French Cystic Fibrosis Registry

Annual data report 2011

VAINCRE LA MUCOVISCIDOSE

ined
INSTITUT NATIONAL D'ÉTUDES DÉMOGRAPHIQUES

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Website:

www.registredelamuco.org

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Information

Percentages may not add up exactly to 100 due to rounding

Children are patients under 18 years of age, adults are patients aged 18 or more.

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 implementation of the systematic newborn screening program, the most common context for diagnosis was as follows: alerted by clinical symptoms (steatorrhoea, bronchial obstruction, recurrent respiratory infections), the physician would carry out a sweat test. An elevated sweat chloride ions concentration would confirm the diagnosis, and this would be 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 and 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 specific enough (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 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 respiratory disease) and digestive and nutritional management (pancreatic enzyme supplements and a hypercaloric diet).

The French Cystic Fibrosis Data Registry

In 1992, the medical Council of the association *Vaincre la Mucoviscidose*, set up a national cystic fibrosis observatory, the *Observatoire national de la mucovicidose* (ONM), with the following objectives:

– improving knowledge on medical and social characteristics of the population with cystic fibrosis and the impact of therapeutics;

– gaining a better understanding of the socioeconomic cost of this disease with a view to obtaining sufficient resources to cover constantly growing needs;

– improving information available to help both parents and patients in their personal choices, and associations and other institutional partners in strategic decisions.

Covering the entire population of patients in France, has since been added to the initial objectives. The association has therefore 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 and then in 2011, 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 the care centres participating in the registry in France (metropolitan France, Reunion Island and Guadeloupe). 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 2011 and were produced by cross-sectional analysis of data. Data on patients seen during the year in at least two centres were processed differently. 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.

Read precautions before use

Comparisons between the indicators from different countries must be done with care, due to a number of bias coming from the implementation of newborn screening programs, transplantation frequency, socioeconomic status and a limited number of patients in some age groups.

Demographics

Characteristics of the population

Figure 1 - Number of patients seen during the year and % of adults, evolution since 1992

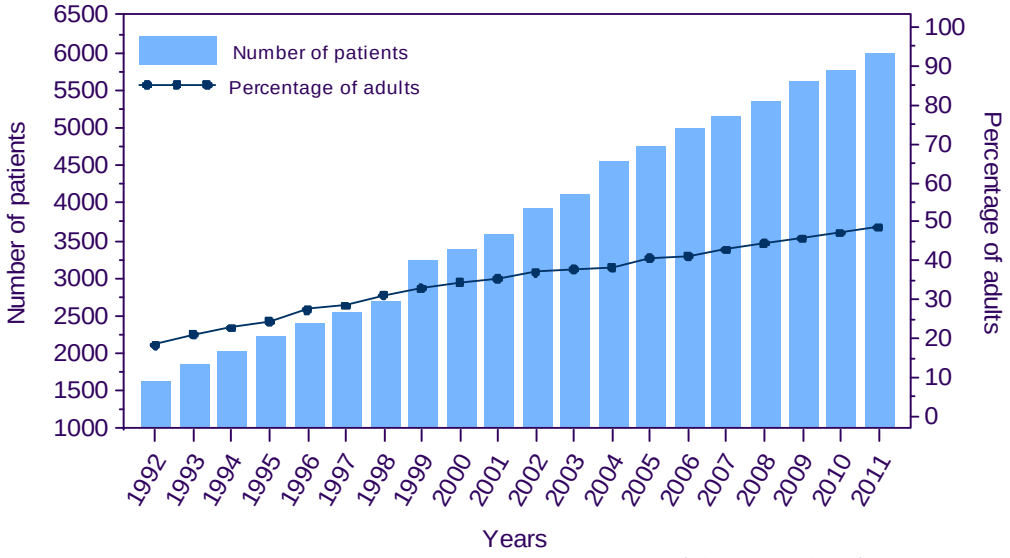

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Table 1. Annual evolution of the main indicators

	Years of follow-up									
Indicators	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
All patients*	3941	4117	4549	4755	5003	5148	5379	5650	5792	6046
Patients seen during the year**	3936	4111	4544	4745	4994	5140	5357	5628	5758	5993
Children	2476	2550	2799	2812	2932	2935	2971	3049	3040	3074
Adults	1460	1561	1745	1933	2062	2205	2386	2579	2718	2919
Over 40 years	119	124	160	175	196	226	272	329	358	415
Men	2054	2157	2368	2497	2595	2686	2786	2916	2958	3100
Women	1882	1954	2176	2248	2399	2454	2571	2712	2800	2893
Mean age (years)	15.6	15.8	16	16.3	16.4	16.8	17.3	17.7	18.1	18.7
Median age (years)	14	14	14	15	15	15	16	16	16	17
Minimum age (years)	0	0	0	0	0	0	0	0	0	0
Maximum age (years)	71	77	78	74	76	77	78	79	80	87

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*Patients whose vital status is known, whether they visited or not the CF centre.

**Reference patients for this report, excepted data on survival.

These figures, along with the total number of patients in the registry, compare against a total of 5,824 CF patients registered on 31 December 2011 under the general social security regime (for wage employees) which covers around 88% of the French population.

Demographics

Characteristics of the population

Table 2. Characteristics of the population, by sex and age

	2009		2010		2011	
Characteristics	Men	Women	Men	Women	Men	Women
Patients seen during the year	2916	2712	2958	2800	3100	2893
Children	1553	1496	1532	1508	1567	1507
Adults	1363	1216	1426	1292	1533	1386
Mean age (years)	17.8	17.6	18.2	18	18.7	18.6
Median age (years)	17	16	17	16	17	17

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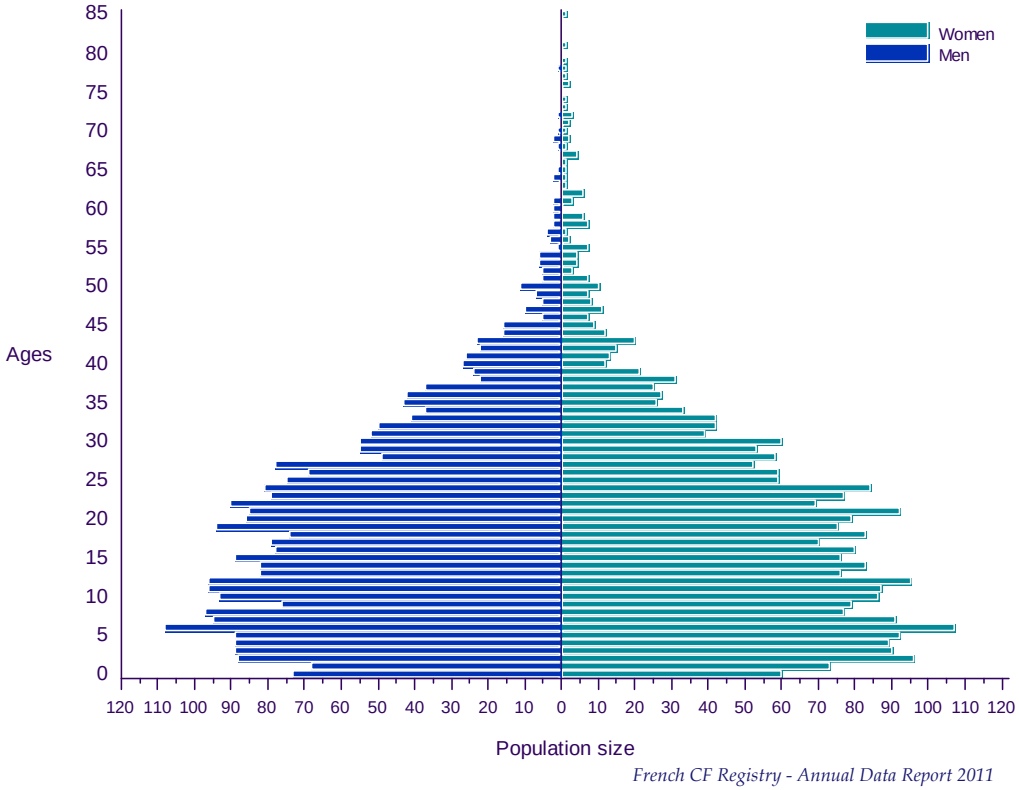
Figure 2. Population pyramid



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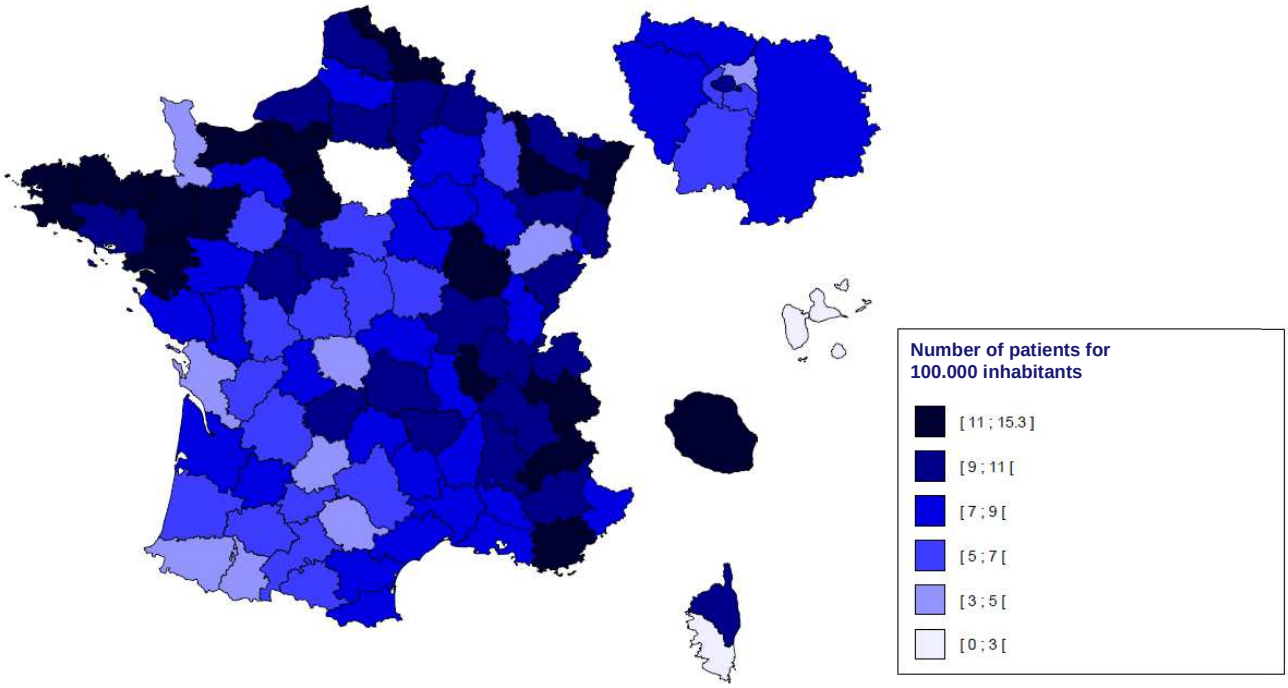
A total of 133 patients are aged below 1 (0 year completed age). Entry into the registry is delayed the first year of life as a certain number of infants diagnosed through neonatal screening in a given year are not registered until the following year.
As an indicative reference, 13 children born in 2010 were diagnosed by neonatal screening in 2011. On the 2010 population pyramid, the number of patients aged 0, which stood at 111, could thus have been 111 + 13 = 124.

Demographics

Geographical location

Map 1. Prevalence of cystic fibrosis by « département » of residence (number of patients for 100 000 inhabitants)



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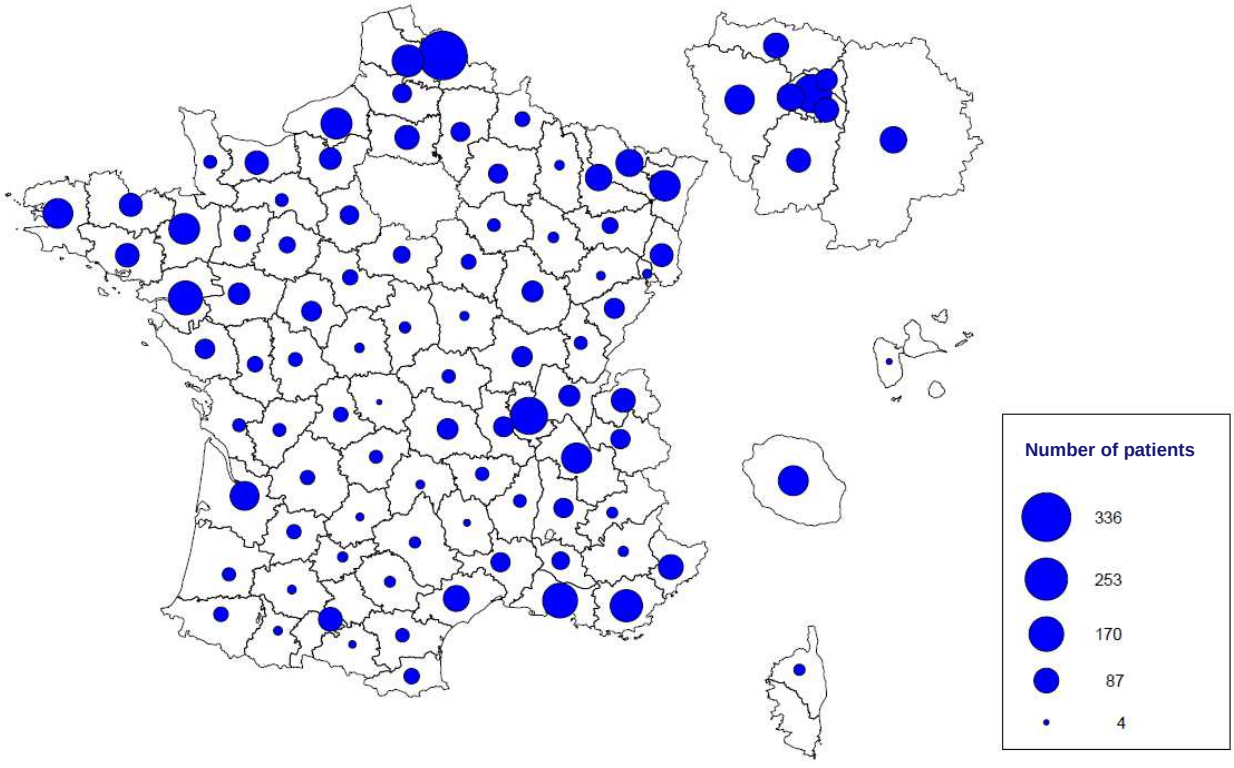
Map 2. Localisation of the patients by « département » of residence (absolute numbers)



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Demographics

Location by type of centre

Table 3. Characteristics of the centres

Centres		Patients' characteristics			Age of patients (years)				
Types of centres	Nb	Nb (a)	%	Mean nb by centre	Min	Max	Mean	Median	Inter-quartile
Paediatric CRCMs*	19	2114	35.3	111.3	0	59	9.8	9	9
Adult CRCMs*	12	1811	30.2	150.9	15	79	30.4	28	12
Paediatric/Adult CRCMs*	18	1917	32.0	106.5	0	87	17.7	15	18
Subtotal	*49*	*5842*	*97.5*	*119.2*	*0*	*87*	*18.8*	*17*	*19*
Paediatric local Centres	8	78 (b)	1.4	9.6	0	39	12.6	12	11
Adult local Centres	1	2 (c)	0.0	2.0	22	34	28.0	28	12
Paediatric/Adult local Centres	2	37 (d)	0.6	18.5	3	37	17.7	16	12
Other Centres	5	34 (e)	0.4	6.5	2	49	18.4	17	12
Subtotal	*16*	*151*	*2.5*	*9.4*	*0*	*49*	*15.3*	*14*	*12*
Total	**65**	**5993**	**100**	**92.2**	**0**	**87**	**18.7**	**17**	**19**

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* CRCM: Specialised CF Centre (Centre de Ressources et de Compétences de la Mucoviscidose)

Notes :
(a) After checking of patients in the multiple account category (cf page 5)
(b) Including 62 patients also seen by a CRCM.
(c) Including 2 patients also seen by a CRCM.
(d) Including 8 patients also seen by a CRCM
(e) Including 7 patients also seen by a CRCM.

Mortality

Characteristics

Figure 3. Annual number of deaths since 1992

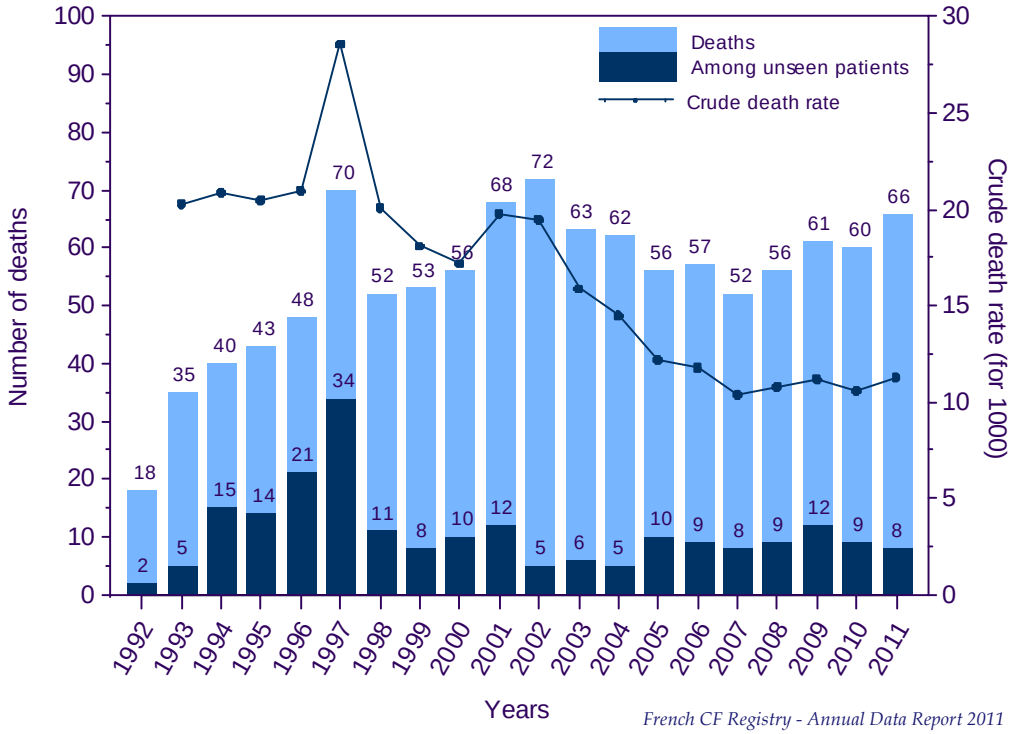

Table 4. Characteristics of mortality

Indicators	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number of deaths	72	63	62	56	57	52	56	61	60	66
- including patients not seen during the year*	5	6	5	10	9	8	9	12	9	8
- including transplanted patients	17	6	10	9	14	22	22	26	27	31
Mean age (years)	22	24	22	24	25	27	28	25	29	26
Median age (years)	21	22	21	21	24	26	27	24	27	26
Minimum age (years)	0	6	0	0	4	10	0	0	0	1
Maximum age (years)	62	65	50	71	68	70	66	73	68	55

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* Information of the death transmitted while the patient did not visit any centre during the year.

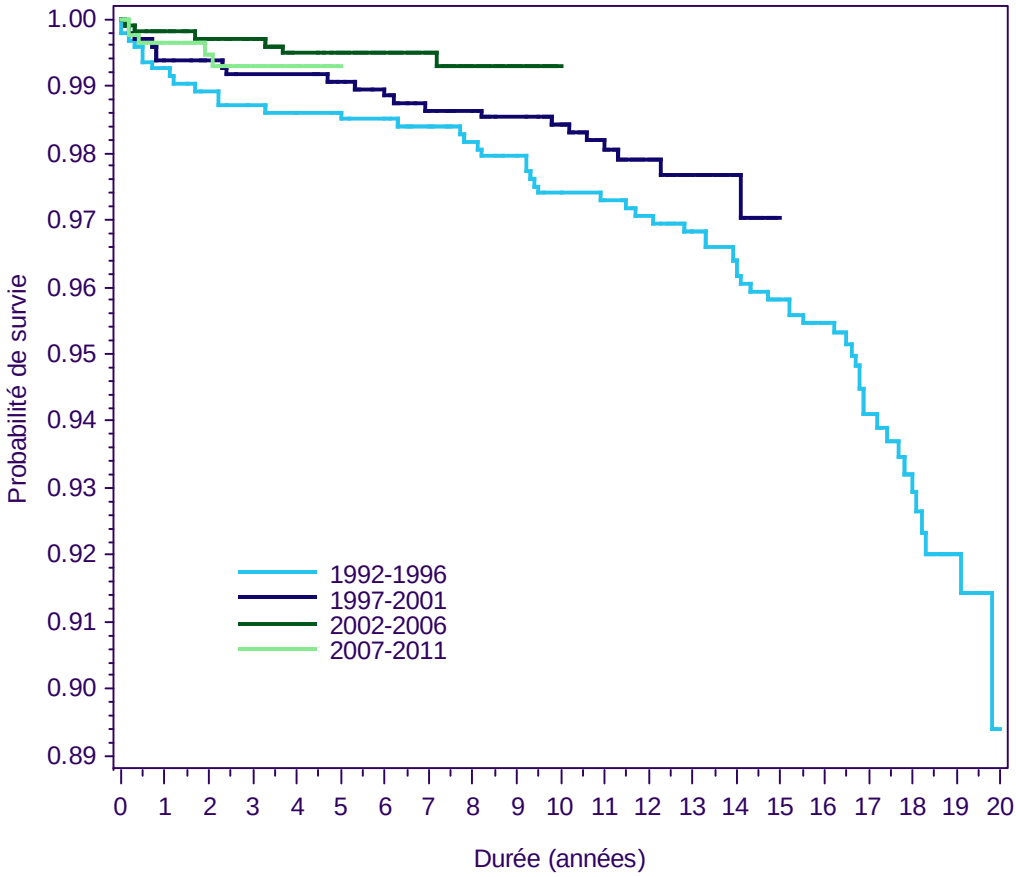
Mortality

Survival analysis

Figure 4. Survival curves by birth cohort (Kaplan-Meier method)

In order to show the evolution of health status of the patients, a survival analysis was performed on 4 birth cohorts; the numbers of patients and of deaths are:

- Births from 1992 to 1996 (in 2011 this cohort was followed during 20 years maximum) : 934 patients, 59 deaths
- Births from 1997 to 2001 (maximum 15 years of follow up) : 965 patients, 21 deaths
- Births from 2002 to 2006 (maximum 10 years of follow up) : 1009 patients, 6 deaths
- Births from 2007 to 2011 (maximum 5 years of follow up) : 848 patients, 5 deaths



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There is no significative survival difference between those cohorts (Log-Rank test = 6.90, p = 0,075).

Survival analysis by genotype and sex are available on annex 1.

Pregnancy

Figure 5. Annual number of early pregnancies, evolution since 1992

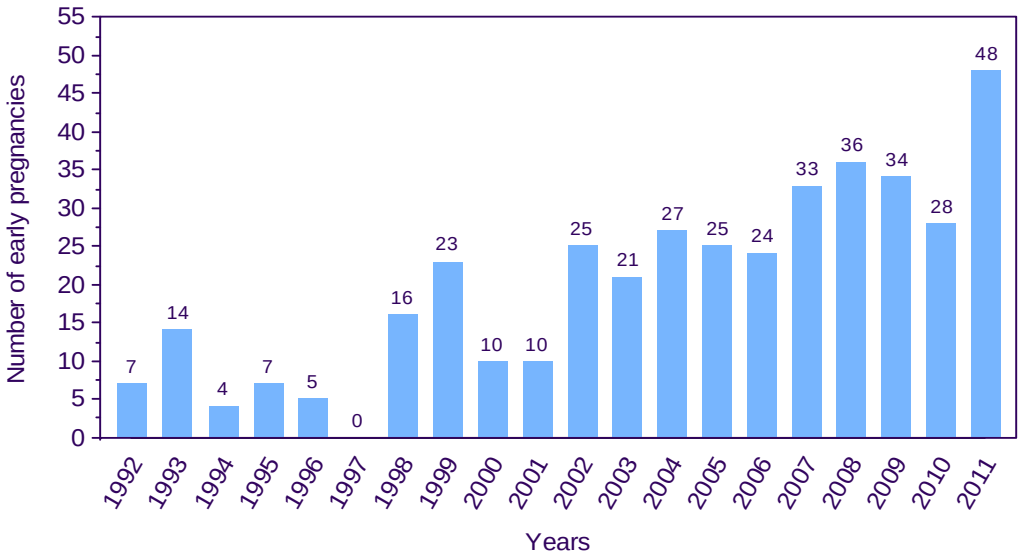

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Table 5. Early pregnancy characteristics

Characteristics	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number of early pregnancies	25	21	27	25	24	33	36	34	28	48
Pregnancy rates in women aged 15 to 49 years (for 1000)	31.6	24.4	28.6	23.9	21.5	28.2	29.1	25.8	20.1	32.8
Mean age at onset of pregnancy	26.7	27	27.5	25.4	25.8	28.6	27	28.4	29.2	28

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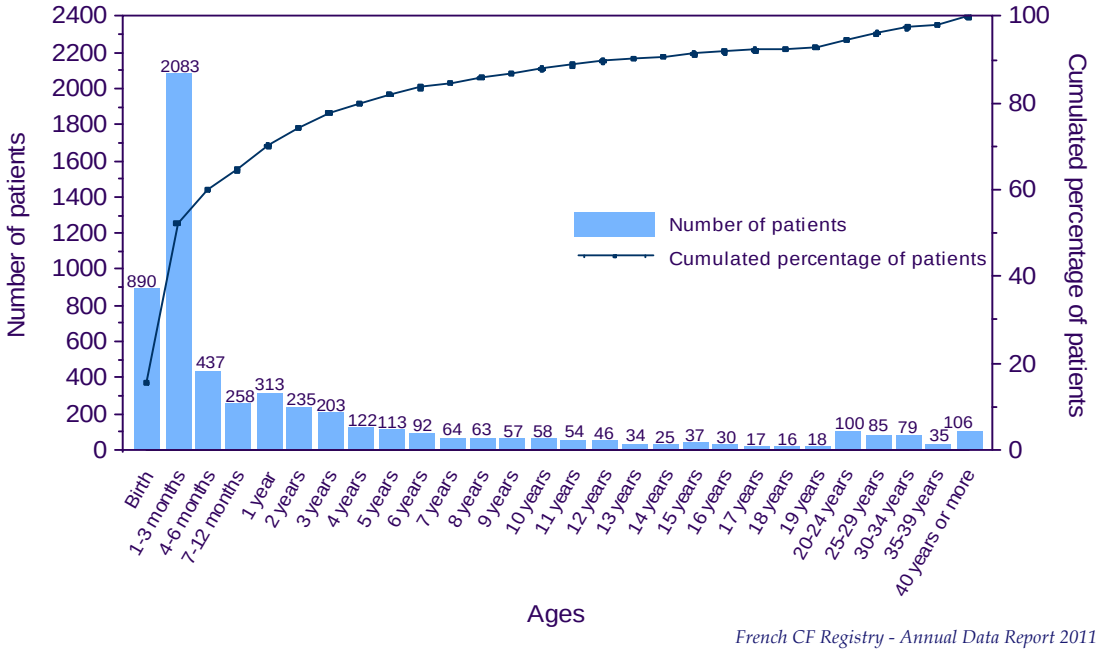
Diagnosis

Main characteristics

Figure 6. Number of patients and aggregate percentage of patients by age at diagnosis

N = 5 669 (number of patients whose age at diagnosis is known).



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Diagnosis

Main characteristics

Table 6. Diagnosis characteristics

Characteristics	2009	2010	2011
ALL PATIENTS			
Patients whose age at diagnosis is known - N (%)	5355 (95.1 %)	5453 (94.7 %)	5669 (94.6 %)
Age at diagnosis			
- Median age (months)	3	3	3
- Mean age (years)	4.2	4.1	4.3
- Minimum age (years)	0	0	0
- Maximum age (years)	75	79	87
NEW PATIENTS DIAGNOSED DURING THE YEAR			
Number of patients			
New patients - N (%)	232 (4.1 %)	181 (3.1 %)	215 (3.6 %)
- Including newborn patients	162	111	133
Age at diagnosis (a)			
- Median age (months)	1	2	1
- Mean age (years)	6.2	6.5	6.9
- Minimum age (years)	0	0	0
- Maximum age (years)	72	69	69
Context of diagnosis			
- Prenatal diagnosis - N (%)	4 (1.7 %)	8 (4.5 %)	10 (4.7 %)
- Meconium ileus - N (%)	12 (5.2 %)	10 (5.6 %)	26 (12.1 %)
- Neonatal screening - N (%)	155 (67.4 %)	112 (62.6 %)	131 (60.9 %)
- Symptoms (excluding MI):			
-- N (%)	68 (29.6 %)	55 (30.7 %)	58 (27 %)
-- Mean age at diagnosis (years)	20.8	19.2	22.0

Notes :
(a) Including family history and antenatal diagnosis.
(b) Patients diagnosed before the results of neonatal screening were excluded.

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Among the 215 new patients, 133 were born in 2011. The method used to compile this report (patients seen in a care centre in 2011) means that infants born in 2011 and seen for the first time in 2012 are excluded (cf note page 7).

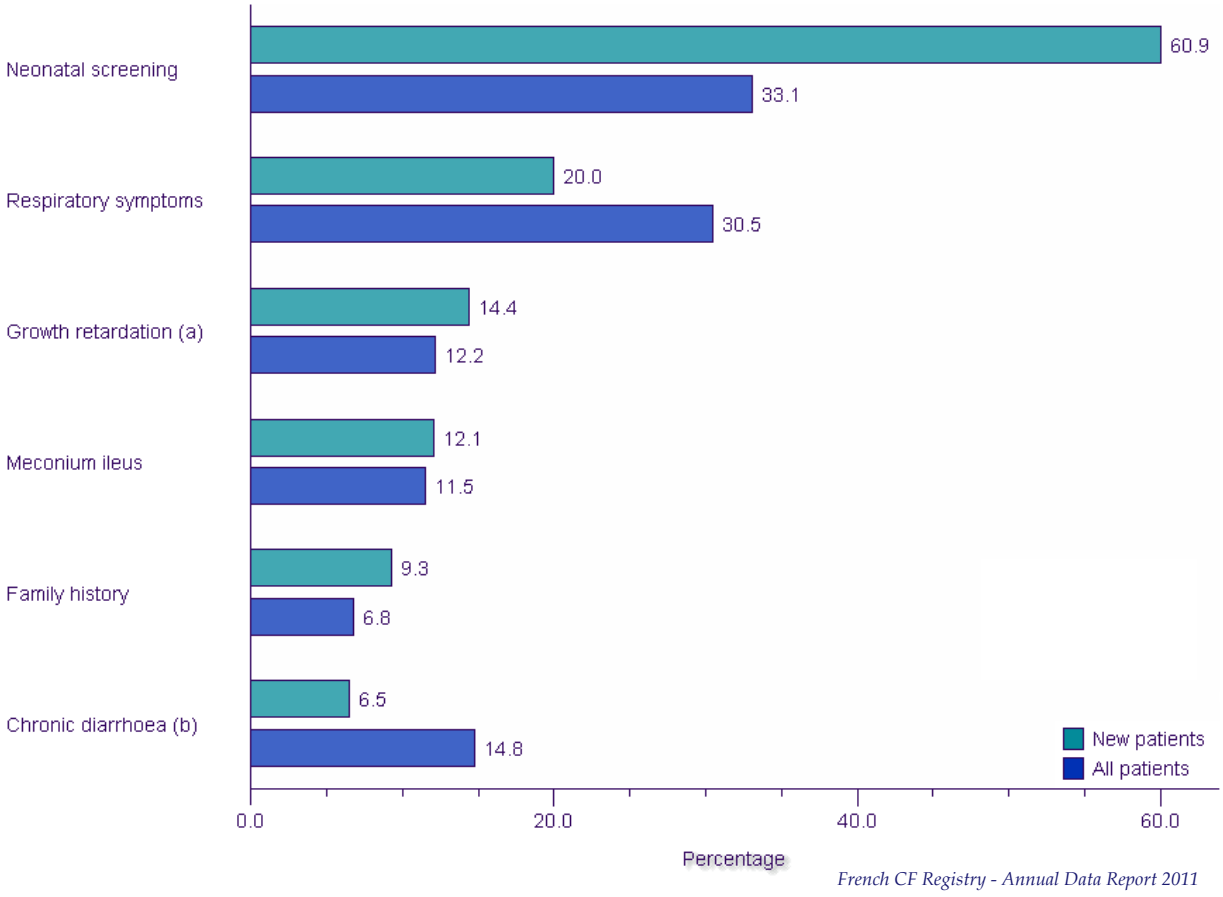
The number of patients diagnosed by neonatal screening (131) given in this report is not the total for France, but represents the patients for whom screening resulted in diagnosis. Patients diagnosed with CF before the screening result was known, (e.g. throught meconium ileus), are not included in the total.

By comparison, 349 new patients were registered in 2011 under the general social security regime (for wage employees).

Diagnosis

Diagnosis signs

Figure 7. Diagnosis signs (most frequent ones)

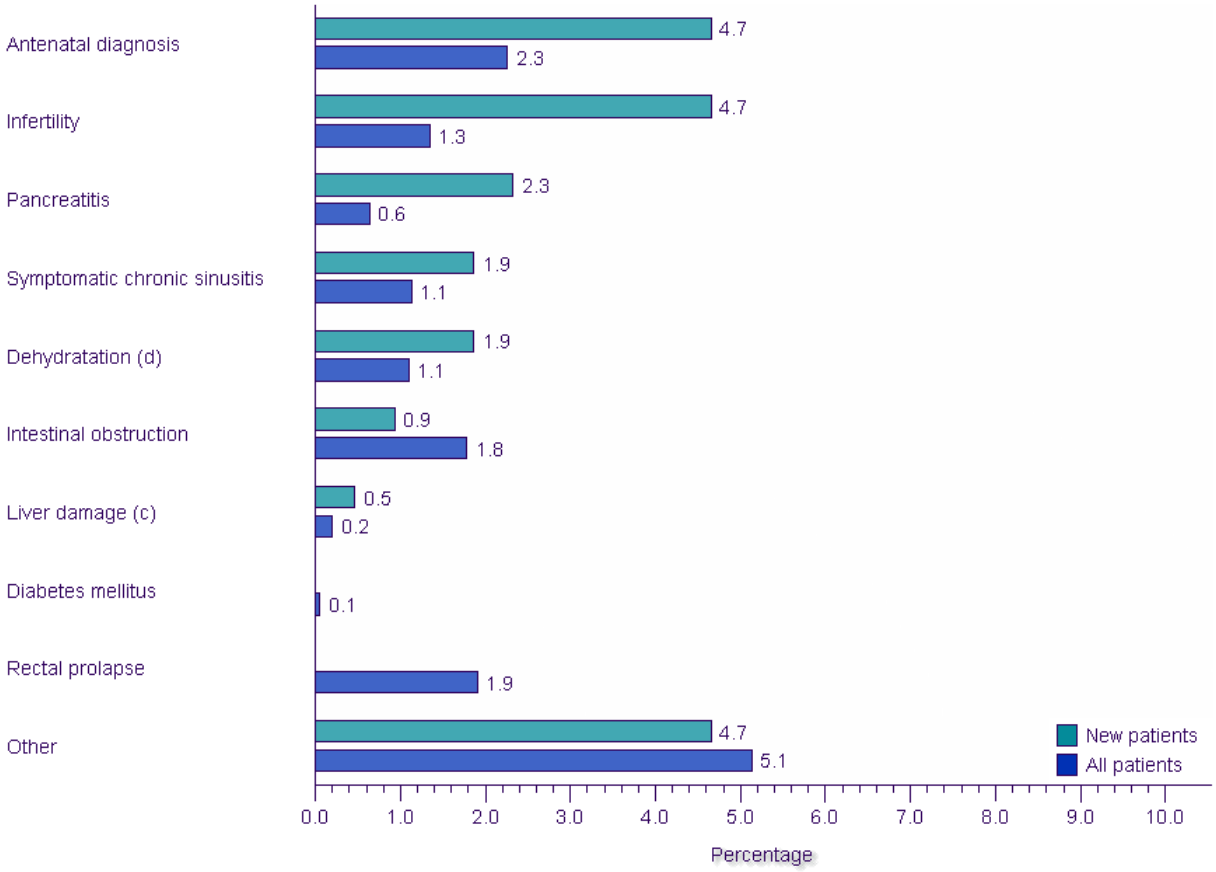


(a) Growth retardation / Malnutrition
(b) Chronic diarrhoea / Steatorrhoea / Malabsorption

Diagnosis

Diagnosis signs

Figure 7. Diagnosis signs (less frequent ones)



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(c) Liver damage / Jaundice / Portal hypertension
(d) Dehydratation / Electrolyte inbalance

Diagnosis

Genotypes

Table 7. Number and proportion of genotypes

Genotypes	Number of patients	%
F508del / F508del	2593	43.3 %
F508del / G542X	188	3.1 %
F508del / N1303K	137	2.3 %
F508del / 2789+5G->A	95	1.6 %
F508del / 1717-1G->A	94	1.6 %
F508del / R117H	87	1.5 %
F508del / R553X	66	1.1 %
F508del / G551D	62	1.0 %
F508del / 3849+10kbC->T	47	0.8 %
F508del / 3272-26A->G	44	0.7 %
F508del / W1282X	40	0.7 %
F508del / Y122X	41	0.7 %
F508del / [delta]I507	41	0.7 %
F508del / L206W	41	0.7 %
F508del / R347P	37	0.6 %
F508del / D1152H	34	0.6 %
F508del / 2183AA->G	34	0.6 %
F508del / 5T	32	0.5 %
F508del / R1162X	29	0.5 %
F508del / A455E	27	0.5 %
F508del / 1078delT	24	0.4 %
F508del / R347H	23	0.4 %
F508del / Y1092X	22	0.4 %
F508del / R334W	22	0.4 %
F508del / 3659delC	21	0.4 %
N1303K / N1303K	21	0.4 %
F508del / 711+1G->T	20	0.3 %
G542X / G542X	20	0.3 %
F508del / S945L	20	0.3 %
F508del / 394delTT	18	0.3 %
F508del / E60X	18	0.3 %
F508del / S1251N	17	0.3 %
F508del / W846X	17	0.3 %
F508del / G85E	17	0.3 %
F508del / R1066C	16	0.3 %
F508del / 1811+1.6kbA->G	16	0.3 %
F508del / 3120+1G->A	16	0.3 %
Y122X / Y122X	14	0.2 %
711+1G->T / 711+1G->T	13	0.2 %
F508del / 621+1G->T	11	0.2 %
F508del / I148T	11	0.2 %
F508del / Q220X	10	0.2 %
Other CFTR genotypes	1503	25.1 %
Subtotal (known genotypes)	5659	94.9 %
F508del / Missing	115	1.9 %
Other / Missing	69	1.2 %
Missing / Missing	150	2.5 %
Subtotal (partial genotypes / Missing)	334	5.6 %
Total	5993	100.5 %

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Diagnosis

Genotypes

Table 8. Age of patients by genotype

Genotypes	Number	%	Age (years) Mean	Median	Max
F508del / F508del	2593	43.3	17.6	17	58
F508del / Other	2279	38	18.5	16	74
Other / Other	787	13.1	18.5	16	87
F508del / Missing	115	1.9	28.4	25	76
Other / Missing	69	1.2	26.1	24	81
Missing / Missing	150	2.5	30	26	78

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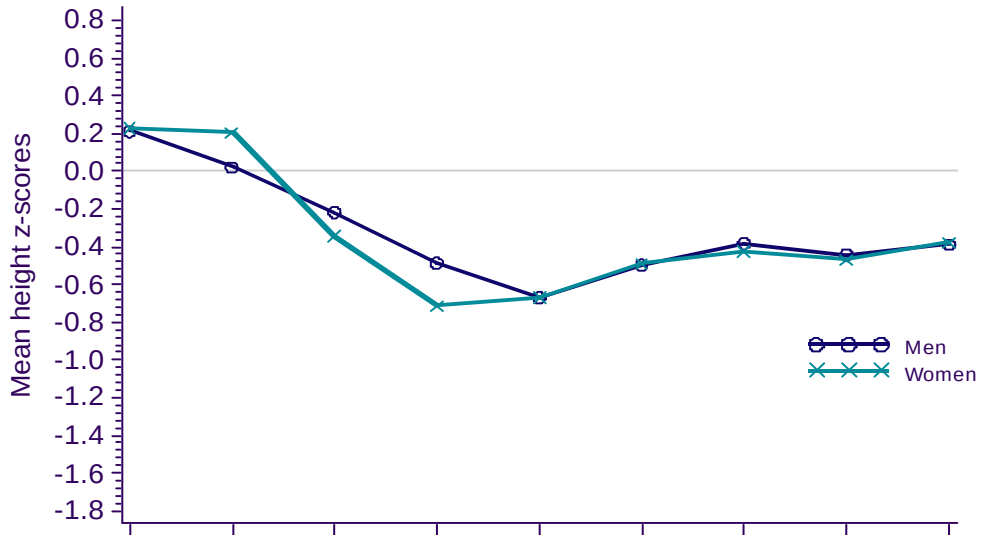
Anthropometry

Height and Weight

Figure 8. Mean height z-scores, by age and sex



Age groups (years)	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +
Men	0.21	0.02	-0.22	-0.48	-0.67	-0.50	-0.38	-0.44	-0.39
Women	0.23	0.20	-0.34	-0.71	-0.67	-0.49	-0.42	-0.47	-0.38

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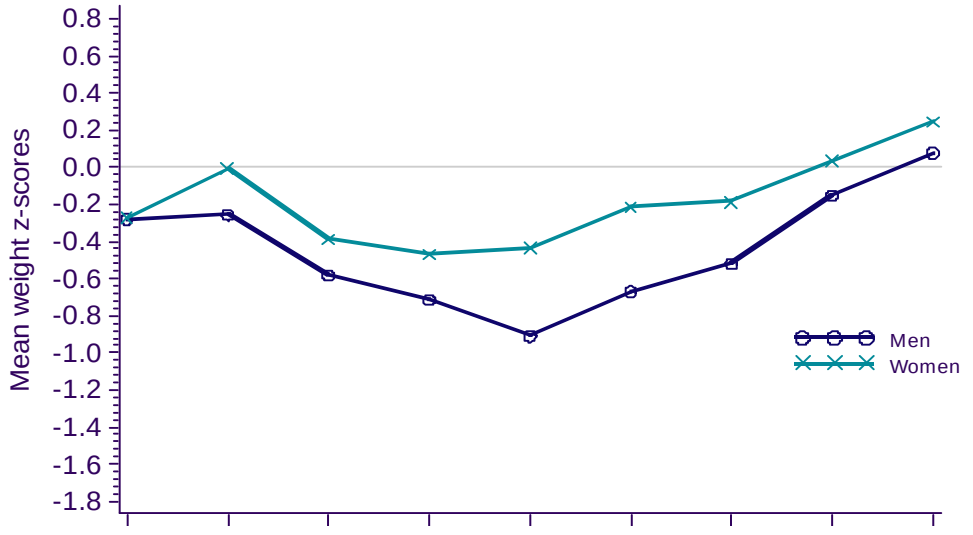
Figure 9. Mean weight z-scores, by age and sex



Age groups (years)	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +
Men	-0.28	-0.26	-0.58	-0.71	-0.91	-0.67	-0.52	-0.15	0.08
Women	-0.27	-0.00	-0.39	-0.47	-0.44	-0.21	-0.18	0.04	0.25

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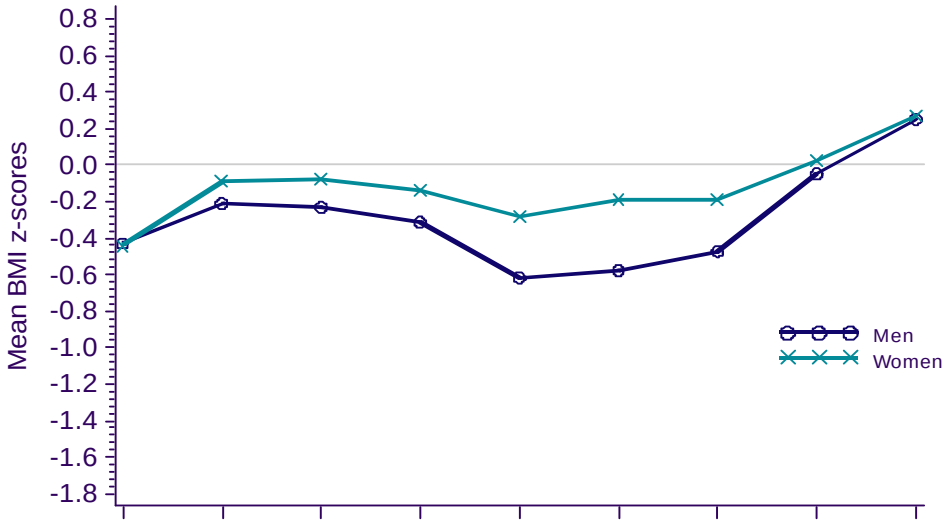
Height and weight z-scores have been calculated with respect to the French reference population (Sempé M., 1997, *Auxologie – Méthode et séquences*, Méditions, Lyon, 205 p.).

Anthropometry

Body Mass Index (BMI)

Figure 10. Mean BMI z-scores, by age



Age groups (years)	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +
Men	-0.43	-0.21	-0.23	-0.31	-0.61	-0.58	-0.47	-0.05	0.25
Women	-0.44	-0.09	-0.08	-0.14	-0.28	-0.19	-0.19	0.02	0.27

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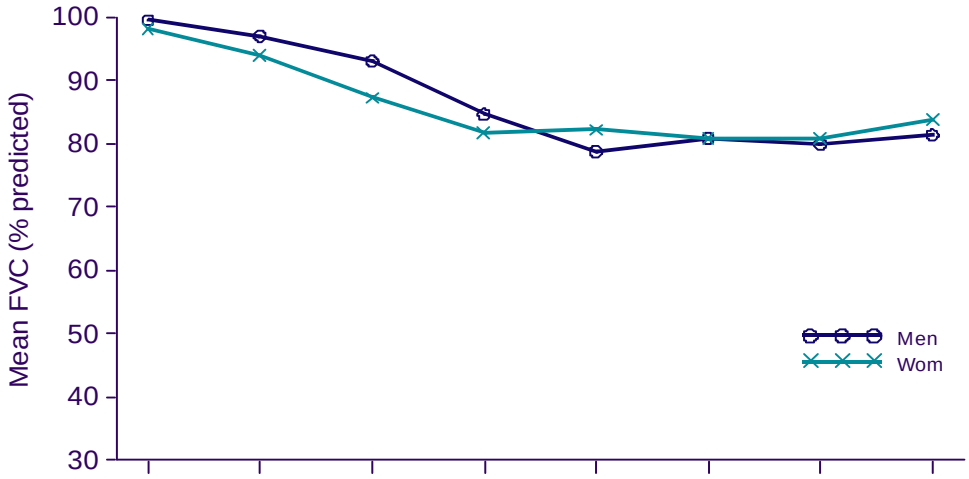
The z-score is a anthropometric reduced centered variable (Z = [measure-mean]/standard deviation), ajusted for sex and age; the mean and standard deviation are taken from the French reference population with the same sex and age as the patient. This index measures the difference with population norms and a negative score means growth retardation.

The BMI z-score was calculated with respect to the French reference population (Rolland-Cachera MF *et al.* A. Body Mass Index variations: centiles from birth to 87 years. Eur J Clin Nutr 1991;45:13-21).

Spirometry

In 2011, 94.6 % of the patients aged 6 or more had at least one spirometry (92.4 % in 2010 and 88.9 % in 2009).

Figure 11. Mean FVC (% predicted), by age



Age groups (years)	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 ou +	*05-80*
Men	99.6	97.1	93.1	84.7	78.8	81.0	80.0	81.5	88.6
Women	98.3	94.2	87.3	81.8	82.3	80.9	80.9	83.9	87.2
All patients	99.0	95.7	90.4	83.3	80.4	80.9	80.4	82.7	87.9

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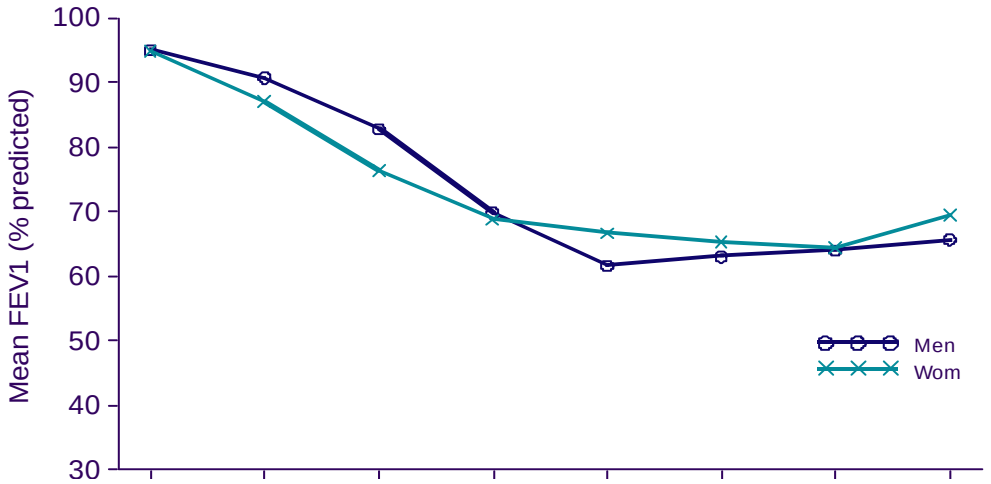
Figure 12. Mean FEV_1 (% predicted)*, by age



Age groups (years)	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 ou +	*05-80*
Men	95.1	90.9	82.9	69.9	61.7	63.1	64.1	65.8	76.7
Women	95.1	87.3	76.4	68.8	66.7	65.4	64.5	69.5	76.2
All patients	95.1	89.1	79.7	69.4	64.0	64.2	64.2	67.6	76.4

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* Since 2011, the best FEV1 of the year is collected instead of the last of the year.

The pulmonary function tests need an active participation of the patient, difficult to obtain before 6 years of age.
The forced vital capacity (FCV) and the forced expiratory volume in the first second (FEV1) are given in % predicted (Knudson *et al*. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis 1983*, 127, pp. 725-734).

See appendix 2 for additional information on spirometry and transplantation.

Spirometry

Figure 13. FEV_1 (% predicted) classes

Values of FEV1% predicted are classified in four « functional » groups according to various degrees of bronchial obstruction.

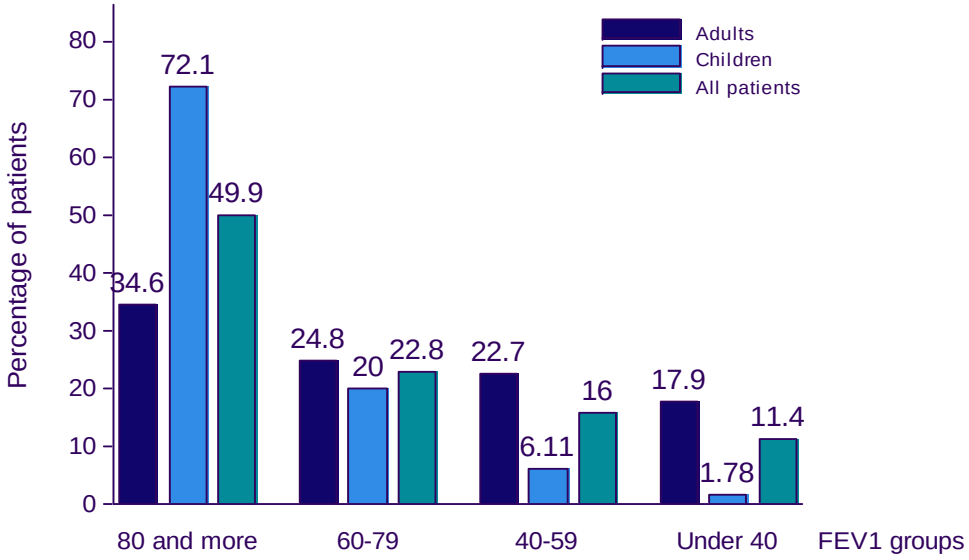

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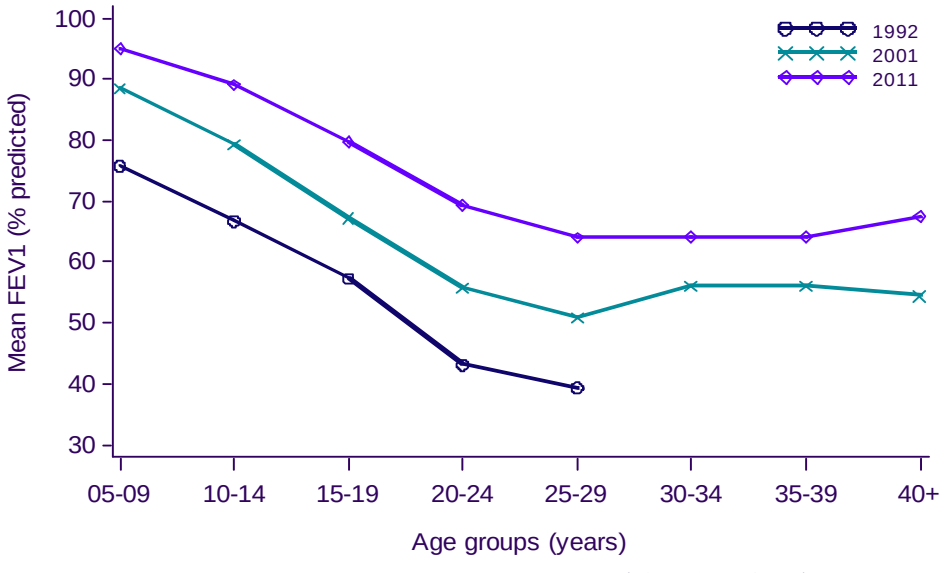
Figure 14. Mean FEV_1 (% predicted)* in 2011 compared with 1992 and 2001, by age



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* In 1992 and 2001 was collected the last FEV1 of the year. In 2011, it was the best value of the year.

Microbiology

Table 9. Sputum cultures

Patients with at least one sputum	N	*Proportion (%)*
All patients	5495	*91.7 %*
Children	2986	*97.1 %*
Adults	2509	*86.0 %*

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In 2011, 91.7 % of the patients had at least one sputum culture; this proportion remains steady as it was 92,9 % in 2010 and 92,4 % in 2009. Among the patients without sputum culture (N=498), 49.3 % of them were transplanted.

Table 10. Distribution of the germs

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%*
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	.
Patients with at least one sputum	**781**	**884**	**859**	**776**	**748**	**529**	**371**	**233**	**314**	**5495**	**91.7 %**
Normal culture	432	419	295	192	95	63	55	25	66	1642	27.4 %
Achromobacter xylosoxidans	11	29	54	60	56	44	24	20	21	319	5.3 %
Aspergillus	35	118	239	261	256	168	130	57	91	1355	22.6 %
Burkholderia cepacia	3	8	16	24	19	23	10	5	3	111	1.9 %
Haemophilus influenzae	307	349	250	146	116	52	40	27	39	1326	22.1 %
Atypical mycobacteria	1	4	17	27	29	22	10	5	17	132	2.2 %
Pneumococcus	84	64	30	10	13	6	6	4	12	229	3.8 %
Pseudomonas aeruginosa, including:	164	204	311	401	489	361	260	170	192	2552	42.6 %
- Chronic P. aeruginosa	7	40	105	177	346	262	175	115	130	1357	22.6 %
- Multidrug resistant P. aeruginosa	21	33	35	80	111	91	62	37	58	528	8.8 %
Staphylococcus, including:	455	629	708	600	507	317	225	113	131	3685	61.5 %
- MSSA	437	587	646	529	420	267	180	93	118	3277	54.7 %
- MRSA	20	53	77	76	96	55	50	18	14	459	7.7 %
Stenotrophomonas maltophilia	75	71	111	108	102	47	27	19	23	583	9.7 %
Streptococcus (non pneumoniae)	51	65	38	34	41	37	18	13	19	316	5.3 %

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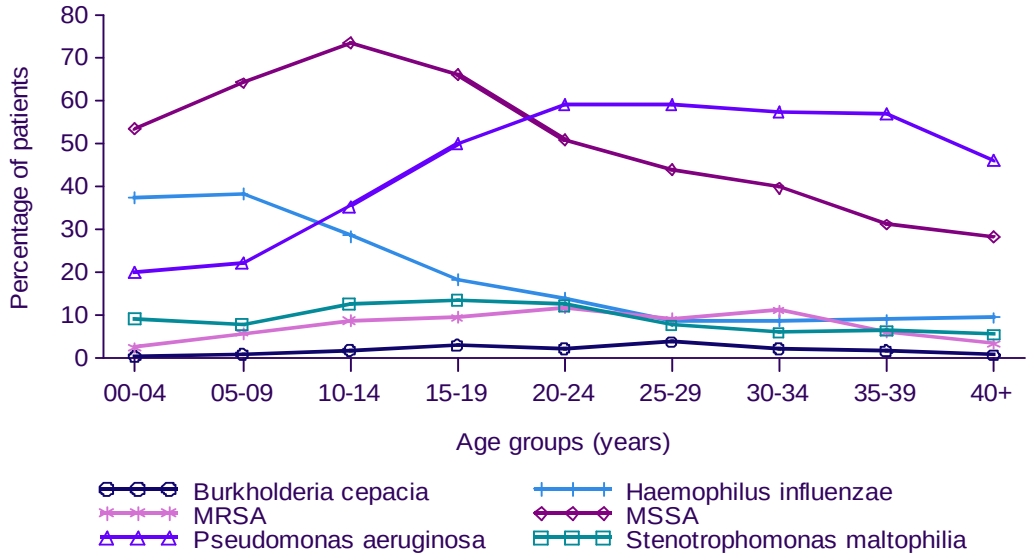
* Percentage with respect to the entire population.

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

Microbiology

Figure 15. Clinically important bacteria



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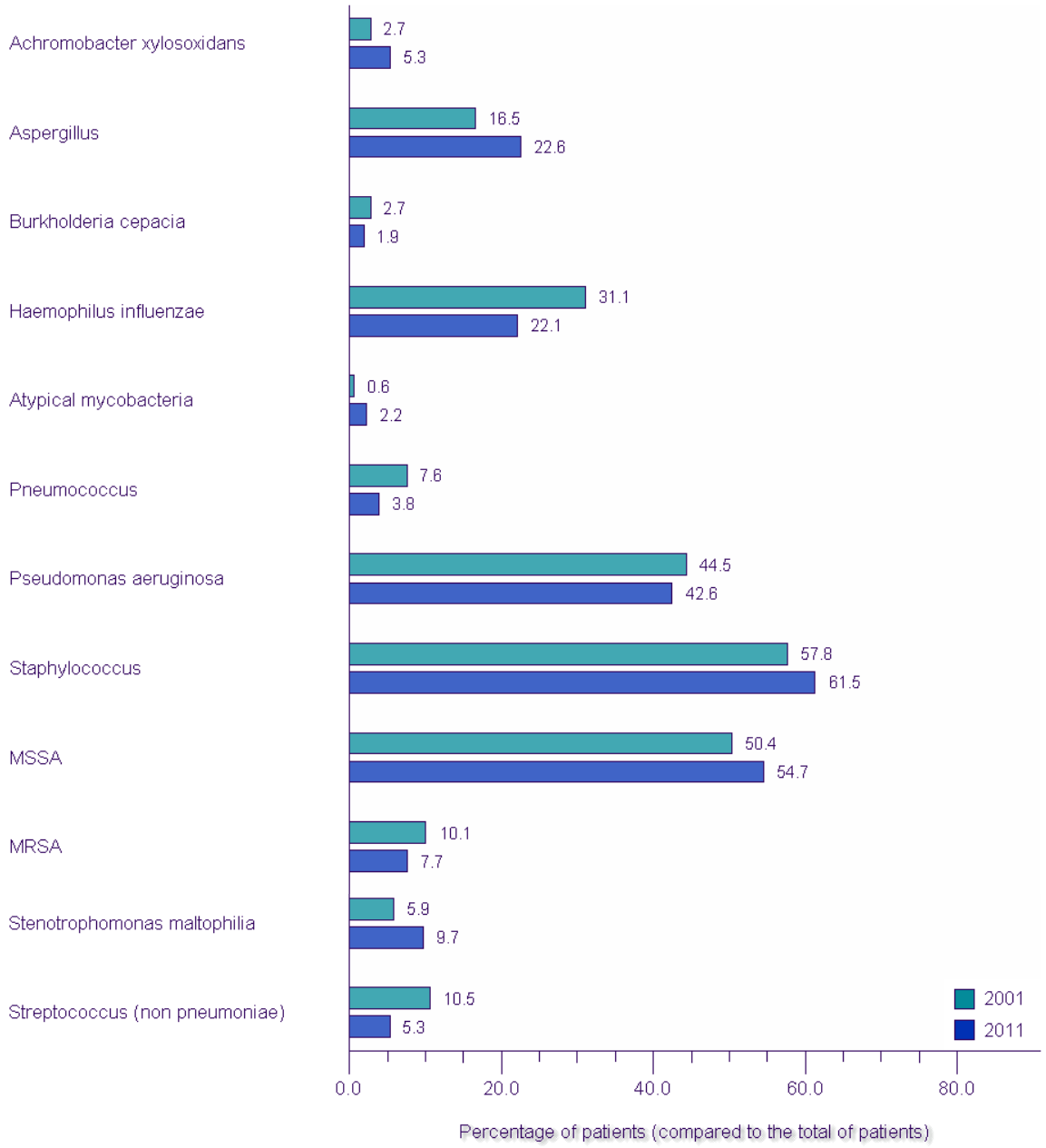
Microbiology

Figure 16. Comparison of germs in 2011 and in 2001



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Complications

Respiratory

Table 11. Respiratory complications

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Treated aspergillosis	2	63	135	147	150	116	57	35	52	757	12.6 %
Asthma	117	181	174	111	73	52	38	30	38	814	13.6 %
Haemoptysis	0	5	13	65	61	61	31	32	34	302	5.0 %
Pneumothorax	0	0	2	14	15	11	8	3	2	55	0.9 %
Nasal polyps	21	97	166	144	153	98	76	65	55	875	14.6 %

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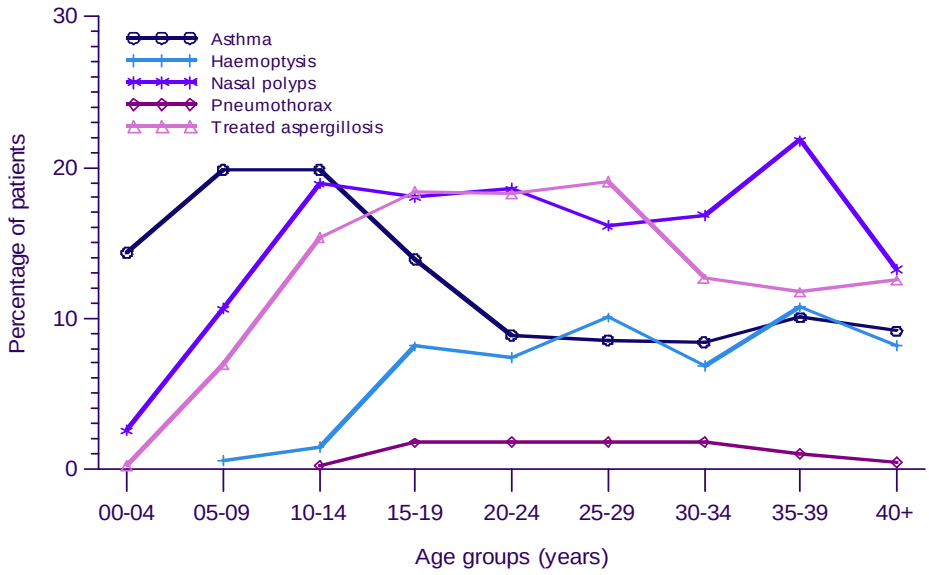
Figure 17. Respiratory complications



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Complications

Gastro-intestinal

Table 12. Gastro-intestinal complications

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Gallstones	3	14	6	19	31	39	20	21	19	172	2.9 %
Cirrhosis/Portal hypertension	3	12	48	54	57	30	20	10	11	245	4.1 %
Elevated liver enzymes	52	67	101	79	63	49	30	19	23	483	8.1 %
Acute pancreatitis	0	2	4	8	15	13	7	8	13	70	1.2 %
Treated gastro-oesophageal reflux disease	130	90	119	96	174	143	92	77	100	1021	17.0 %
Intestinal obstruction	18	22	37	33	44	41	28	13	14	250	4.2 %

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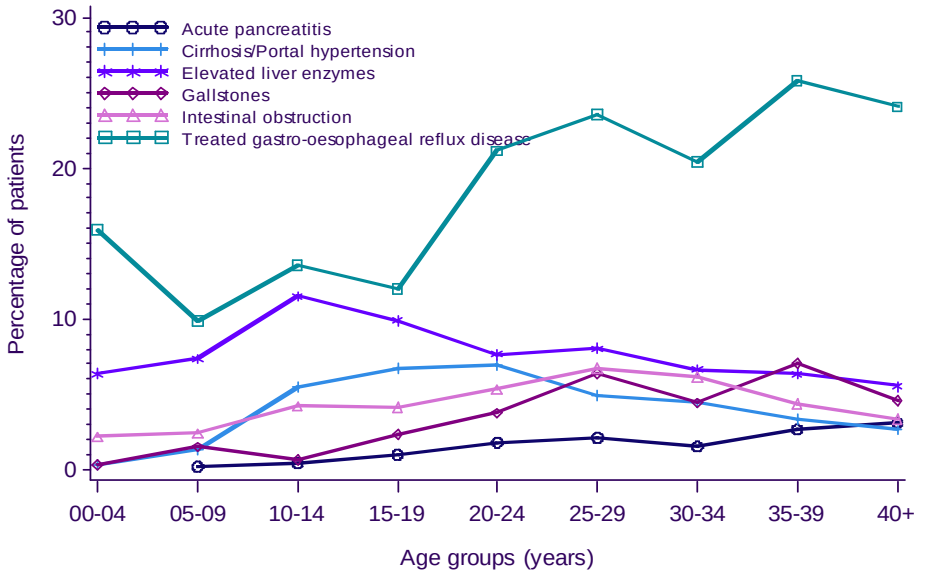
Figure 18. Gastro-intestinal complications



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Complications

Diabetes mellitus

Table 13. Diabetes mellitus and degenerative complications of diabetes

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Degenerative complications of diabetes	0	0	0	1	4	10	10	7	6	38	0.6 %
Non insulin-dependent diabetes	0	0	9	21	50	34	37	30	29	210	3.5 %
Insulin-dependent diabetes	1	3	27	95	145	144	125	74	101	715	11.9 %
Total diabetes (ID and non ID	1	3	35	115	192	176	159	101	129	911	15.2 %

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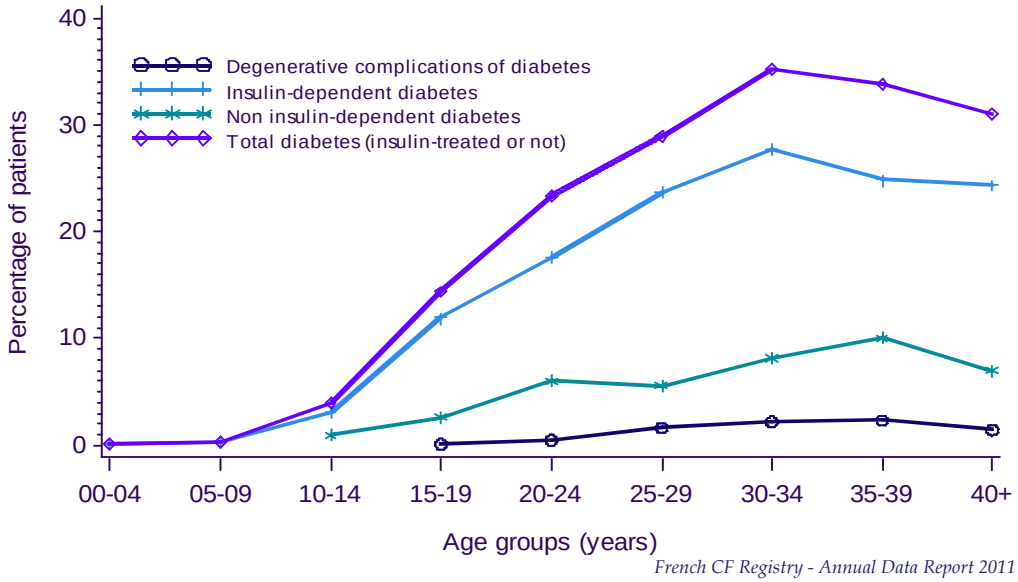
The line « Total diabetes » sums the number of patients having at least one type of diabetes. Among the 911 patients, 14 patients presented with both types of diabetes during the year.

Figure 19. Diabetes mellitus and degenerative complications of diabetes



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Complications

Other complications

Table 14. Other complications

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Arthropathy	1	2	11	13	16	20	19	11	23	116	1.9 %
Cancer	0	0	1	2	1	2	2	2	7	17	0.3 %
Depression (evaluated and followed)	0	1	6	21	38	30	28	22	48	194	3.2 %
Urinary incontinence	1	4	7	11	6	4	2	2	5	42	0.7 %
Terminal renal failure	0	0	0	2	2	4	7	4	13	32	0.5 %
Bone disease	1	4	7	31	56	74	59	38	69	339	5.7 %
Deafness/Hypoacusia	5	6	10	10	26	28	24	19	25	153	2.6 %

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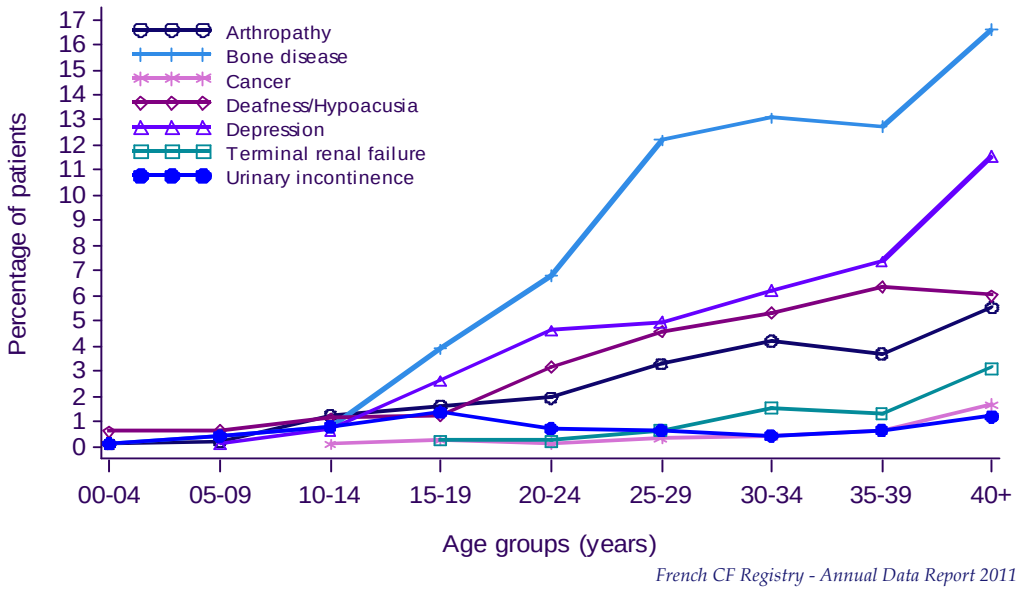
Figure 20. Other complications



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Transplantations

Tableau 15. Characteristics of the transplantations

Characteristics	All years	In 2011
WAITING LIST	All waiting patients	Listed in 2011
Number of patients	177	98
Mean age (years)	28.2	28
Extremes of age (years)	6-59	6-59
Deaths on waiting list	1	0
TRANSPLANTATION	All transplanted	Transplanted in 2011
Number of patients	529	97
- incl. patients with heart-lung transplants - N (%)	31 (5.9 %)	2 (2.1 %)
- incl. patients with bilateral lung transplants - N (%)	475 (89.8 %)	93 (95.9 %)
- incl. patients with liver transplants - N (%)	36 (6.8 %)	4 (4.1 %)
- incl. patients with kidney transplants - N (%)	30 (5.7 %)	2 (2.1 %)
- incl. patients with other organs - N (%)	13 (2.5 %)	2 (2.1 %)
Mean age (years)	30.7	27.3
Extremes of age (years)	10-59	10-59
Post-transplantation deaths	31	13

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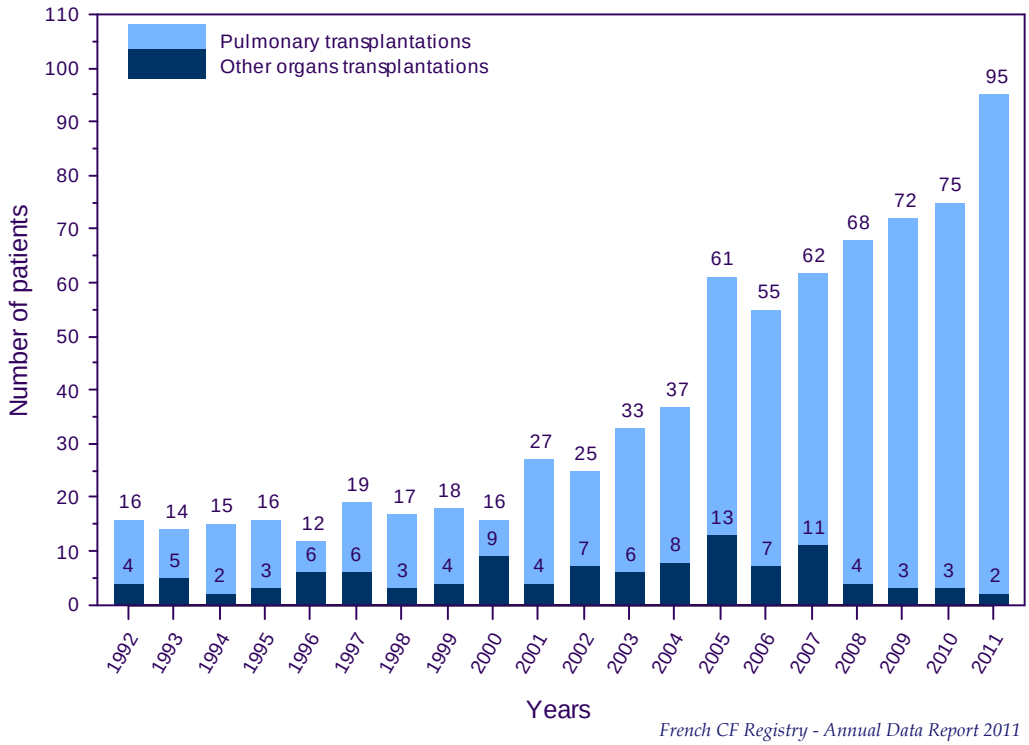
Figure 21. Annual number of patients transplanted, since 1992



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Inpatient and outpatient visits

Table 16. Characteristics of the visits

	Age groups (years)									
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*
< 4 visits* per year	147	229	152	181	228	180	153	108	161	1539
>= 4 visits* per year	668	682	724	617	594	427	298	190	254	4454
Outpatient visits										
Median	4	3	3	3	3	3	3	3	3	3
Mean	4.4	3.5	3.9	4.1	4.0	3.8	3.6	3.3	3.2	3.7
One-day visits										
Median	1	1	1	1	2	2	2	2	2	2
Mean	2.5	2.3	2.6	2.6	3.1	3.1	3.1	2.7	2.7	2.7
Inpatient visits										
Median	1	1	1	2	2	2	2	2	2	2
Mean	1.7	2.0	2.0	2.2	2.2	2.5	2.4	2.3	2.3	2.2
Days (median)	9	5	6	8	10	13	9	11	11	9
Days (mean)	17	12	16	19	21	22	19	23	21	19

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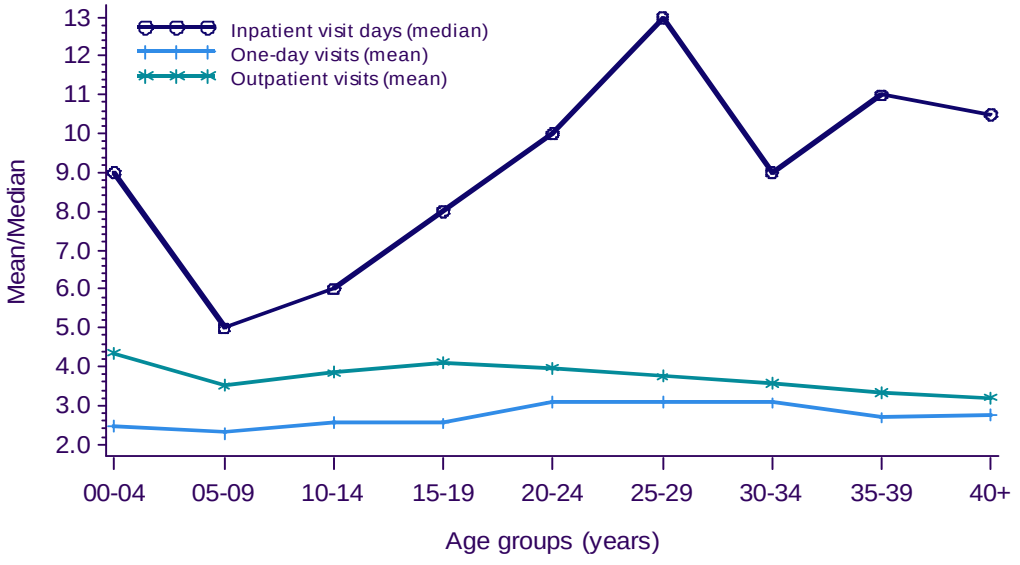
* Outpatient, One-day and Inpatient visits.

Figure 22. Visits, by age



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Therapeutic management

IV antibiotic courses – TIVAD

Table 17. Patients with IV antibiotic courses

	Age groups (years)									
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*
Nb of patients with at least 1 course	**82**	**129**	**225**	**338**	**446**	**332**	**225**	**142**	**156**	**2075**
- and with TIVAD*	11	33	96	169	255	181	120	69	75	1009
Nb of courses	113	223	467	759	1160	782	495	322	349	4670
Nb of days of courses incl:	1460	2986	6829	11157	17155	11040	7305	4640	4976	67548
- at hospital	994	1017	2028	2751	3375	2092	1225	1399	1509	16390
- at home	451	1805	4646	7959	12381	8672	5831	3017	3404	48166
TIVAD* (with and without course)	12	46	112	184	293	206	148	87	103	1191

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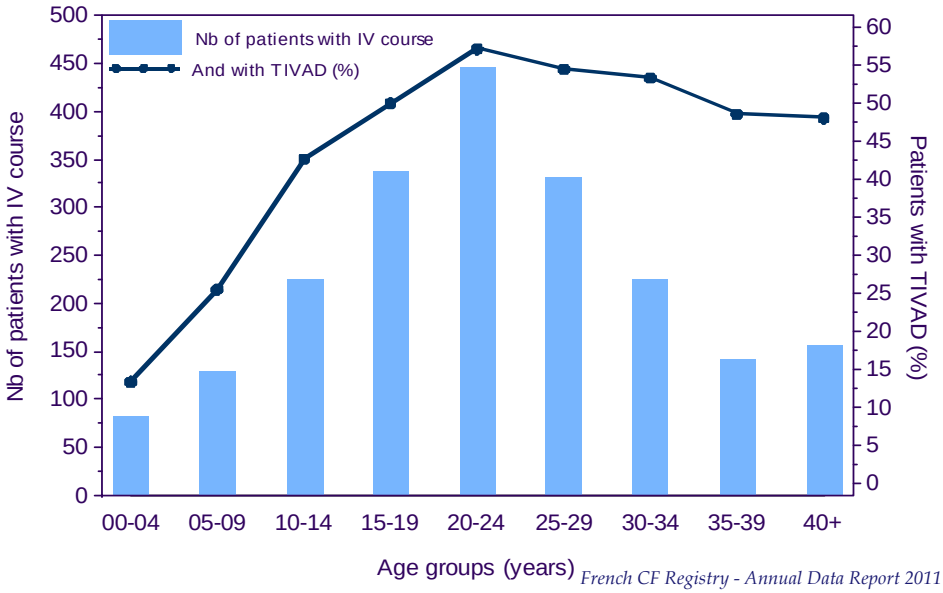
Figure 23. Patients with at least one IV antibiotic course and a TIVAD*, by age



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* TIVAD: Totally Implantable Vascular Access Device

Therapeutic management

Antibiotic courses

Table 18. Repartition of courses

	Age groups (years)									
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total
Mean number of courses	1.4	1.7	2.1	2.4	2.7	2.5	2.4	2.4	2.3	2.3
Mean number of days of courses	18.3	23.9	31.8	35.8	41.1	36.7	36.9	35.2	35.0	35.1

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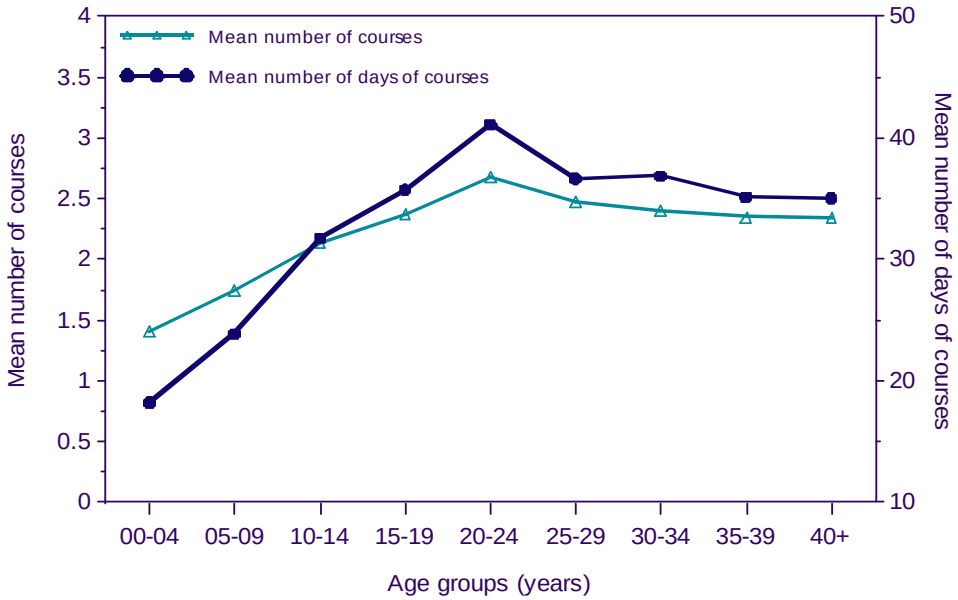
Figure 24. Mean number of courses and of days of courses



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Therapeutic management

Respiratory

Table 19. Respiratory therapeutics

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Aerosol therapy*	327	655	756	710	705	488	369	220	315	4545	75.8 %
NSAID	0	3	7	13	11	7	3	5	16	65	1.1 %
Azithromycin	73	221	357	417	477	343	262	173	200	2523	42.1 %
Oxygen therapy	1	6	24	53	69	57	39	39	66	354	5.9 %
Oral steroids	10	19	45	62	110	103	100	58	87	594	9.9 %
Nasal ventilation	4	17	37	46	58	39	27	18	44	290	4.8 %

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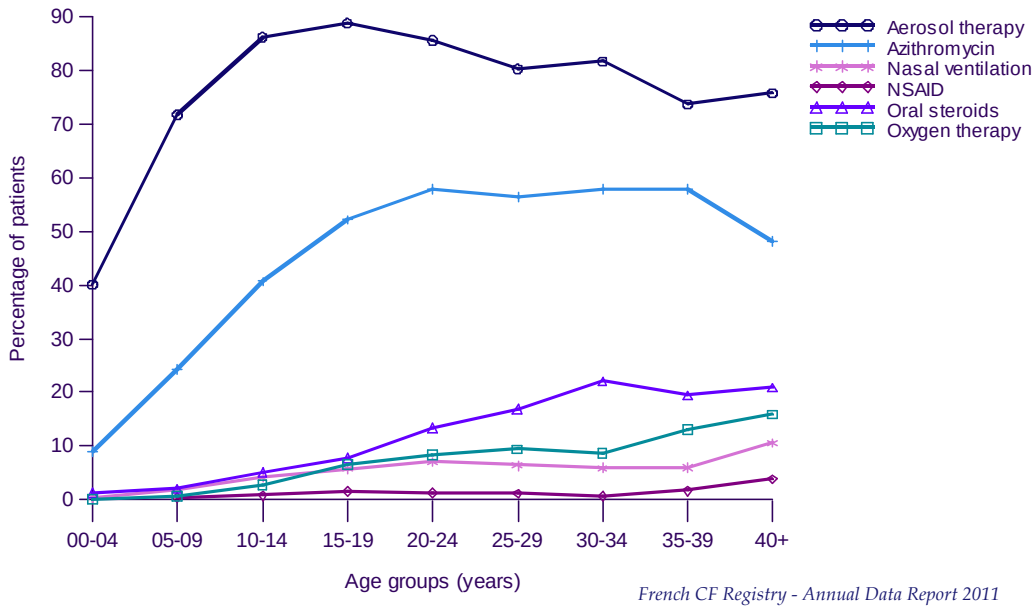
*by nebulization, spray or powder

Figure 25. Respiratory therapeutics



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Therapeutic management

Aerosoltherapy

Table 20. Aerosoltherapy treatments

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Patients under aerosol therapy*	**327**	**655**	**756**	**710**	**705**	**488**	**369**	**220**	**315**	**4545**	**75.8 %**
Inhaled antibiotics	111	195	327	378	430	295	230	112	160	2238	37.3 %
Inhaled bronchodilatators	180	380	459	436	483	334	254	170	238	2934	49.0 %
Inhaled corticosteroids	172	336	406	368	343	239	182	114	190	2350	39.2 %
Inhaled hypertonic saline	19	17	31	34	26	31	23	16	17	214	3.6 %
RhDNase	92	481	615	551	429	260	163	93	128	2812	46.9 %

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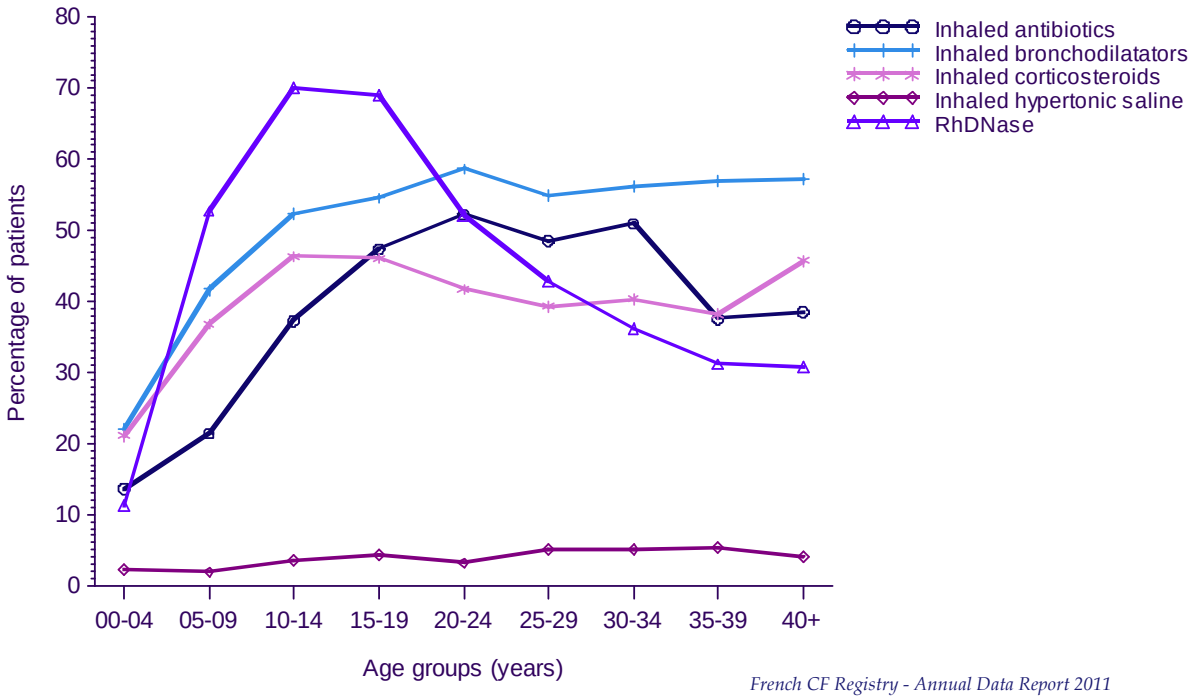
*by nebulization, spray or powder

Figure 26. Aerosoltherapy treatments



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Therapeutic management

Digestive and nutritional

Table 21. Digestive and nutritional treatments

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*815*	*911*	*876*	*798*	*822*	*607*	*451*	*298*	*415*	*5993*	
Ursodeoxycholic acid	86	202	301	291	334	215	138	82	86	1735	29.0 %
Anti-acids	189	226	312	286	389	290	214	156	190	2252	37.6 %
Pancreatic enzymes	656	724	771	694	731	537	383	239	253	4988	83.2 %
Tube supplemental feeding	22	39	69	72	52	27	15	8	5	309	5.2 %
Oral supplemental feeding	123	226	318	240	287	204	139	73	79	1689	28.2 %
Fat-soluble vitamins	740	800	816	721	726	528	401	231	292	5255	87.7 %

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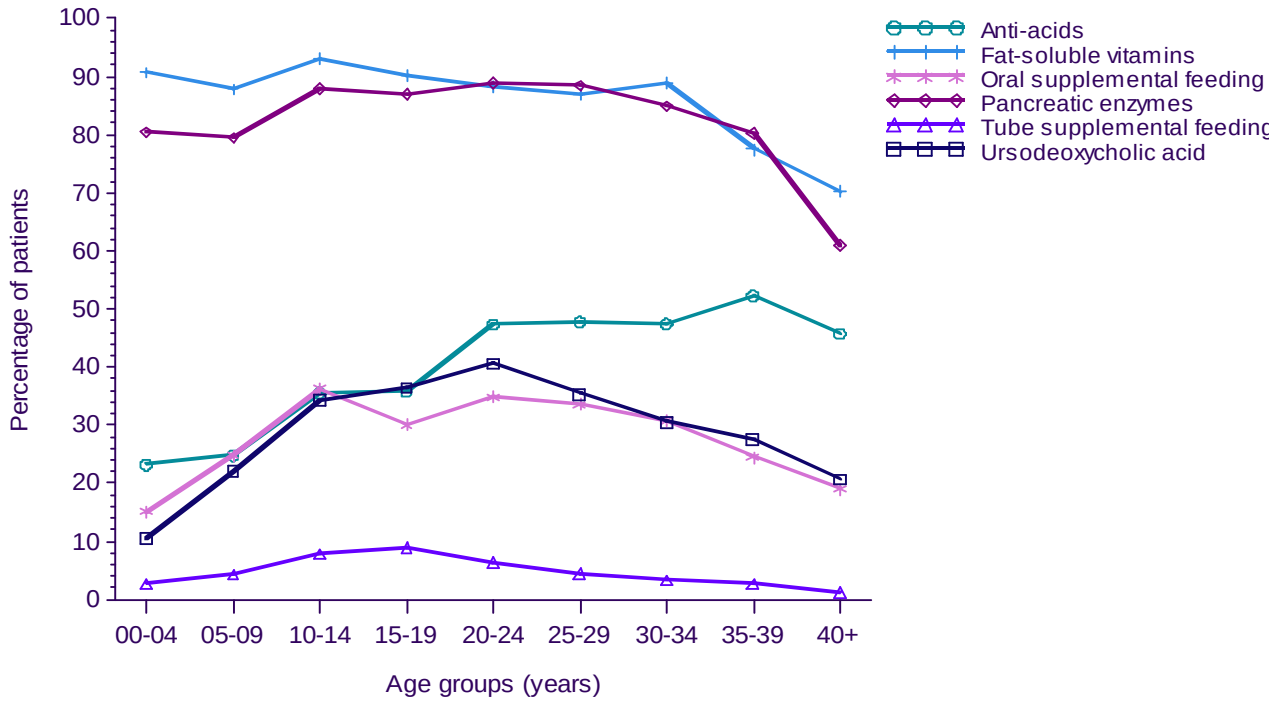
Figure 27. Digestive and nutritional treatments



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Social data

Employment

Figure 28. Employment of men ≥ 18 years

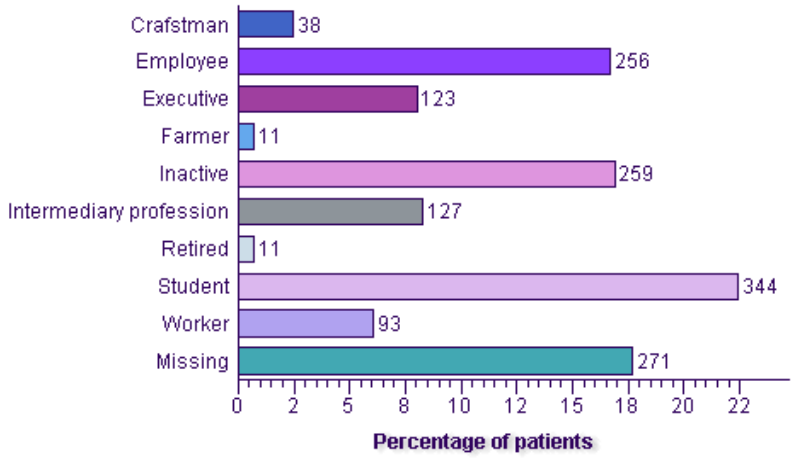

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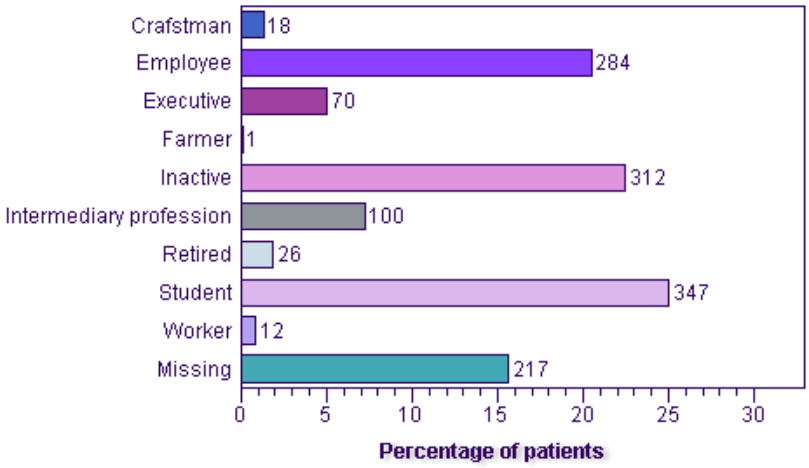
Figure 29. Employment of women ≥ 18 years



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Social data

Marital status

Figure 30. Marital status of men ≥ 18 years

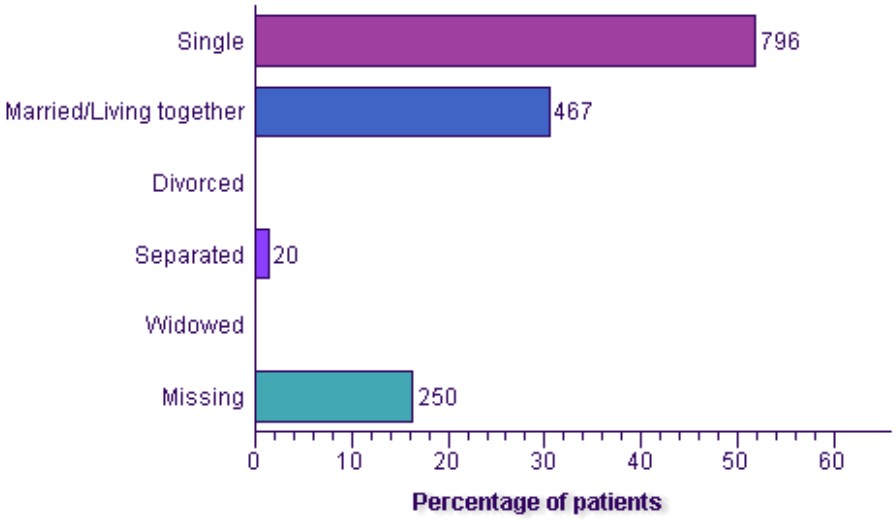

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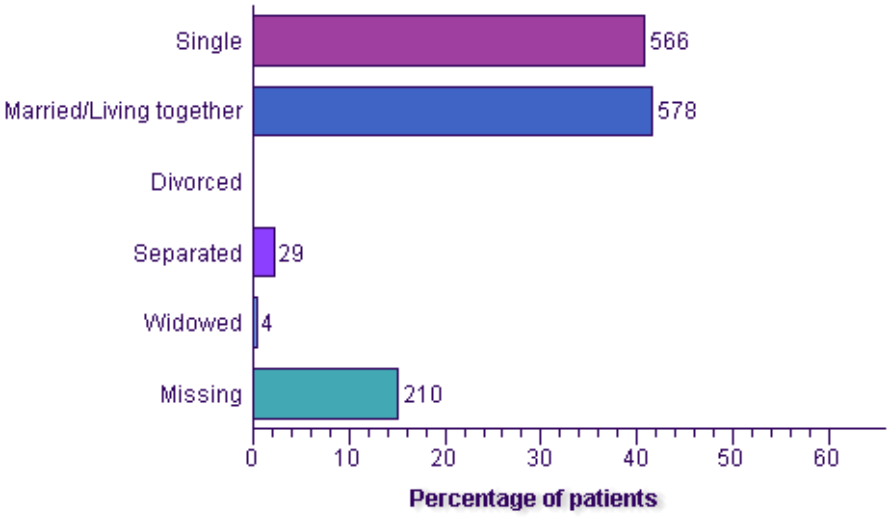
Figure 31. Marital status of women ≥ 18 years



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Annex 1 (1/2)

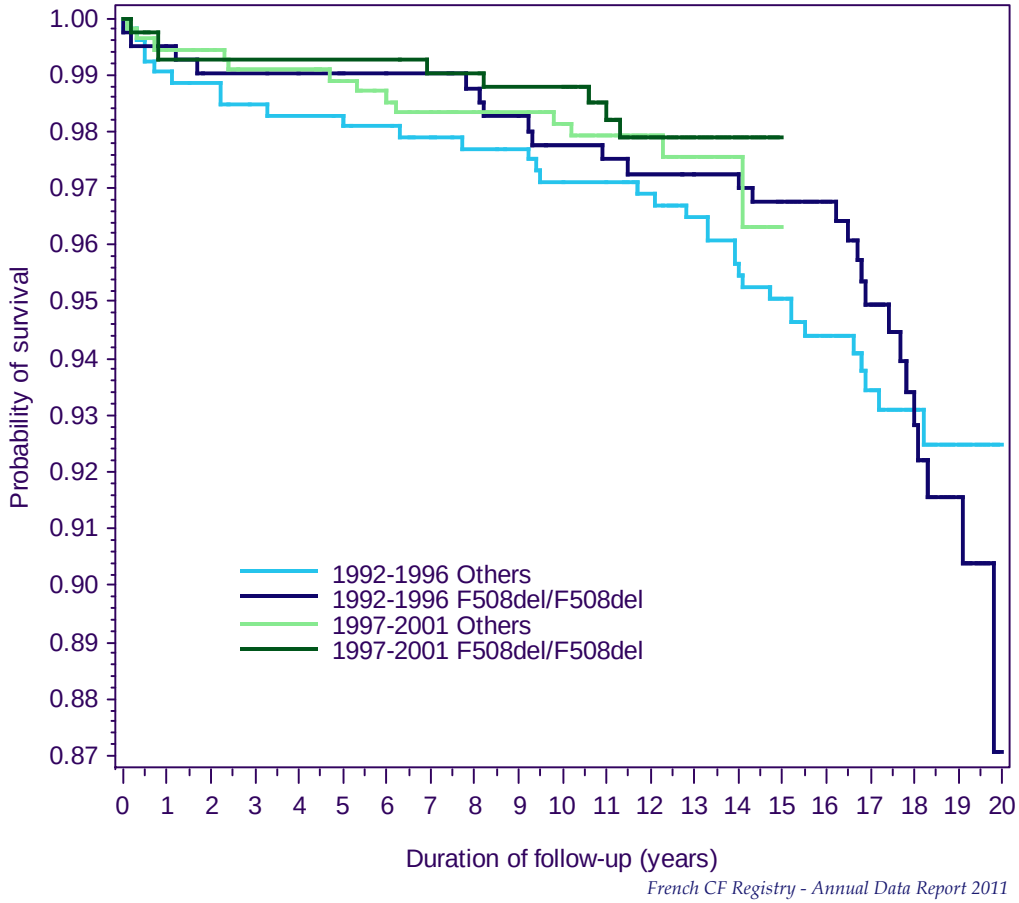
Complement on survival analysis – stratification by genotype

Figure 32. Survival curves by birth cohort and genotype (Kaplan-Meier method)

The survival analysis (fig. 4) was completed with the oldest birth cohorts, stratified according to the **genotype:**

- Births from 1992 to 1996:
  - *F508del/F508del* : 409 patients, 26 deaths;
  - *other genotypes*: 525 patients, 33 deaths

- Births from 1997 to 2001:
  - *F508del/F508del* : 417 patients, 8 deaths;
  - *other genotypes*: 548 patients, 13 deaths



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There is no significative survival difference between those cohorts (Log-Rank test = 1.86, p = 0,601).

Annex 1 (2/2)

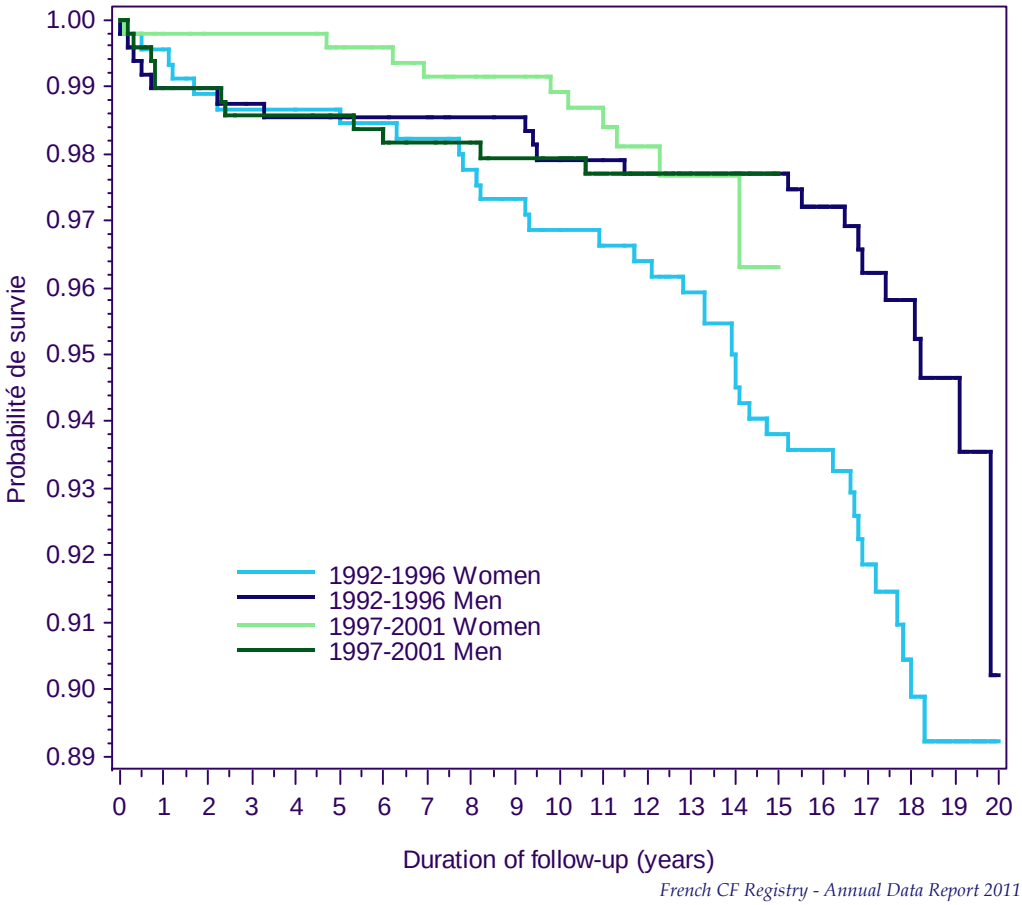
Complement on survival analysis – stratification by sex

Figure 33. Survival curves by birth cohort and sex (Kaplan-Meier method)

The survival analysis (fig. 4) was completed with the oldest birth cohorts, stratified according to the **sex:**

- Births from 1992 to 1996:
  - *men*: 483 patients, 21 deaths;
  - *women*: 451 patients, 38 deaths

- Births from 1997 to 2001:
  - *men*: 490 patients, 11 deaths;
  - *women*: 475 patients, 10 deaths



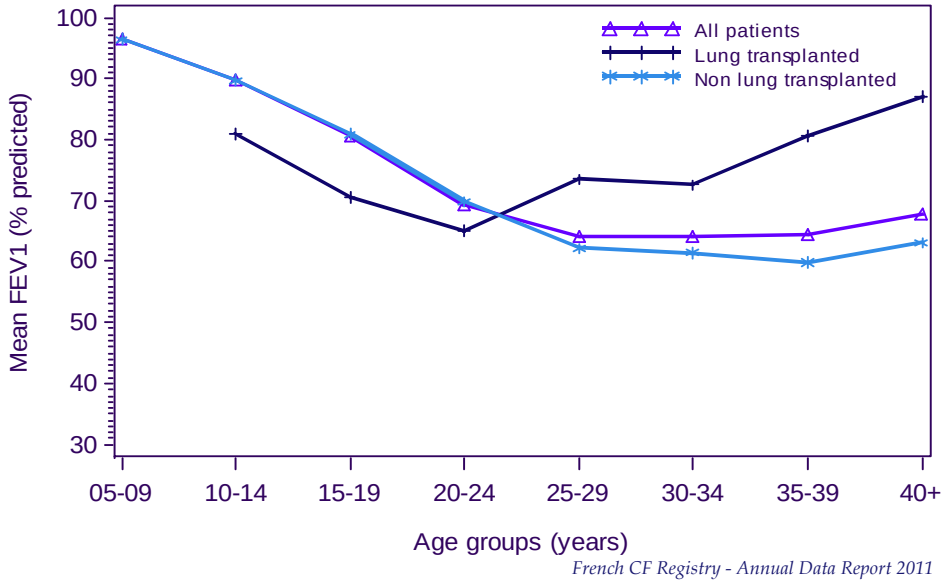
There is a significative survival difference in the 1992-1996 cohorts, men vs women (Log-Rank test = 6.59, p = 0,01) but no difference in the 1997-2001 cohorts.

Annex 2

Spirometry and transplantation

Figure 34. Mean FEV_1 (% predicted) and transplantation

To provide a more comprehensive picture, further comparisons were made using the curves of FEV_1 by age: FEV_1 (% predicted) of all patients was compared to that of patients who had or had not received a heart-lung or bilateral lung transplant.



The curves of the whole population and of non-transplanted patients are identical up to age 20-24. Above 25 years, FEV_1 (% predicted) of non-transplanted patients drops more sharply than that of the total population, with a difference of almost 5 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.

Among lung transplanted patients, for whom the average FEV_1 (% predicted) is available only from ages 10-14, the initial values are high (about 81 %), they decrease to 65 % up to ages 20-24, and increase afterwards (above 74 % from ages 25-29 onwards).

Annex 3

Participating centres

Table 22. List of the participating CRCMs

CRCMs	Number of patients*
Paediatric CRCMs	
AMIENS Hôpital Nord	89
BORDEAUX Groupe Pellegrin Hôpital d'Enfants	151
GRENOBLE Hôpital de la Tronche Pédiatrie	106
LE HAVRE Hôpital Flaubert	23
LILLE Hôpital Jeanne de Flandres Pédiatrie	206
LISIEUX Centre Hospitalier Robert Bisson	21
LYON Hôpital Mère-Enfant / Groupt Hosp. Est	303
MARSEILLE Hôpital La Timone Pédiatrie	112
NANCY Hôpital d'enfants	131
NANTES Hôpital Mère-Enfant	92
NICE CHU de Lenval et Pasteur	60
PARIS Hôpital Armand Trousseau	97
PARIS Hôpital Necker	175
PARIS Hôpital Robert Debré	167
RENNES Hôpital Sud Pédiatrie	121
ST DENIS DE LA REUNION Hôpital d'Enfants	62
TOULOUSE Hôpital des Enfants	121
TOURS Hôpital de Clocheville Pédiatrie	121
VERSAILLES Hôpital Mignot Pédiatrie	72
Adult CRCMs	
BORDEAUX-PESSAC Groupe Sud Hospitalier	81
GRENOBLE Hôpital de la Tronche Pneumologie	107
LILLE Hôpital Calmette Pneumologie	170
LYON SUD Centre Hospitalier	244
MARSEILLE CHU Nord	171
NANCY Hôpital de Brabois Pneumologie	105
NANTES Hôpital Laënnec	172
PARIS Hôpital Cochin	381
RENNES Hôpital Pontchaillou Pneumologie	84
SURESNES Hôpital Foch	317
TOULOUSE Hôpital Larrey Pneumologie	138
TOURS Hôpital Bretonneau Pneumologie	53
Paediatric and Adult CRCMs	
ANGERS - LE MANS	121
BESANCON Adultes et Pédiatrie	112
CAEN Adultes et Pédiatrie	103
CLERMONT-FERRAND CHU d'Estaing	90
CRETEIL Centre Hospitalier Intercommunal	97
DIJON Hôpital d'Enfants du Bocage	117
DUNKERQUE Centre Hospitalier	65
GIENS Hôpital Renée Sabran	214
LENS Centre Hospitalier	47
LIMOGES Hôpital Mère/Enfant	52
MONTPELLIER Hôpital Arnaud de Villeneuve	190
POITIERS Hôpital La Milétrie	39
REIMS American Memorial Hospital	112
ROSCOFF Centre de Perharidy	145
ROUEN Adultes et Pédiatrie	162
ST PIERRE DE LA REUNION Groupe Hosp. Sud	58
STRASBOURG Adultes et Pédiatrie	230
VANNES-LORIENT	87

Annex 3

Participating centres

Table 23. List of the participating centres (CRCMs excepted)

Centres	Number of patients*
Paediatric local centres	
BREST Hôpital Augustin Morvan	7
COLMAR CHG Louis Pasteur Pédiatrie	8
DAX Centre Hospitalier	12
ELBEUF Hôpital des Feugrais	1
MONTLUCON Centre Hospitalier	9
MULHOUSE Centre Hospitalier Pédiatrie	14
ST BRIEUC Centre Hospitalier Yves Le Foll	40
ST ETIENNE Hôpital Nord	3
ST TROJAN LES BAINS Centre Hélio Marin	7
Adult local centres	
MULHOUSE Centre Hospitalier Pneumologie	4
Paediatric and Adult local centres	
BRIVE Centre Hospitalier	16
ST NAZAIRE Centre Hospitalier	22
Other centres	
DIEULEFIT Centre Médical/Climatique Bellevue	2
PARIS Hôp. Européen G.Pompidou Greffes	18
MONTARGIS Centre Hospitalier	6
ST QUENTIN Centre Hospitalier Général	1

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* Number of patients who visited the centre during the year. Patients followed by a centre and who did not visit it in 2011 were excluded from those statistics.

Annex 4

Table 24. Summary of data (1/2)

	2011	2010	2009
Patients seen during the year and centres participating to the registry			
- Patients registered* (N):	6046	5792	5 650
- Patients seen during the year in a centre** (N):	5993	5758	5 628
- Centres (N) :	65	64	64
Paediatric CRCMs***:	19	19	19
Adult CRCMs***:	12	12	12
Paediatric and Adult CRCMs***:	18	18	18
Other centres:	16	15	15
Demographics			
- Male patients (%) :	51.7	51.4	51.8
- Age of patients, in years (mean):	18.7	18.1	17.7
- Age of patients, in years (median):	17	16	16
- Age of patients. in years (min-max):	0 – 87	0 – 80	0 – 79
- Patients aged 18 years and over (%):	48.7	47.2	45.8
- Early pregnancies during the year (N):	48	28	34
- Pregnancy rates in women aged 15 to 49 ans (for 1 000):	32.8	20.1	25.8
- Age of patients at onset of pregnancy, in years (mean):	28	29	28.4
- Deaths (N):	66	60	61
Including death of patients not seen during the year:	8	9	12
- Crude death rate (for 1 000):	11.3	10.6	11.2
- Age at death, in years (mean):	26	29	25.5
- Age at death, in years (median):	26	27	24
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	3	3	3
- New patients diagnosed during the year (N):	215	181	232
Including by neonatal screening:	131	112	155
- Age at diagnosis of the new patients, in years (median):	1	2	1
- Age at diagnosis of the new patients, in years (min-max):	0 – 69	0 – 69	0 – 72
- Full genotypes identified (%):	94.9	93.9	93.9
F508del / F508del:	43.3	43.6	43.6
F508del / Other:	38	37.5	37.2
Other / Other:	13.1	12.8	13.1
F508del / Missing:	1.9	1.8	2.0
Other / Missing:	1.2	1.1	1.2
Missing / Missing:	2.5	3.2	2.9
Anthropometry and spirometry			
- Height z-score, patients aged 17 years and less (mean):	-0.08	- 0.13	- 0.16
- Height z-score, patients aged 18 years and over (mean):	-0.52	- 0.53	- 0.54
- Weight z-score, patients aged 17 years and less (mean):	-0.33	- 0.37	- 0.39
- Weight z-score, patients aged 18 years and over (mean):	-0.41	- 0.46	- 0.46

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* Patients whose vital status is known, whether they visited or not a centre during the year.

** Reference patients for the statistics of this report, with the exclusion of survival data.

*** CRCM: Specialised CF Centre (Centre de Ressources et de Compétences de la Mucoviscidose)

Annex 4

Table 24. Summary of data (2/2)

	2011	2010	2009
Spirometry			
- FEV_1 (% predicted) - Knudson, patients aged 17 years and less (mean):	89.7*	85.4**	84.3**
- FEV_1 (% predicted) - Knudson, patients aged 18 years and over (mean):	67.3*	62.9**	62.3**
Microbiology			
- Patients with at least one sputum during the year (%):	91.7	93	92.4
H. influenzae:	22.1	23.4	24.1
MSSA:	54.7	53.5	48.9
MRSA:	7.7	8	7.9
P. aeruginosa:	42.6	42.9	41.4
S. maltophilia:	9.7	8.5	7.8
B. cepacia:	1.9	2	1.9
Aspergillus:	22.6	21	19.2
Complications and transplantations			
- Haemoptysis (%):	5.0	5.8	5.3
- Cirrhosis / portal hypertension (%):	4.1	3.9	3.6
- Insulin-dependent and non insulin-dependant diabetes (%):	15.2	14.8	14.1
- Transplanted patients (N):	529	440	400
Including patients transplanted during the year:	97	78	74
- Patients on waiting list (N):	177	136	161
Including patients listed during the year:	98	75	65
Deaths on waiting list:	0	1	3
Therapeutic management			
- IV courses (%):	34.6	34.4	35.3
- Oxygenotherapy (%):	5.9	6.5	6.3
- Nasal ventilation (%):	4.8	3.9	4.1
- Azithromycin (%):	42.1	42.4	40.6
- Inhaled antibiotics (%):	37.3	38.8	35.9
- rhDNase (%):	46.9	45.1	43.4
- Inhaled bronchodilatators (%):	49	48.8	49.1
- Inhaled corticosteroids (%):	39.2	40.8	40.5
- Pancreatic enzymes (%):	83.2	82.8	82.7

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* Best FEV_1 of the year.

** Last FEV_1 of the year.

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