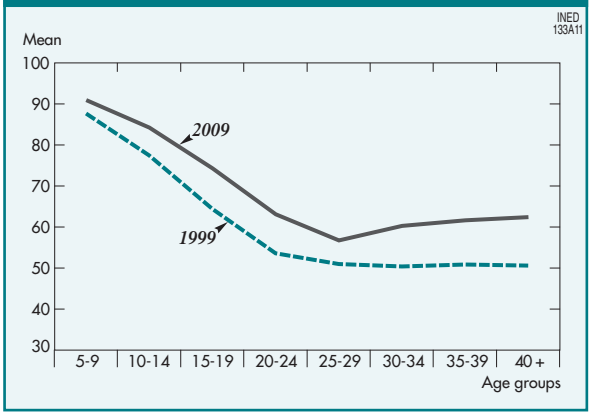


Figure 14 – French CF Registry 2009. FEV_1 percentage of the predicted value in 2009 compared with 1999 (mean by age)



The FEV_1 values are divided into four «functional» classes corresponding to different degrees of bronchial obstruction (Figure 13). The majority (63.3%) 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 24.9% having an FEV_1 below 40% of the predicted normal.

For comparison, the mean FEV_1 values at different ages in 2009 are given with those of 1999 (Figure 14). The two curves have practically identical profiles, but the 2009 means are always higher than those of 1999. The difference is generally around 8.5 percentage points; lower in 25-29 age group (difference of 5.7 points) and higher from ages 30-34 (difference of 10 points). This improvement above age 30 is linked to the large proportion of transplant patients among patients aged 30 and above, and probably also to the selection effect of older patients.

6 – Microbiology

In 2009, 92.4% of the patients had at least one sputum culture (Table 6), a proportion that has remained stable (92.6% in 2008, 93.5% in 2007). Note that among patients who did not have a sputum culture in the year, almost 39% were transplanted patients.

Table 6 – French CF Registry 2009. Sputum cultures

Patients who had at least 1 sputum culture during the year	NUMBER	PERCENTAGE
Overall	5,200	92.4
Children (below age 18)	2,932	96.2
Adults (age 18 or above)	2,268	87.9

Figure 15 – French CF Registry 2009. Clinically important bacteria (percentage by age)

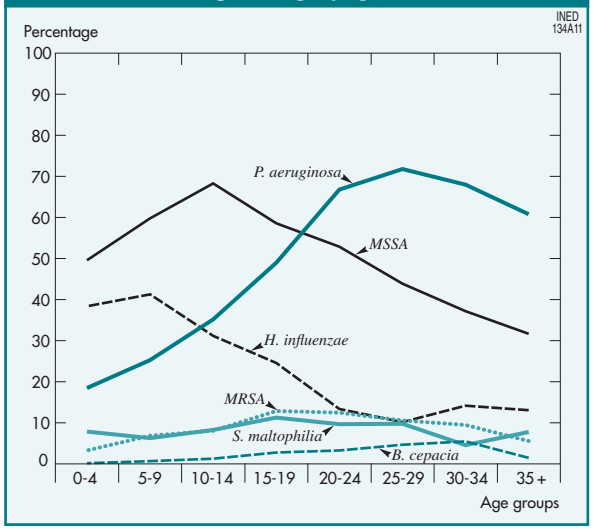


Figure 16 – French CF Registry 2009. Bacteria in 2009 compared with 1999 (percentage by age)

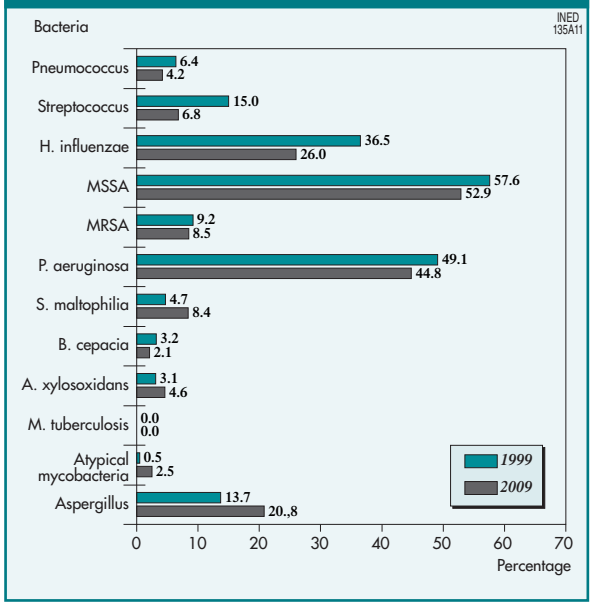


Figure 15 shows the distribution by age of five bacteria considered to be of clinical importance, *Staphylococcus aureus* being divided into MSSA (meticillin-susceptible) and MRSA (meticillin-resistant).

The patients' age distribution profile by bacteria remains practically unchanged with respect to previous years. Some of these micro-organisms are frequently detected at a very young age: at age 0-4 years, *Haemophilus influenzae* is present in 38.4% of patients and MSSA in 49.6% (in 2005, the proportions were 50.5% and 57.7%, respectively, in this age group). *Pseudomonas aeruginosa*, present in 18.5% of patients aged 0-4, is most frequent (71.8%) in patients aged 25-29. MRSA was detected among 3.3% of the 0-4 age group. The proportion rises to 12.9% among the 15-19 age group (14.6% in this age group in 2006) then falls slightly at the highest ages.

Figure 16 gives the variations observed for the organisms documented in 2009 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 2009 ($p < 10^{-9}$), *Haemophilus influenzae* (36.5% to 26.0%; $p < 10^{-9}$), *Streptococcus pneumoniae* (6.4% to 4.2% ; $p < 10^{-4}$), MSSA (57.6% to 52.9%; $p < 10^{-4}$), *Pseudomonas aeruginosa* (49.1% to 44.8%; $p < 10^{-3}$) and *Burkholderia cepacia* (3.2% to 2.1%; $p < 0.01$)

Upward: *Aspergillus* (from 13.7% in 1999 to 20.8% in 2009; $p < 10^{-9}$), atypical mycobacteria (0.5% to 2.5%; $p < 10^{-9}$) *Stenotrophomonas maltophilia* (4.7% to 8.4%; $p < 10^{-9}$), and *Achromobacter xylosoxidans* (3.1% to 4.6%; $p < 10^{-3}$).

In addition, out of the 2,332 patients colonized by *Pseudomonas aeruginosa*, chronic colonization [12] was observed in 56.5% of cases (multi-resistant or otherwise); colonization with multi-resistant strains [13] (chronic or non-chronic) represented 22.4% of cases. However, information was missing for 26% of them.

(12) 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).

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

7 – Complications Transplants

Patients with no reported complications represent 7.8% of the total.

The main events recorded during the year 2009 are grouped into broad categories and shown by age in Figures 17 to 20.

In brief, among the youngest patients, the most frequent complications are treated aspergillosis, nasal polyps treated gastro-oesophageal reflux disease, asthma and elevated liver enzymes (14.5%, 14.3%, 13.4%, 13.1% and 11.3%, respectively, at ages 10-14 for example). Cirrhosis/portal hypertension and intestinal obstruction are also relatively frequent (5.9% and 3.8%, respectively at ages 10-14). Last, diabetes (insulin-dependent and non-insulin-dependent) affects 3.9% of children aged 10-14.

In adult patients, where morbidity is tending to increase, treated aspergillosis, nasal polyps and treated gastro-oesophageal reflux are still very frequent (21.1%, 18.3% and 20.4%, respectively, at age 20-24 for example). Elevated liver enzymes have tended to stabilize, however (8.2% at age 20-24, for example).

More than one-third (33.4%) of patients aged 25-34 have insulin-dependent or non insulin-dependent diabetes. In adults, bone diseases and arthropathy, already frequent at ages 25-29 (8.3% and 5.1%, respectively) tend to increase with age (13.1% and 6.1%, respectively at age 40 and above) despite the selection bias which affects the oldest population aged above 34 years.

In adults, a non-negligible percentage also suffer from depression (7.6% at ages 25-29, 9.1% at age 40 and above); deafness, which concerns 1.3% of patients, is observed primarily from ages 20-24 (2.5% at these ages).

Only 31 patients (0.6% of the total), the majority of whom were women (24), 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 83.2% of patients

Figure 17 – French CF Registry 2009. Events occurring during the year: 1 – Respiratory complications (percentage by age)

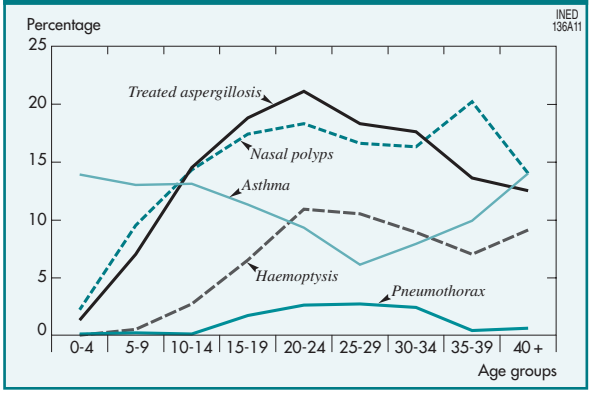
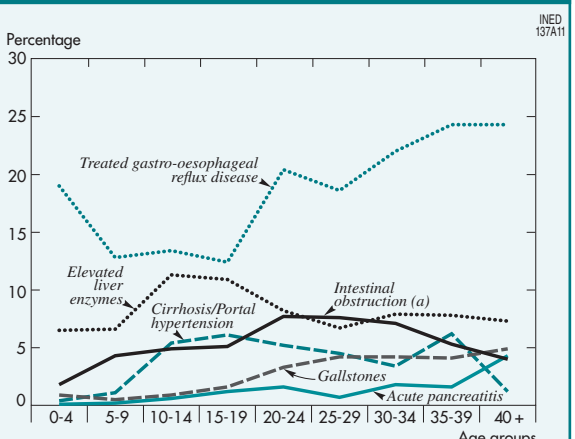


Figure 18 – French CF Registry 2009. Events occurring during the year: 2 – Gastro-intestinal problems (percentage by age)



Note : (a) other than meconium ileus.

Figure 19 – French CF Registry 2009. Events occurring during the year: 3 – Diabetes mellitus (percentage by age)

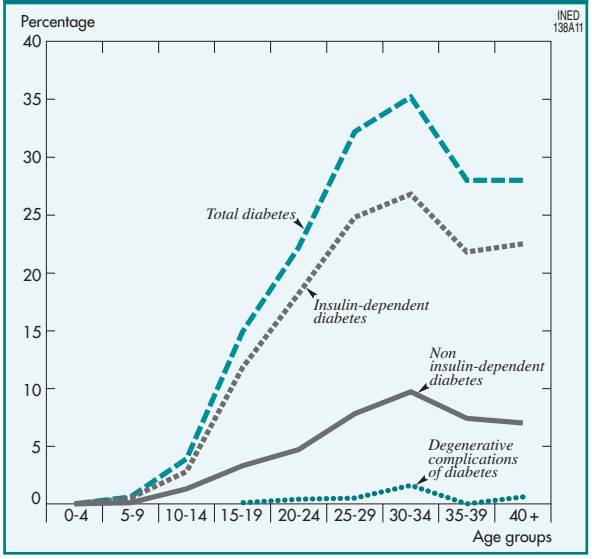
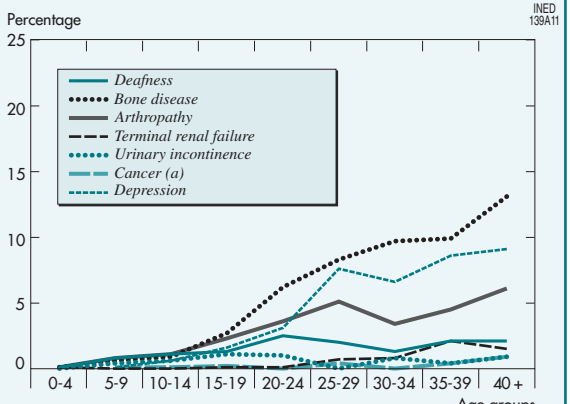


Figure 20 – French CF Registry 2009. Events occurring during the year: 4 – Other events (percentage by age)



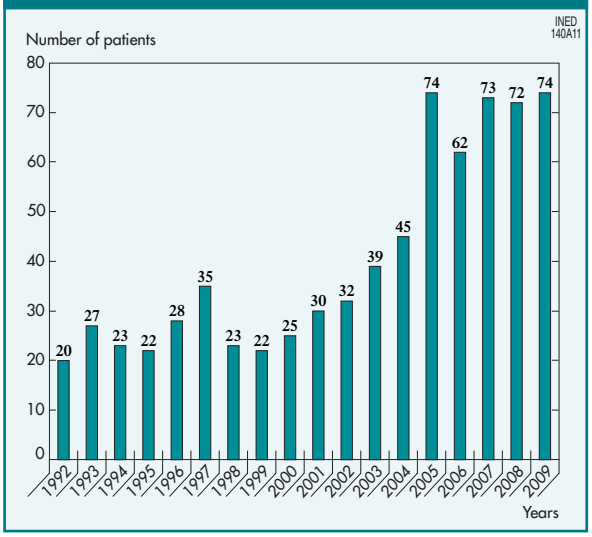
Note : (a) Among patients of all ages, 10 have cancer, of whom 4 are transplanted.

Table 7 – French CF Registry 2009. Transplants: 1 – Main characteristics

CHARACTERISTICS	2009 REGISTRY	
TRANSPLANTED PATIENTS	ALL PATIENTS (a)	TRANSPLANTED IN 2009 (b)
Number of patients	400	74
Mean age (in years)	30.1	26.3
Extremes of age (in years)	10 – 56	14 – 49
Bilateral lung transplants (number and %)	332 – 83.0	67 – 90.5
Heart-lung transplants (number and %)	21 – 5.3	4 – 5.4
Liver transplants (number and %)	31 – 7.8	3 – 4.0
Kidney transplants (number and %)	20 – 5.0	2 – 2.7
Other and unidentified transplants (number and %)	14 – 3.5	1 – 1.4
Patients deceased in 2009	24	10
PATIENTS ON THE TRANSPLANT WAITING LIST (C)		
Number of patients	161	
Mean age (in years)	26.7	
Extremes of age (in years)	5 – 49	
New patients registered on the waiting list in 2009 (number and %)	65 – 40.4	
Patients on the waiting list who died in 2009	3	

Notes: (a) All patients transplanted in 2009 or before.
(b) Patients transplanted in 2009 only.
(c) All patients registered on the transplant waiting list in 2009 or before.

Figure 21 – French CF Registry 2009. Transplants: 2 – Annual number of transplanted patients: trend since 1992



had pancreatic insufficiency (83.0% in 2008 and 74.8% in 2007). This proportion remains reasonably stable with age: 78.6% at ages 0-4, 88.4% at ages 20-24, peaking at 89% at ages 25-29 then decreasing to 67.3% beyond age 35 (selection effect already mentioned).

In 2009, 400 patients (7.1% of the population) had received a transplant (Table 7). In 83% of cases, they were bilateral lung transplants. A total of 74 transplant operations (1.3% of the total population) were performed in 2009 alone, 90% of which were bilateral lung transplants.

In 2009, a total of 161 patients were on the waiting list (2.9% of the population), of whom 65 were added in 2009. Three patients awaiting a transplant died in 2009, representing 4.9% of deaths in the year.

On a par with 2005, the number of transplants in 2009 is the highest recorded since 1992 (Figure 21).

8 – Outpatient and inpatient visits Therapeutic management

On average, 4.1 outpatient visits were counted by patient during the year and 2.5 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 (5-6 days for patients aged under 15) and more variable for adults (8 to 14 days in the years, depending on age).

A total of 1,984 patients received at least one course of intravenous antibiotic treatment in 2009 (i.e. 35.3% of the total population), of whom 772 were in the 15-19 and 20-24 age groups. These two age groups accounted for 38.9% of patients receiving courses of treatment (Figure 23).

In all, 20.8% 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 (higher mortality of adults with severe forms of the disease).

Patients receiving IV antibiotic treatment had 2.5 treatment courses, on average, in the year, rising from 1.3 courses per year among the youngest patients (aged 0-4) to 2.8 in adolescence (ages 15-19). The annual number of courses remains fairly stable between ages 20 and 39 before falling to an average of 2.1 at age 40 and above, due to selection bias (Figure 24).

The total number of days of IV treatment in the year spans a broad range, from 1 day to a maximum of 193 days. However, these treatment courses generally take place over a period of 2 weeks (32.7% of patients), one month (18.9% of patients) or 42-45 days (12.6% of patients). The mean number of days of IV treatment per year is 35.6 for all patients receiving IV treatments, with a highest mean of 41.7 days of treatment at age 15-19 (Figure 24).

Figure 22 – French CF Registry 2009. Outpatient and inpatient visits (by age)

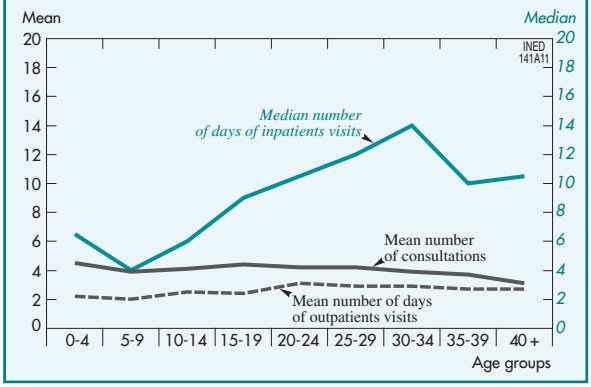


Figure 23 – French CF Registry 2009. Courses of IV antibiotic treatment: 1 – Patients receiving at least one course of treatment; patients with a TIVAD (by age)

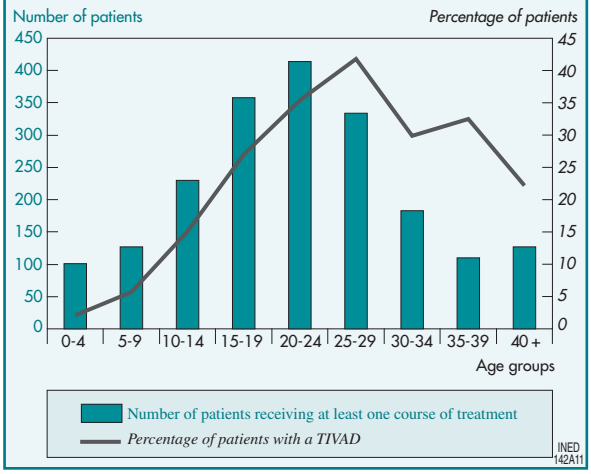


Figure 24 – French CF Registry 2009. Courses of IV antibiotic treatment: 2 – Mean number of courses and of days of treatment by age

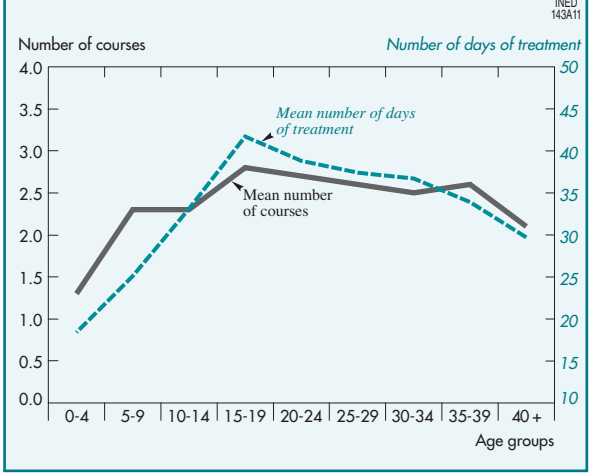


Figure 25 – French CF Registry 2009. Therapeutic management: 1 – Respiratory treatment (percentage by age)

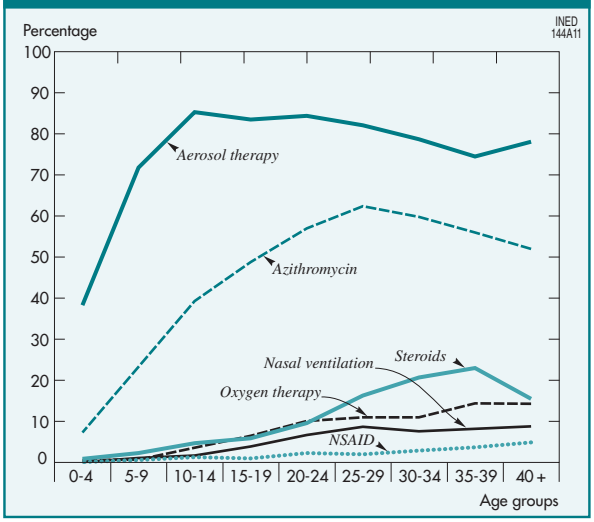


Figure 26 – French CF Registry 2009. Therapeutic management: 2 – Products administered by aerosol therapy (percentage by age)

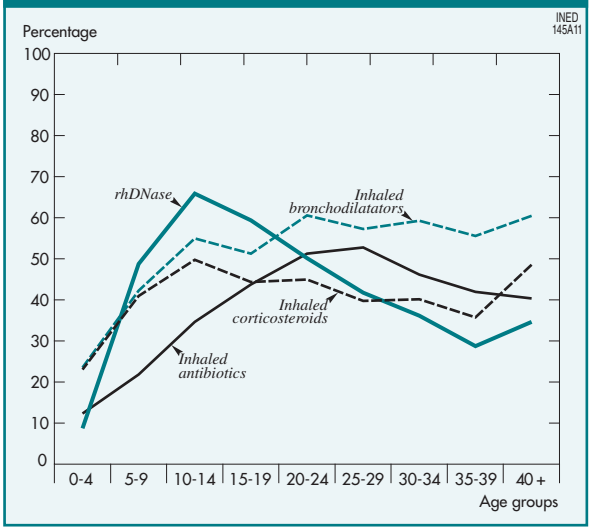
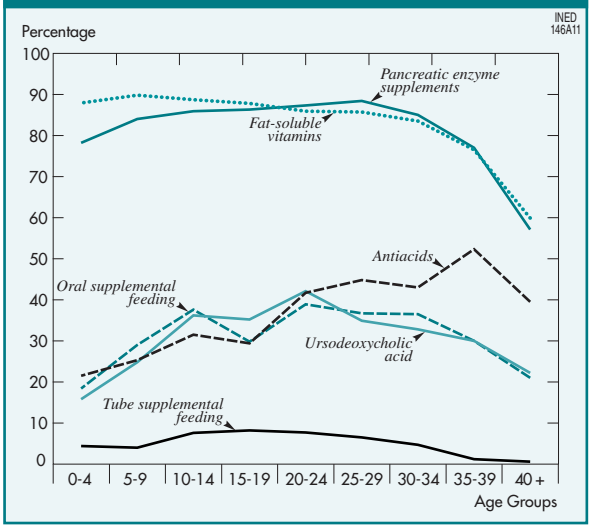


Figure 27 – French CF Registry 2009. Therapeutic management: 3 – Digestive and nutritional treatment (percentage by age)



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 (Figure 25), oxygen therapy, non-invasive ventilation and anti-inflammatory drugs (NSAID and steroids) were administered to 8.2%, or less, of all patients. Frequencies were much higher for azithromycin (40.6% of patients on average, 49.0% to 62.4% in patients aged 15-39) and for long-term aerosol therapy (73.7% of patients on average and more than 82% in patients aged 10-29).

The products administered by aerosol therapy (Figure 26) were most often inhaled bronchodilators (49.1% on average) and rhDNase (43.4%). Inhaled corticosteroids were administered to 40.5% of patients and antibiotics to 35.9% of patients.

In 34% of cases, aerosol therapy was administered by nebulization. For 43% of patients, nebulization was associated with a spray or powder; while for 14%, 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 (Figure 27), pancreatic enzyme supplements were given to 82.7% of all patients (fat-soluble vitamins to 85.4% of pateints). The sharp drop in the number of patients receiving these supplements or vitamins after the age of 35 is the result of selection bias due to the higher mortality of the most severely affected patients. Overall, 30.8% of patients received long-term oral supplemental feeding and 5.7% long-term tube supplemental feeding. Among the latter, 65.9% received feeding by gastrostomy and 27.5% by nasogastric tube. In addition, 30.4% of patients took ursodeoxycholic acid and 33.4% took antacids (H2 blockers or Proton Pomp Inhibitors).

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 2009:

– the FEV_1 of all patients was compared to that of patients who had or had not received a heart-lung or bilateral lung transplant (Figure 28). The curves of the total population and of non-transplanted patients are identical up to age 20-24. After that, the FEV_1 percent predicted of non-transplanted patients drops more sharply than that of the total population, with a difference of almost 4.7 percentage points at ages 35-39. Among older patients (aged 40 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. For patients who had received a lung transplant, for whom the average FEV_1 is given only from ages 20-24, the values are very high, and above 70% of the predicted values from ages 25-29.

– the FEV_1 percent predicted values calculated using the Knudson reference equations was compared with the values obtained using the Wang-Hankinson equations [14] (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 2.1 and 2.7 percentages points – than those obtained with the Knudson equations.

Figure 28 – Cystic Fibrosis Registry 2009. FEV_1 percentage of the predicted value Comparison between total population and patients who had or had not received a lung transplant

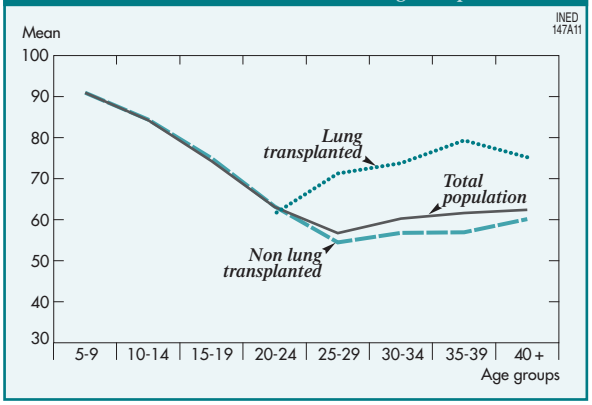
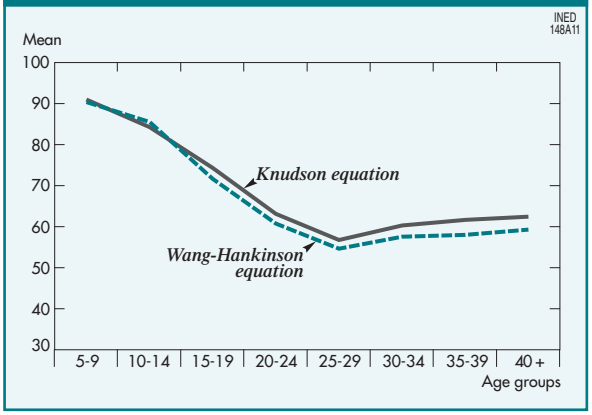


Figure 29 – Cystic Fibrosis Registry 2009. FEV_1 percentage of the predicted value Comparison between Knudson and Wang-Hankinson methods

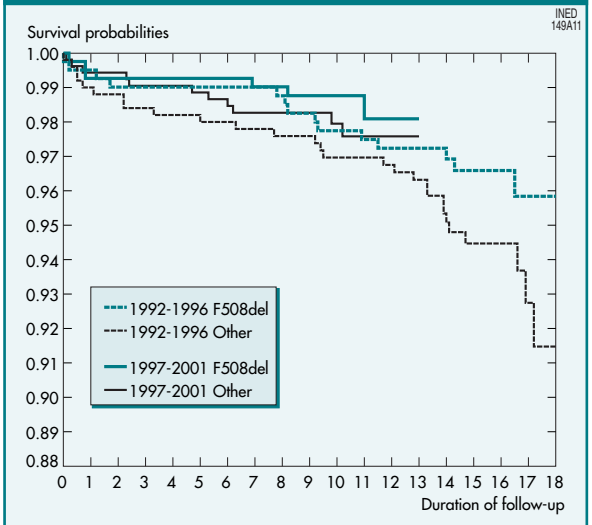


(14) In line with the recommendations to the CFF National Patient Registry, we referred to Wang *et al.* for males aged 6-17 and females aged 6-15; we referred to Hankinson *et al.* for males aged 18+ and for females aged 16+ .

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.

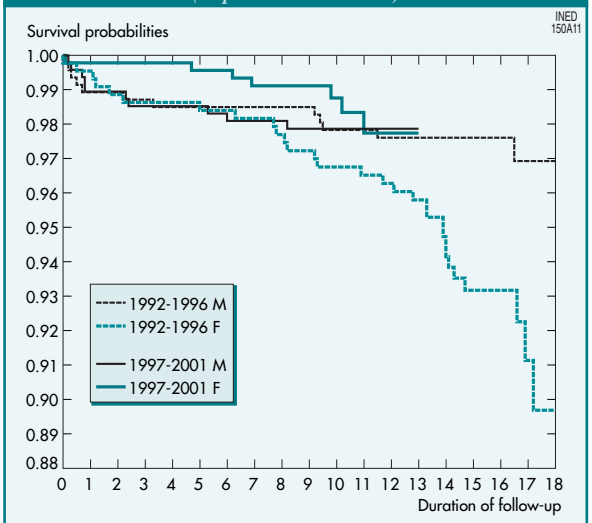
Hankinson J. L., Odencrantz J. R. and Fedan K. B., 1999, "Spirometric reference values from a sample of the general US population", *Am J Respir Crit Care Med*, 159, pp. 179-187.

Figure 30 – French CF Registry 2009.
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 2009.
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 (**longitudinal** Kaplan-Meier analysis) was performed for the two oldest cohorts, those of patients born in 1992-1996 and those of patients born in 1997-2001, to obtain sufficiently long follow-up periods. These cohorts totalled 1,846 patients and 59 deaths. 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 (called "1992-1996 F508del", for example, in the first cohort), and second, patients with a quite different genotype, including composite heterozygotes for F508del (called "1992-1996 Other" in the first cohort). The proportion of F508del homozygous genotypes is 44.8%, in the 1992-1996 cohort and 43.7% 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". 51.5% of patients in the 1992-1996 cohort are male and 50.8% in the 1997-2001 cohort.

For the 1992-1996 birth cohort, survival probabilities are higher for males than for females, except in the first years of life. The survival probability at age 18 is 96.93% (CI 95% [94.29 – 98.36]) for males, and 89.69% (CI 95% [83.96 – 93.45]) for females (Log-Rank test = 9.34; significant difference with p = 0.002). The opposite appears to be the case for the 1997-2001 cohort.

9.3 – Summary of data

	2009	2008 (for comparison)
Patients seen during the year and centres participating in the registry		
– Patients included in the registry* (number):	5,650	5,379
– Patients seen in the year by the centres** (number):	5,628	5,357
– Centres (number):	64	65
Paediatric CRCM	19	19
Adult CRCM	12	12
Paediatric and Adult CRCM	18	18
Demographic characteristics		
– Male patients (%)	51.8	52.0
– Patient age in years (mean)	17.7	17.3
– Patient age in years (median)	16.0	16.0
– Patient age in years (extremes)	0 – 79	0 – 78
– Patients aged 18 or above (%)	45.8	44.5
– Early pregnancies in the year (number)	34	36
– Conception rate among women aged 15-49 (per 1,000)	25.8	29.1
– Age in years of patients reporting an early pregnancy (mean)	28.4	27.0
– Deaths (number)	61	56
of which deaths of patients lost to follow-up	12	9
– Crude death rate (per 1,000)	11.2	10.8
– Age of deceased patients in years (mean)	25.5	28.2
– Age of deceased patients in years (median)	24.0	27.5
Diagnosis and genetics		
– Age at diagnosis in months (median)	2.0	2.0
– New patients diagnosed in the year (number)	230	235
of whom diagnosed by newborn screening	146	144
– New patient age at diagnosis in years (extremes)	0 – 72	0 – 58
– Complete genotypes identified (%)	93.9	93.4
F508del/F508del	43.6	43.8
F508del/Other	37.2	37.2
Other/Other	13.1	12.4
F508del / Unidentified	2.0	2.2
Other / Unidentified	1.2	1.2
Unidentified / Unidentified	2.9	3.2
Anthropometry and spirometry		
– Height z-score, patients aged 17 and above (mean)	- 0.16	- 0.17
– Height z-score, patients aged 18 and above (mean)	- 0.54	- 0.54
– Weight z-score, patients aged 17 and above (mean)	- 0.39	- 0.41
– Weight z-score, patients aged 18 and above (mean)	- 0.46	- 0.47
– FEV_1 percent predicted, Knudson method, patients aged 17 and above (mean)	84.31	83.53
– FEV_1 percent predicted, Knudson method, patients aged 18 and above (mean)	62.26	61.90

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* Patients whose vital status was known at the end of the year, whether or not they were seen by a centre.

** Reference patients for the statistics given in this summary, except for data on deaths

	2009	2008
Microbiology		
Patients who had at least 1 sputum culture during the year (%)	92.4	92.6
H. influenzae	26.0	28.0
MSSA	52.9	52.1
MRSA	8.5	8.5
P. aeruginosa	44.8	44.7
S. maltophilia	8.4	7.3
B. cepacia	2.1	2.3
Aspergillus	20.8	21.0
Complications and transplants		
– Hemoptysis (%)	5.3	5.4
– Cirrhosis/portal hypertension (%)	3.6	3.5
– Insulin-dependent and non-insulin-dependent diabetes (%)	14.1	13.1
– Transplanted patients (number)	400	353
of whom transplanted in the year	74	72
– Patients on the transplant waiting list (number)	161	171
of whom registered in the year	65	70
deceased before receiving a transplant	3	6
Therapeutic management		
– Courses of IV antibiotic treatment (%)	35.3	34.7
– Oxygen therapy (%)	6.3	6.7
– Non-invasive ventilation (%)	4.1	4.4
– Azithromycin (%)	40.6	40.8
– Inhaled antibiotics (%)	35.9	36.8
– rhDNase (%)	43.4	45.1
– Inhaled bronchodilators (%)	49.1	45.6
– Inhaled corticosteroids (%)	40.5	37.7
– Pancreatic enzyme supplements (%)	82.7	83.0