FRENCH CYSTIC FIBROSIS
Registry

2015

Annual data report

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Editorial

2015: 25 years after the first pulmonary transplantation (a treatment of last resort), patient care - with the advent of new genetically targeted therapies - as well as the profile of the CF population (54% are adult patients) are at an important turning point. This questions the place of transplantation in today's and tomorrow's care.

The Registry shows a steady increase in the median age (19.4 years in 2015, + 4 years in the last 10 years), an increase in median FEV1 (+ 24% in 20 years despite the aging of the population)... These indicators confirm the continuous improvement of health status of CF patients.

More than 700 adult patients are pulmonary transplant recipients (20% of adult patients), about 150 are on waiting list each year since 2010, with about 100 new entries per year. Compared to the years 2011-2013, the number of pulmonary transplantations in 2015 tend to decrease by 10%. Is it good or bad news? After an increase in activity due to the implementation of a "super-emergency" waiting list status, a wider access to donors, the advent of ex-vivo repackaging techniques, has pulmonary transplantation reached a cruising speed? The Biomedicine Agency report shows that global pulmonary transplant activity (of which CF represents the second indication, 23%) increased by 5.5% between 2014 and 2015; But also that the decline in the number of new patients on waiting list in 2015 (88 for CF) seems to have reduced organ scarcity. Indeed, the ratio "number of recipients pending on January 1 (any indication) / number of grafts" decreased from 0.7 to 0.4 between 2010 and 2015.

However, progress has still to be made and is a shared responsibility for all. Fifteen patients died on waiting list in the past 6 years (4 in 2015), and 21 died post-transplant in 2015, of which 5 were enrolled in 2015: it's still too much! Differences between centers are still significant in terms of eligibility criteria for entry onto the waiting list, transplant activity, waiting time to transplantation. Transplant recipients are older than the general population (median age 33 years vs. 19 years) and express different difficulties and needs. Their nutritional status (represented by weight and BMI z-scores) is significantly worse at any age than the one of non-transplanted patients, incidence of diabetes is much higher (more than 60% in transplant recipients), as well as other comorbidities such as bone disease or gastroesophageal reflux disease.

This information from the Registry advocate a quicker anticipation in referring a severe patient to a transplant center and the inclusion on the waiting list, as well as even more multidisciplinarity care; in a nutshell, to optimize patient care before and after transplantation.

Aware of these challenges, the Steering Committee of the Registry decided to provide specific data, and ultimately a specific report, on transplant patients.

Let's hope that in the next few years, the progress of targeted therapies, global care management and transplantation will have delayed age at entry into severe forms of the disease and given extra chances to patients who would otherwise have been sent to transplantation.

Table of contents

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 1,900 mutations have been identified, the most common (encountered in about 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 (meconium ileus, 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 and the French overseas territories 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 the most frequent *CFTR* mutations (30 up to 31/12/2014 then 29). 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% 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 10%). A 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 negative, information concerning the heterozygous nature of the newborn will be given to the parents during genetic counselling ;

– the D3 IRT level is high and no mutation is found (or parents refused geneting testing). 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).

A sweat test giving an intermediate value has to be repeated.

On the pathological level, functional abnormalities occur in the digestive tract, respiratory tract, sweat glands and 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 (physiotherapy, inhaled, antibiotic treatment, oxygen therapy), digestive and nutritional management (pancreatic enzyme supplements and a hypercaloric diet). Lung transplantation is the last resort in case of end stage respiratory disease. During the last few years, new therapies targeting some CFTR mutations (CFTR modulators or correctors) impact the causative mechanism of the disease. Patient education is an integral part of care.

The French Cystic Fibrosis Registry

Objectives

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, in particular regarding fundings granted to centres in proportion to the number of patients;
- help research by facilitating pre-selection of patients eligible for clinical trials
- facilitate access to new treatments.

Covering the entire population of patients in France, has since been added to the initial objectives. The patient organization 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 and 2015, the registry was certified by the national committee of rare disease registries (*Comité National des Registres Maladies Rares*), an organ composed of the *Institut de Veille Sanitaire* (InVS), the *Institut National de la Santé et de la Recherche Médicale* (INSERM) and the national institute of cancer (Institut National des cancers, Inca).

Population and data

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. In thematic questionnaires are collected data on pregnancies, *Burkholderia Cepacia* complex and related, and inclusion in clinical trials.

Multi-sources data collection

Since 2010, data are no more exclusively collected from the CF centers. Other sources have been added in order to allow a better quality and exhaustivity of the diagnosis data (AFDPHE and molecular biology laboratories sources), death (CépiDc-Inserm) and transplantation data (Hôpital européen Georges-Pompidou (HEGP), Paris). Moreover, the online questionnaire has been simplified for social and transplantation data enabling more complete and accurate data collection.

Data use

Statistical analysis is performed on anonymized data. Unless otherwise indicated, the results presented hereafter relate to the population seen during the year 2015 and were produced by cross-sectional analysis of data. Data on patients seen during the year in at least two centres (said to have multiple accounts) were counted only once and allocated to the centre they visited most often during the year.

The French CF Registry also sends anonymised data to the European ECFS Patient Registry, in the aim of a broader use of the data with other countries.

Precautions before reading this report

The comparison of CF populations has to be careful and must take into account numerous bias such as newborn screening programme, transplantation strategy, socioeconomic aspects as well as the respect of guidelines, the use of different reference populations and the limits of the statistics regarding small numbers in age groups.

1. Demographics

Characteristics of the population

Figure 1.1. Evolution of the number of patients since 1992

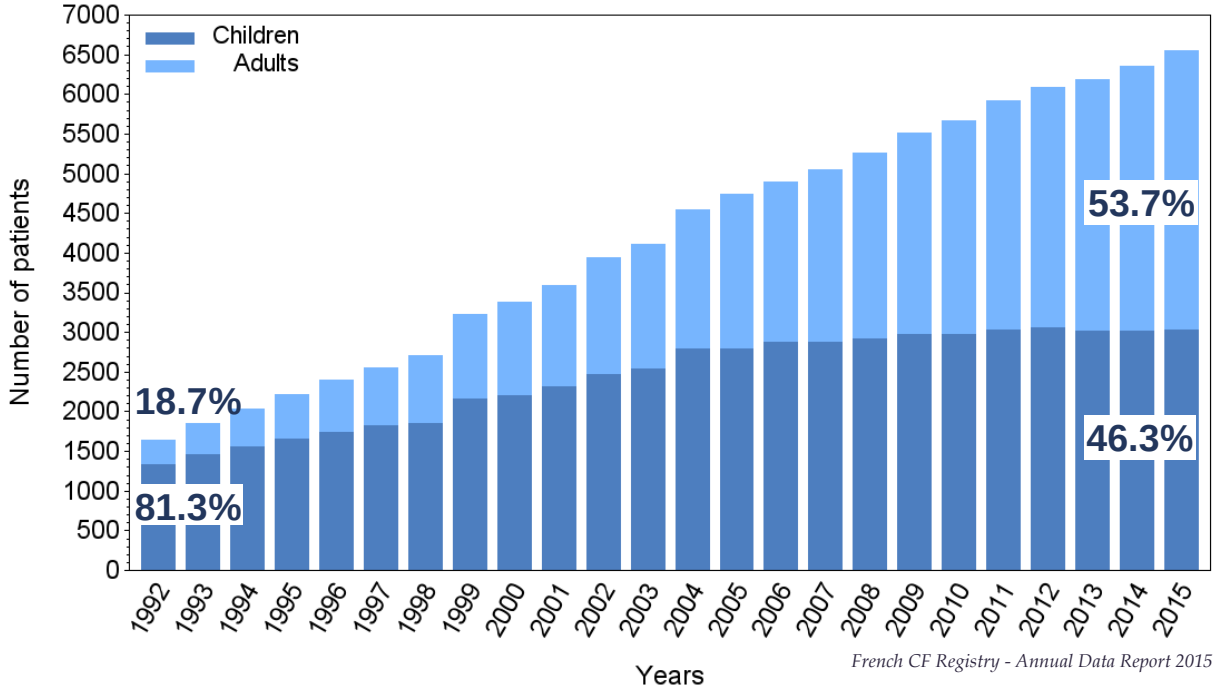

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Table 1.1. Annual evolution of the main indicators

	Years of follow-up									
Indicators	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
All patients*	4909	5060	5270	5529	5676	5967	6130	6235	6405	6585
Patients seen during the year**	4898	5046	5259	5511	5662	5917	6087	6186	6354	6547
Children	2870	2883	2912	2973	2976	3028	3059	3021	3018	3029 (46.3 %)
Adults	2028	2163	2347	2538	2686	2889	3028	3165	3336	3518 (53.7 %)
Over 40 years	174	200	247	307	342	400	453	512	587	670 (10.2 %)
Men	2546	2650	2743	2868	2919	3067	3151	3202	3288	3408 (52.1 %)
Women	2352	2396	2516	2643	2743	2850	2936	2984	3066	3139 (47.9 %)
Mean age (years)	16.8	17.1	17.6	18.1	18.5	19.1	19.6	20.2	20.8	21.3
Median age (years)	15.5	15.8	16.3	16.6	17	17.5	17.9	18.4	18.9	19.4
Minimum age (years)	0.1	0.1	0	0	0.1	0	0.1	0.1	0	0
Maximum age (years)	74.8	75.8	76.8	77.8	80	88	86.8	82.5	82.8	83.2

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

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

Note: patients with an unconfirmed diagnosis were withdrawn from the report (96 in 2015).

The number of patients in the Registry compares to 6,540 (rounded figure) patients registered on December 31, 2015 under the general social security regime (for wage employees) which covers around 88% of the French population.

1. Demographics

Characteristics of the population

Table 1.2. Characteristics of the population, by sex and age

Characteristics	2013		2014		2015	
	Men	Women	Men	Women	**Men**	**Women**
Patients seen during the year	3202	2984	3288	3066	**3408**	**3139**
Children	1546	1475	1535	1483	**1559**	**1470**
Adults	1656	1509	1753	1583	**1849**	**1669**
Mean age (years)	20.3	20.1	20.9	20.7	**21.3**	**21.2**
Median age (years)	18.6	18.2	19.2	18.7	**19.6**	**19.2**

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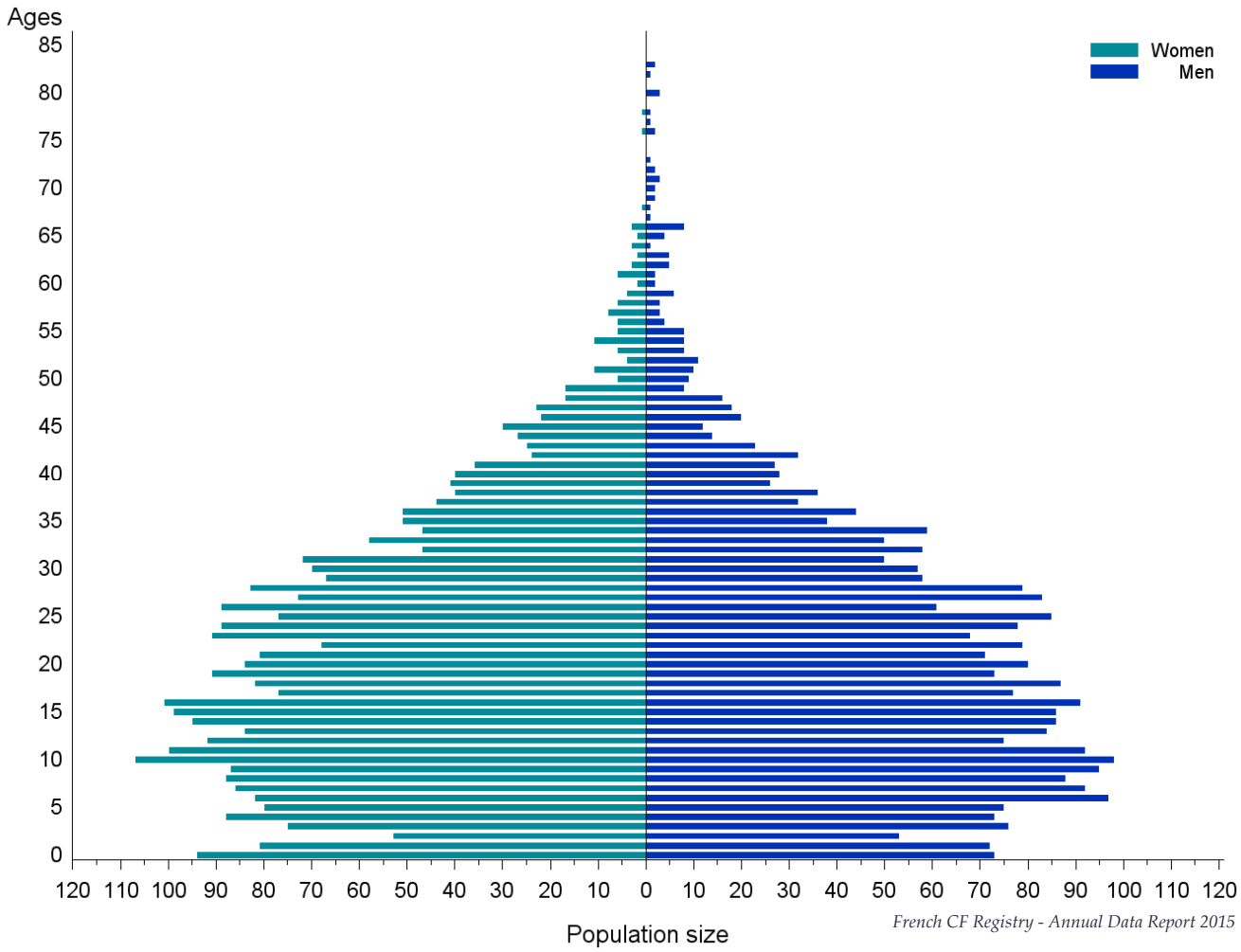
Figure 1.2. Population pyramid



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For the first year of life, the number of patients born in 2015 was 160 according to AFDPHE, and 144 seen in a CF center and collected in the Registry. Except for this age pyramide, only data of the 144 patients are used in this report (cf note p15).

The short bar corresponding to children born in 2013 has been validated with the AFDPHE data. To date there is no clear explanation.

1. Demographics

Location by type of centre

Table 1.3. Patients' characteristics by type of centre

Types of centres	Nb	Patients' characteristics			Age of patients (years)				
		Nb (a)	%	Mean nb by centre	Min	Max*	Mean	Median	Inter-quartile
CRCMs									
Paediatric	16	2019	30.8	126.2	0	41.1	10.2	10.2	9.2
Adult	12	2248	34.3	187.3	16.1	83.2	32.7	30.4	13.3
Paediatric/Adult	17	2099	32.1	123.5	0.2	83.1	20	17.6	18.6
Subtotal	45	6366	97.2	141.5	0	83.2	21.4	19.7	19.9
Other centres									
Paediatric	6	39 (b)	0.6	6.5	0.3	30.4	11.3	11.1	9.7
Adult	1	3 (c)	0.0	3.0	35	43.2	38.8	38.2	8.2
Paediatric/Adult	4	92 (d)	1.4	23.0	2.3	56.9	12	10.95	7.55
Other Centres	1	47 (e)	0.7	47.0	14.6	61.1	27.7	26.3	11.7
Subtotal	12	181	2.8	15.1	0.3	61.1	16.4	13.7	13.5
Total	57	6547	100	114.9	0	83.2	21.3	19.4	19.8

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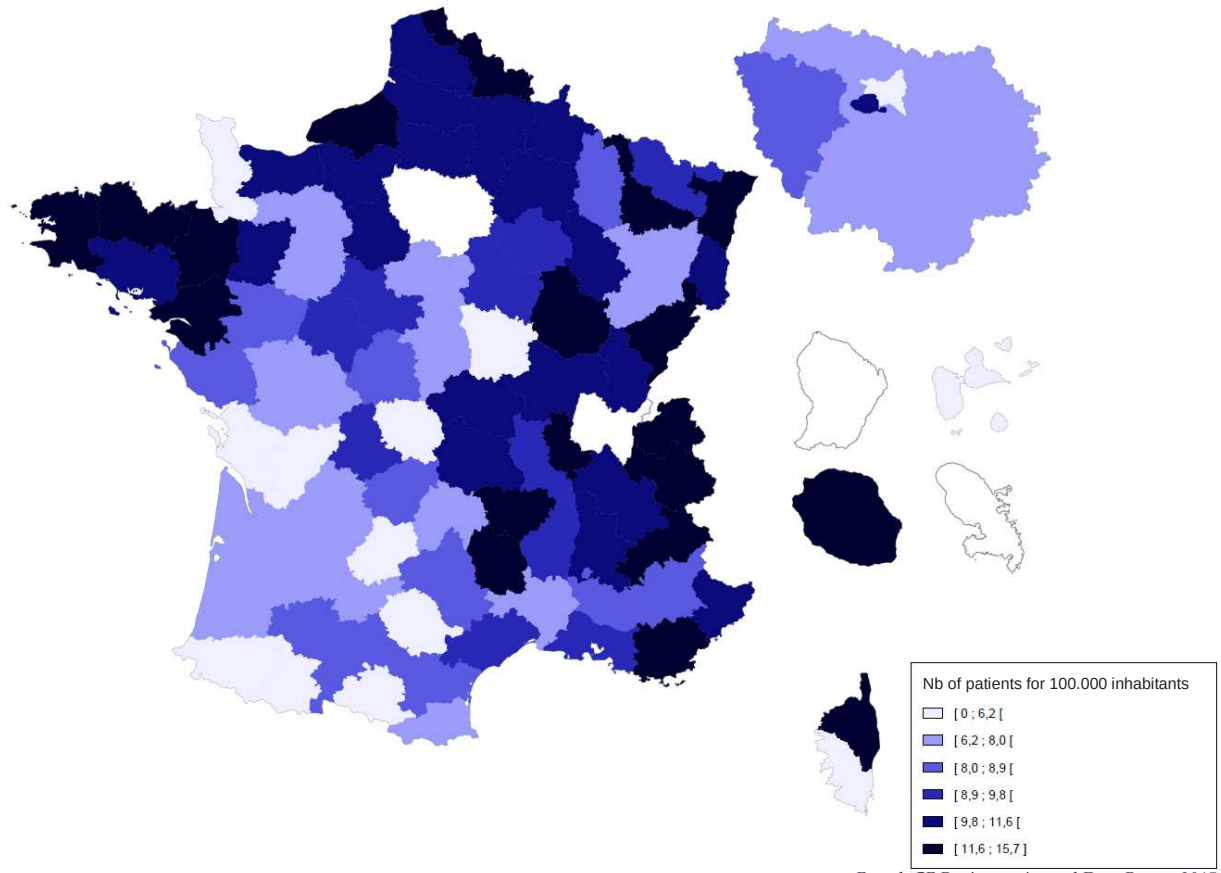
Notes : (a) After checking of patients in the multiple account category (cf page 6)
(b) Including 16 patients also seen by a CRCM.
(c) Including 1 patients also seen by a CRCM.
(d) Including 11 patients also seen by a CRCM
(e) Including 19 patients also seen by a CRCM.

* Cases when adult centres care children and vice versa are very rare.

1. Demographics

Geographical location

Map 1.1. Prevalence of cystic fibrosis by « département » of residence (number of patients for 100 000 inhabitants)



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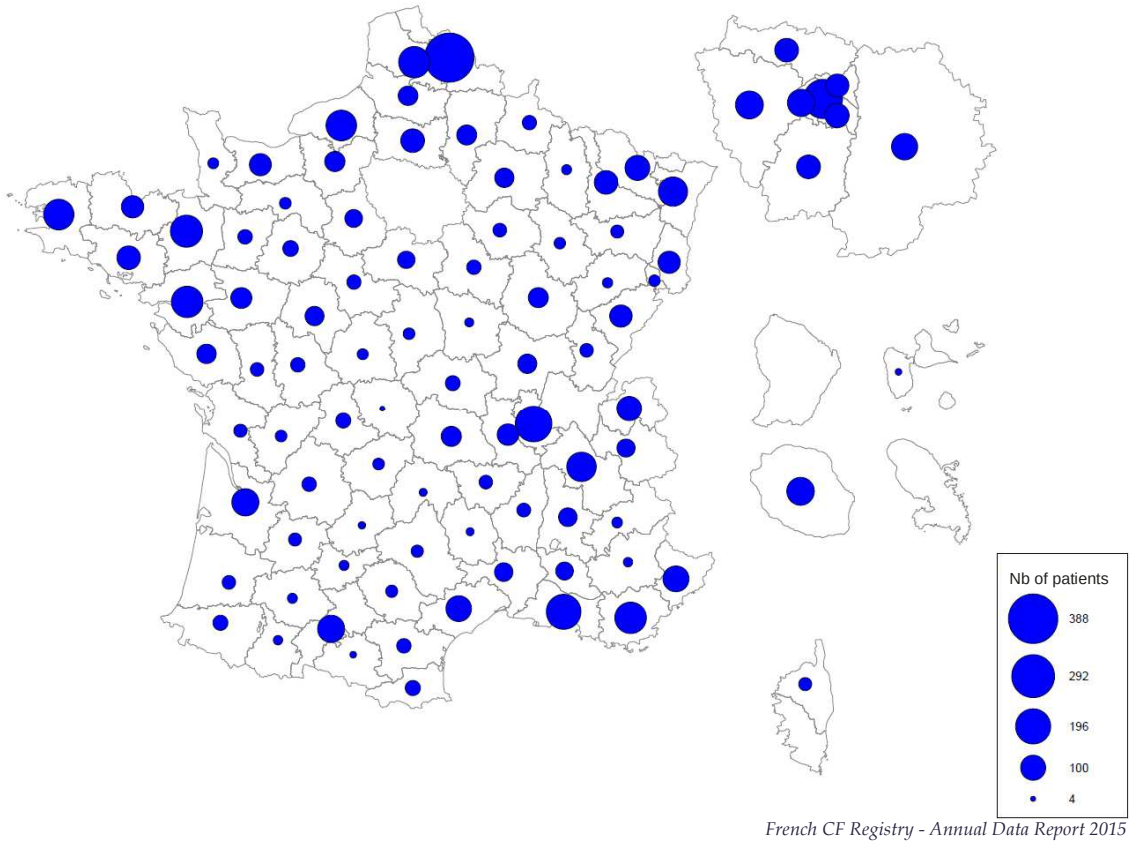
Map 1.2. Localisation of the patients by « département » of residence (absolute numbers)



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2. Mortality

Characteristics

Figure 2.1. Annual number of deaths since 1992

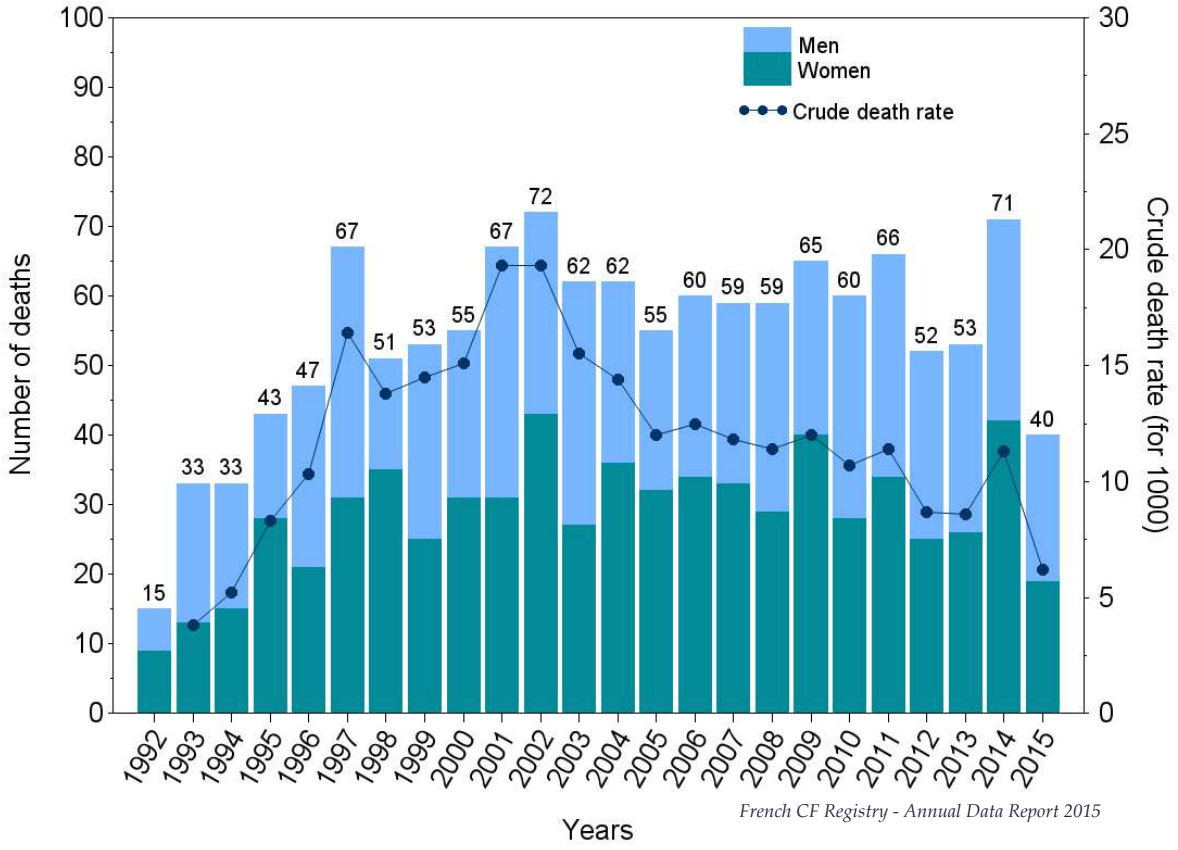

Table 2.1. Mortality characteristics

	Years of follow-up									
Indicators	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of deaths	60	59	59	65	60	66	52	53	71	40
- including patients not seen during the year*	11	14	11	17	10	9	12	11	13	6
- including transplanted patients	19	29	27	33	31	35	27	30	43	21
Crude death rate (per 1000)	12.5	11.8	11.4	12.0	10.7	11.4	8.7	8.6	11.3	6.2
Mean age (years)	26	28	29	25	29	26	32	34	29	34
Median age (years)	24	26	28	23	28	25	28	31	27	31
Minimum age (years)	5	2	0	0	0	2	2	1	0	9
Maximum age (years)	76	70	66	73	69	56	88	83	71	83

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

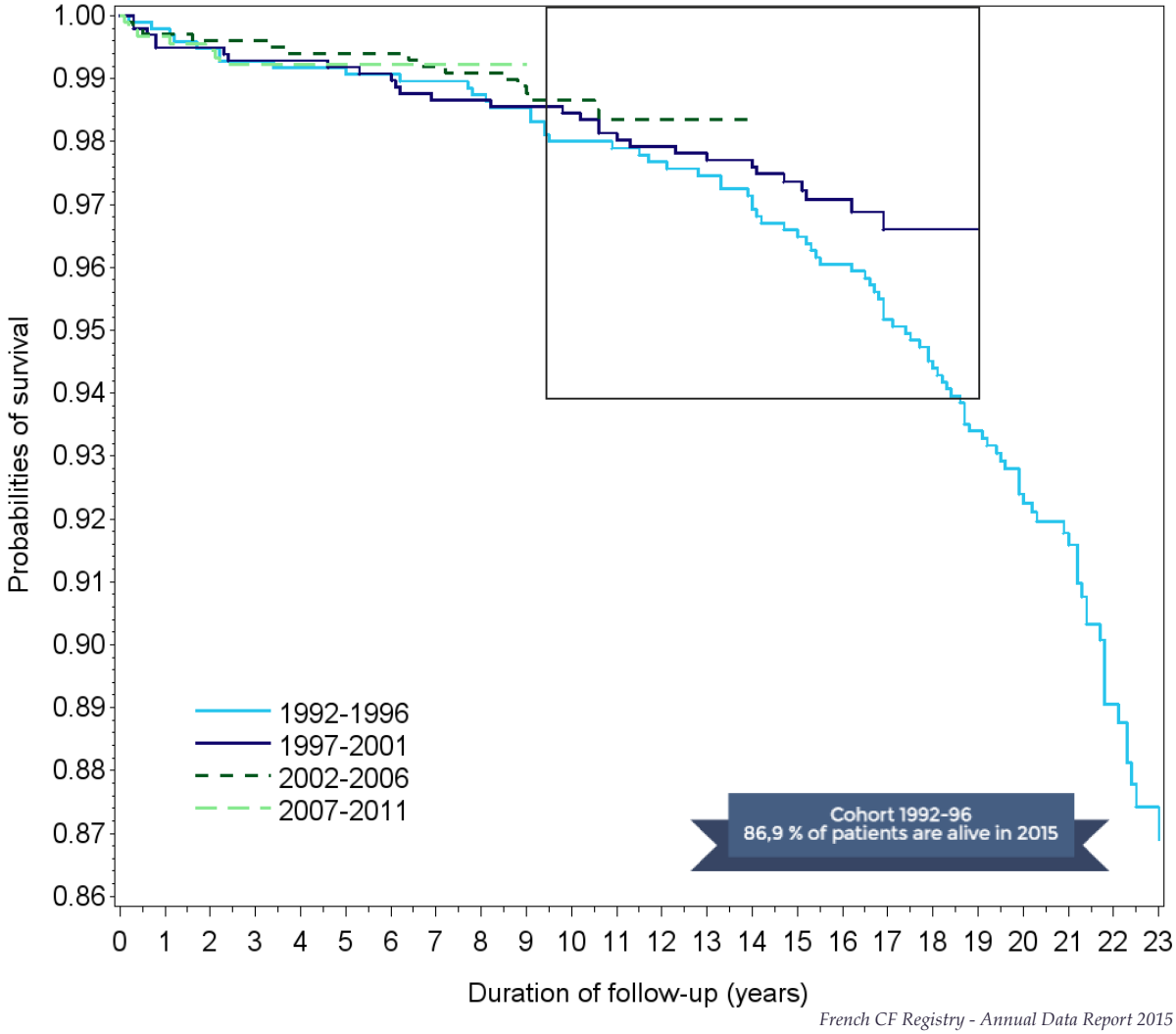
2. Mortality

Survival analysis

Figure 2.2. 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 2015 this cohort was followed during 24 years maximum): 971 patients, 91 deaths
- Births from 1997 to 2001 (maximum 19 years of follow up): 985 patients, 29 deaths
- Births from 2002 to 2006 (maximum 14 years of follow up): 1014 patients, 15 deaths
- Births from 2007 to 2011 (maximum 9 years of follow up): 909 patients, 7 deaths



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Until the age of 9, there is no difference in survival between the different birth cohorts.

After this age, a difference in survival between the two oldest cohorts (1992-1996 and 1997-2001) appears, and this difference is statistically significant (Log-Rank test = 4.87, p = 0,03).

Survival analysis by sex is available on annex 1.

3. Pregnancy – Paternity

Figure 3.1. Annual number of early pregnancies, evolution since 2006

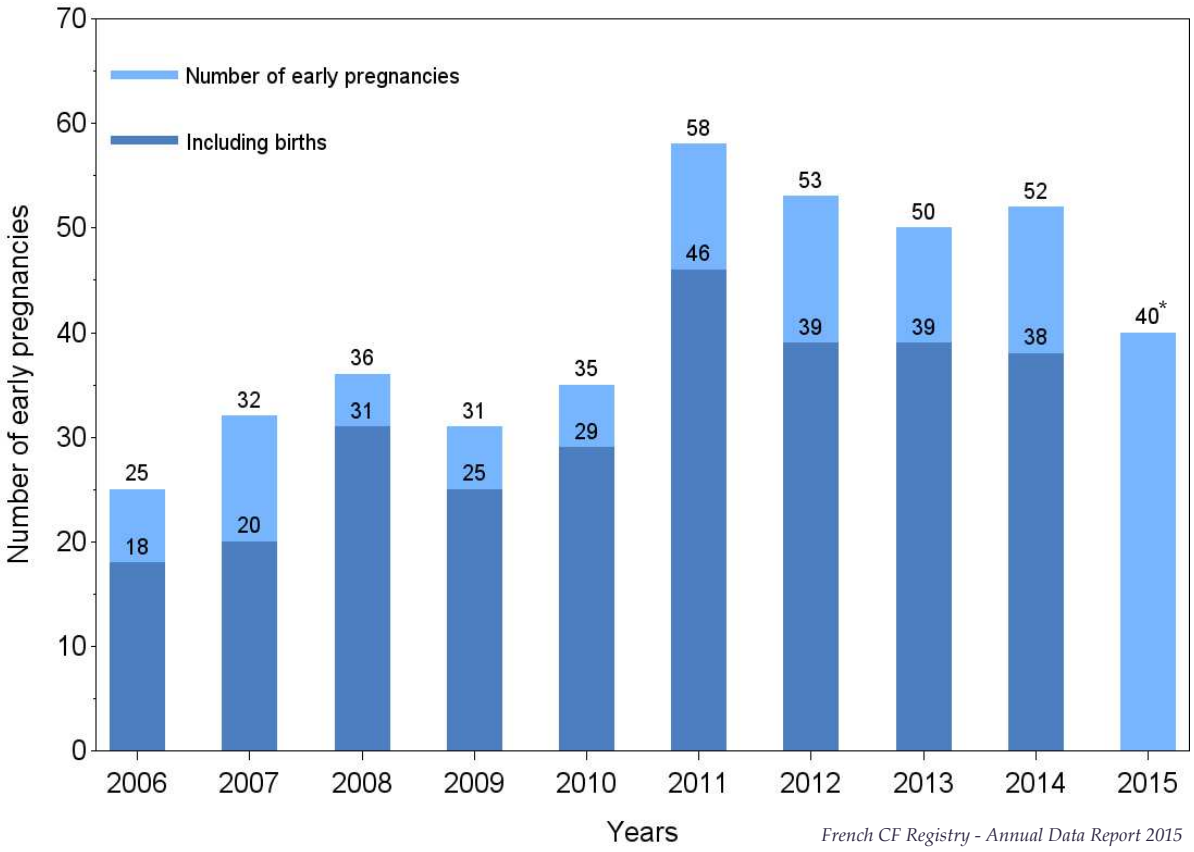

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Table 3.1. Early pregnancy characteristics

Characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	*2015**
Number of early pregnancies	25	32	36	31	35	58	53	50	52	*40*
Pregnancy rates in women aged 15 to 49 years (for 1000)	22	27.1	29	23.5	25.1	39.5	34.4	31.1	30.9	*22.7*
Mean age at 31st December of the year of early pregancy	27.3	26.7	26.9	27.3	28.8	28.4	28.3	28.4	28.8	*30.6*
Number of lung transplanted women starting a pregnancy	1	2	1	3	3	3	7	4	1	*2*

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* Part of pregnancies started in 2015 were not known at the time of data collection (early 2016), as were the outcomes of these pregnancies. The 2015 figures are not definitive and don't include the number of births.

3. Pregnancy – Paternity

Table 3.2. Paternities

Characteristics	N	Proportion (%)
Number of paternities, including:	33	
- Natural father	11	33.3
- Adoption	1	3.0
- Medically assisted reproduction, including:	21	63.6
+ Intracytoplasmic Sperm Injection / in vitro fertilization	19	90.5
+ Artificial insemination with sperm donor	2	9.5

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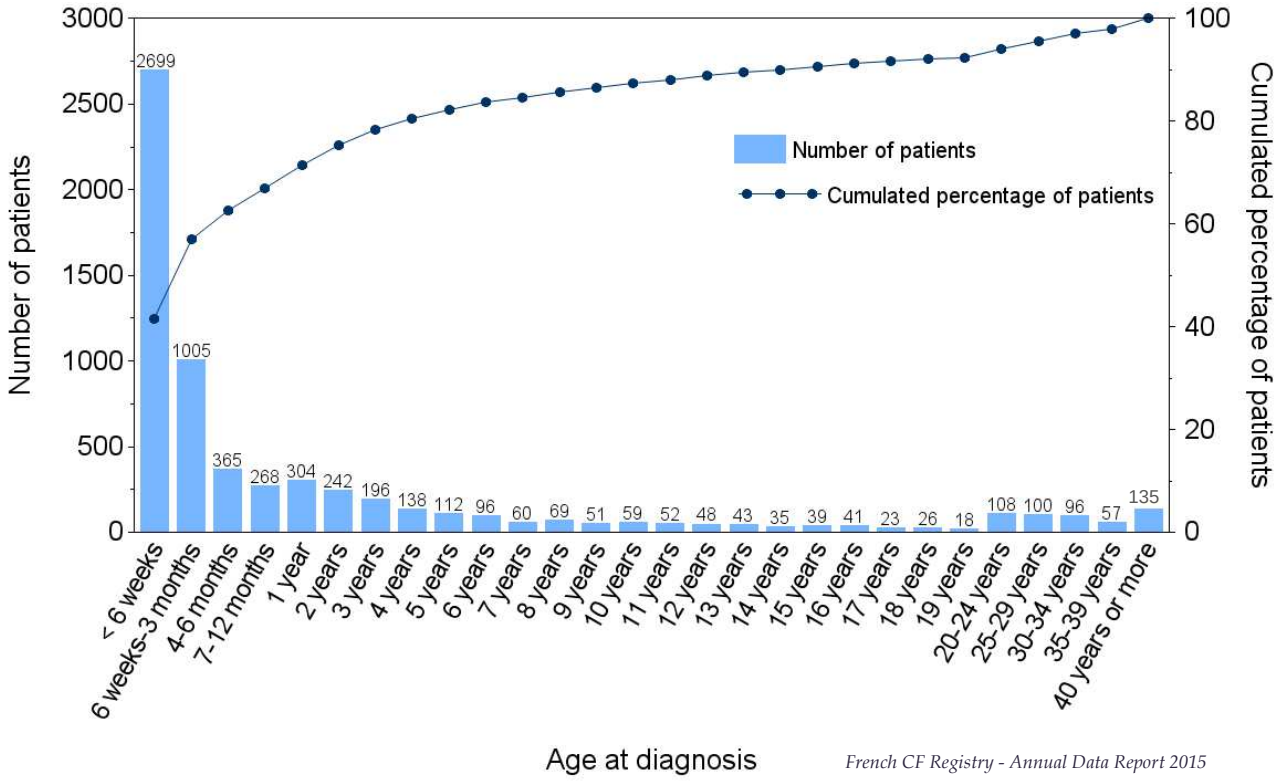
4. Diagnosis

Main characteristics

Figure 4.1. Number of patients and cumulative percentage of patients by age at diagnosis

N = 6,485 (number of patients whose age at diagnosis is known).



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4. Diagnosis

Main characteristics

Table 4.1. Diagnosis characteristics

Characteristics	2013	2014	**2015**
ALL PATIENTS			
Patients whose age at diagnosis is known - N (%) *	6157 (99.5 %)	6306 (99.2 %)	**6485 (99.1 %)**
Age at diagnosis			
- Median age (months)	2.5	2.3	**2.2**
- Mean age (years)	4.2	4.2	**4.4**
- Minimum age (years)	0	0	**0**
- Maximum age (years)	79	77	**78**
NEW PATIENTS DIAGNOSED DURING THE YEAR			
Number of patients			
New patients - N (%)	156 (2.5 %)	185 (2.9 %)	**226 (3.5 %)**
- Including 2015 newborn patients - N	84	126	**144**
Age at diagnosis (a)			
- Median age (months)	1.7	1.3	**1.3**
- Mean age (years)	10.1	6.8	**6.5**
- Minimum age (years)	0	0	**0**
- Maximum age (years)	72	77	**66**
Context of diagnosis			
1. Screened positive newborns (NBS)	84	124	**136**
- including Prenatal diagnosis - N (%)	2 (2.4 %)	1 (0.8 %)	**1 (0.7 %)**
- including Meconium ileus - N (%)	8 (9.5 %)	9 (7.3 %)	**6 (4.4 %)**
2. Diagnosis on symptoms (NBS excluded)	72	61	**90**
- including Meconium ileus - N (%)	7 (9.7 %)	13 (21.3 %)	**12 (13.3 %)**
- including Symptoms (other than MI):- N (%)	65 (90.3 %)	48 (78.7 %)	**78 (86.7 %)**
- Mean age at diagnosis (years)	21.7	20.4	**16.2**

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* Data from AFDPHE were used to complete the Registry data when possible.

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

Among the 226 new patients, 144 were born in 2015. The method used to compile this report (patients seen in a care centre in 2015) means that infants born in 2015 and seen for the first time in 2016 are not included yet. For information purposes only, 18 newborns in 2014 were diagnosed in 2015 through neonatal screening. In the 2014 age pyramide, the number of patients aged 0 was 125 and should have been 125+18=143.

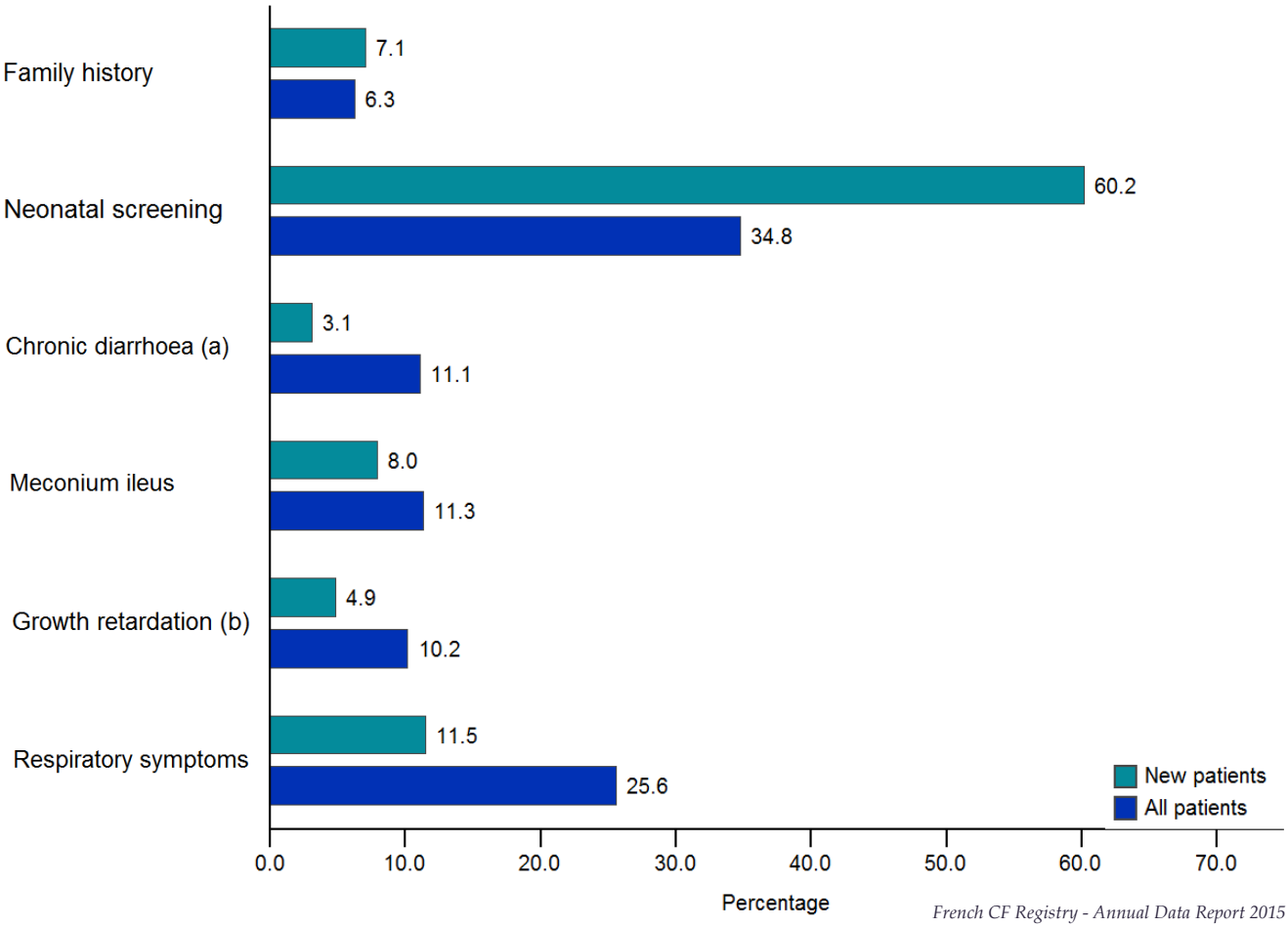
The number of patients diagnosed by neonatal screening (136) given in this report is not the total for France, but represents the patients for whom screening resulted in diagnosis. Patients diagnosed with CF before the screening result was known, (e.g. throught meconium ileus), are not included in those 136 patients.

For comparison, 410 new patients (round figure) were registered in 2015 under the general social security regime (for wage employees).

4. Diagnosis

Diagnosis signs

Figure 4.2. Diagnosis signs (most frequent ones)



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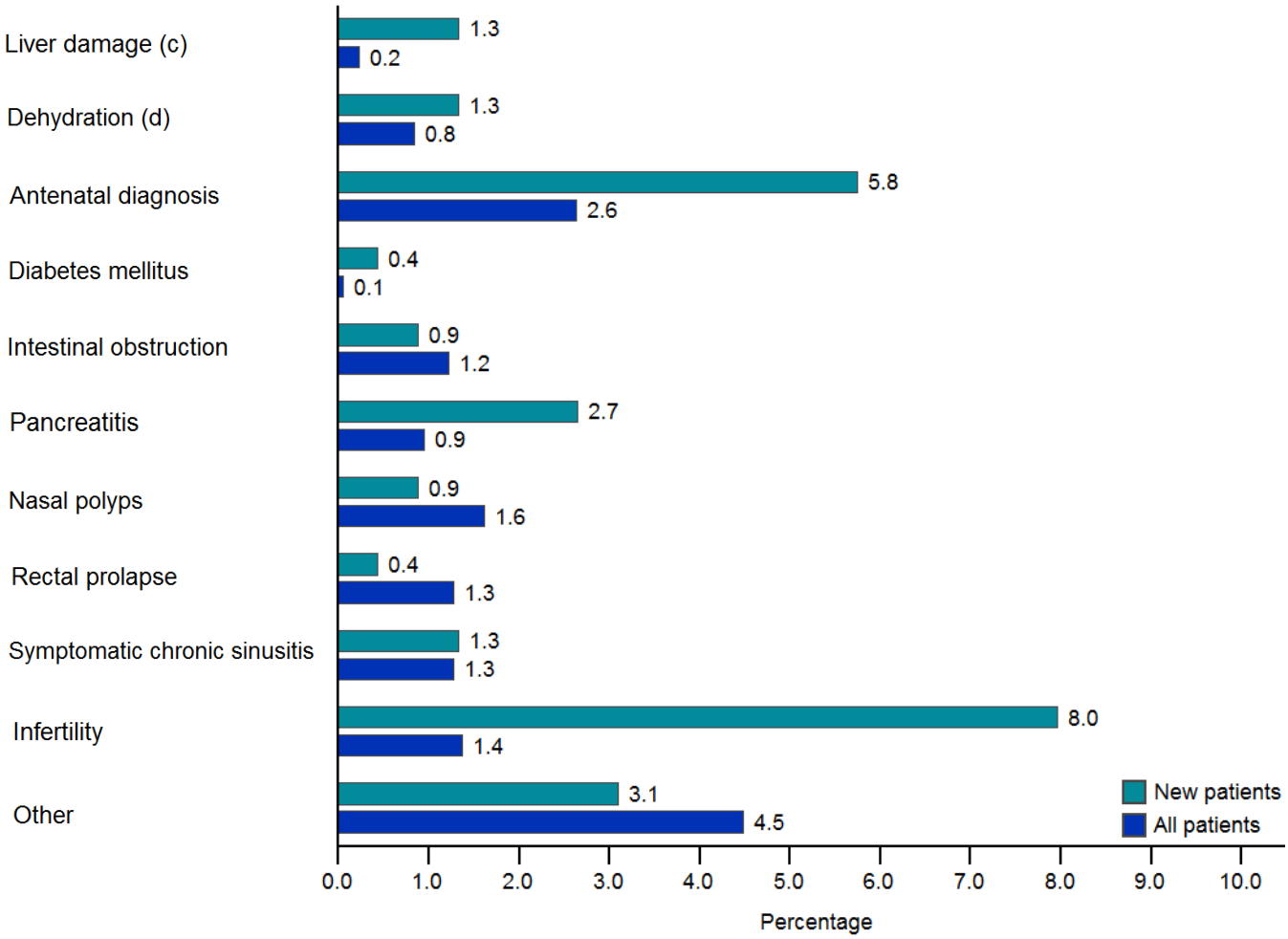
(a) Chronic diarrhoea / Steatorrhoea / Malabsorption
(b) Growth retardation / Malnutrition

4. Diagnosis

Diagnosis signs

Figure 4.3. Diagnosis signs (less frequent ones)



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

4. Diagnosis

Genotypes

Table 4.2. Prevalence of the 40 most common mutations

Mutations	Number of patients *	Proportion (%)
F508del	5453	83.3 %
G542X	353	5.4 %
N1303K	279	4.3 %
2789+5G->A	159	2.4 %
1717-1G->A	136	2.1 %
R117H	130	2.0 %
R553X	120	1.8 %
G551D	113	1.7 %
W1282X	92	1.4 %
3849+10kbC->T	88	1.3 %
3272-26A->G	80	1.2 %
Y122X	74	1.1 %
L206W	71	1.1 %
D1152H	69	1.1 %
I507del	69	1.1 %
2183AA->G	64	1.0 %
711+1G->T	62	0.9 %
R1162X	57	0.9 %
R347P	56	0.9 %
3120+1G->A	48	0.7 %
G85E	45	0.7 %
R334W	45	0.7 %
3659delC	43	0.7 %
A455E	42	0.6 %
Y1092X	41	0.6 %
S945L	39	0.6 %
1078delT	36	0.5 %
1811+1.6kbA->G	36	0.5 %
R347H	36	0.5 %
394delTT	33	0.5 %
W846X	29	0.4 %
621+1G->T	27	0.4 %
S1251N	25	0.4 %
E60X	24	0.4 %
R1066C	24	0.4 %
L997F	19	0.3 %
1677delTA	18	0.3 %
E585X	18	0.3 %
G1244E	18	0.3 %
2711delT	17	0.3 %

* With at least one copy of the considered mutation.

4. Diagnosis

Genotypes

Table 4.3. Age of patients by genotype

Genotypes	Patients		Age (years)		
	Number	%	Mean	Median	Max
F508del / F508del	2742	41.9	20.2	19.2	61.1
F508del / Other	2620	40.0	21.4	19.0	78.7
Other/ Other	933	14.3	21.4	18.3	83.2
Subtotal (known genotypes)	6295	96.2	20.8	19.0	83.2
F508del / Missing	91	1.4	29.4	26.9	80.6
Other/ Missing	70	1.1	29.3	28.3	72.0
Missing/ Missing	91	1.4	35.8	31.3	80.2
Subtotal (partial genotypes / missing)	252	3.8	31.7	28.6	80.6
Total	6547	100			

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Table 4.4. Age of patients with a gating, nonsense or R117H mutation

	Patients		Age (years)		
	Number	%	Mean	Median	Max
At least one gating mutation	187	2.9	22.1	18.8	65.0
At least one nonsense mutation	1007	15.4	19.8	18.0	83.2
At least one R117H mutation	130	2.0	15.3	10.7	80.0

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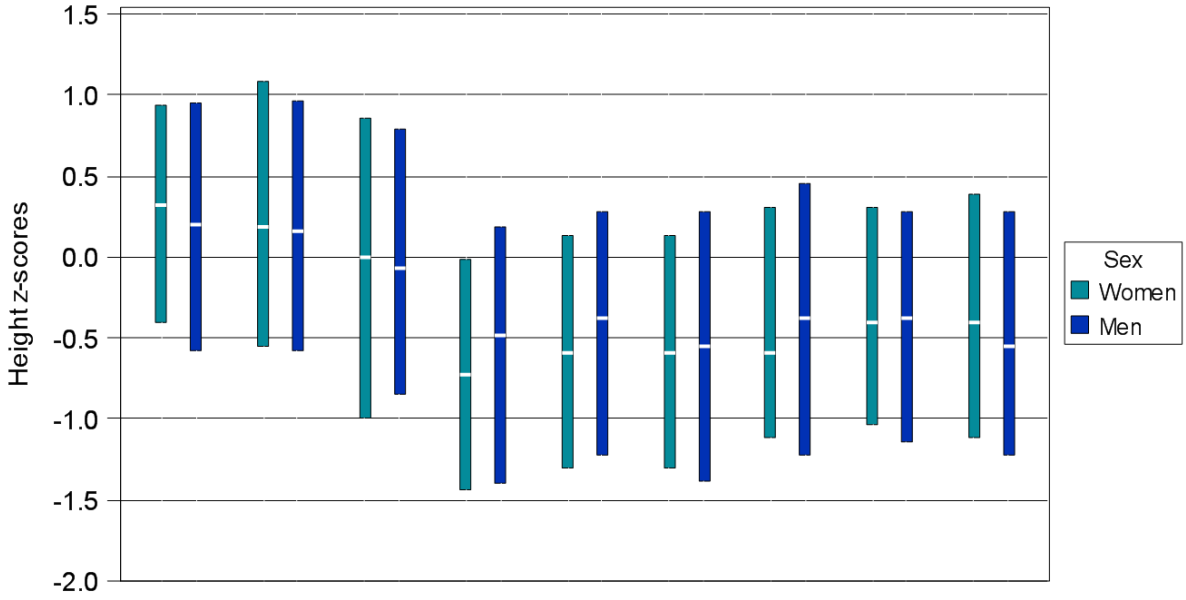
Gating mutations doesn't prevent the CFTR protein from reaching the cell membrane but alter choride transport.

Nonsense mutations cause a premature stop codon thus an absence of CFTR protein production.

5. Anthropometry

Height and weight

Figure 5.1. Height z-scores*, by age group and sex



Age groups (years)		00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +	Total
Mean height z-score	Women	0.21	0.29	-0.06	-0.71	-0.62	-0.57	-0.42	-0.39	-0.37	-0.28
	Men	0.20	0.16	-0.02	-0.52	-0.47	-0.58	-0.42	-0.40	-0.41	-0.26
Median height z-score	Women	0.32	0.19	0.00	-0.72	-0.59	-0.59	-0.59	-0.41	-0.41	-0.30
	Men	0.20	0.16	-0.07	-0.48	-0.38	-0.55	-0.38	-0.38	-0.55	-0.23

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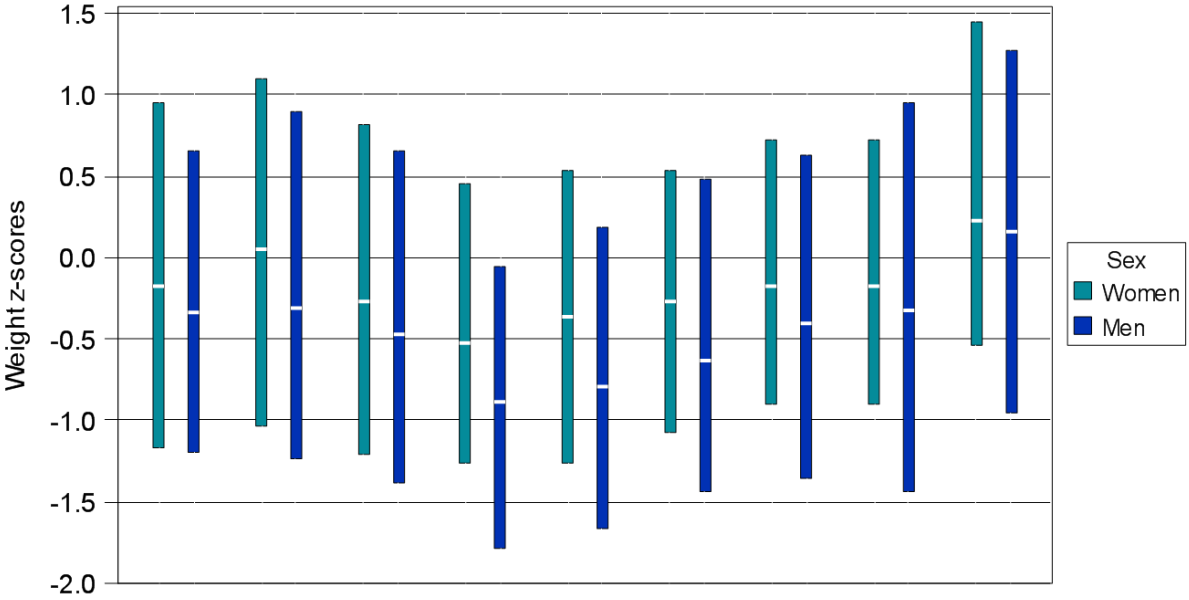
Figure 5.2. Weight z-scores*, by age group and sex



Age groups (years)		00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 ou +	Total
Mean weight z-score	Women	-0.13	0.11	-0.13	-0.37	-0.30	-0.14	-0.06	0.02	0.43	-0.08
	Men	-0.25	-0.12	-0.29	-0.83	-0.65	-0.43	-0.25	-0.20	0.22	-0.34
Median weight z-score	Women	-0.18	0.05	-0.27	-0.53	-0.36	-0.27	-0.18	-0.18	0.23	-0.18
	Men	-0.34	-0.31	-0.47	-0.89	-0.79	-0.63	-0.41	-0.32	0.16	-0.48

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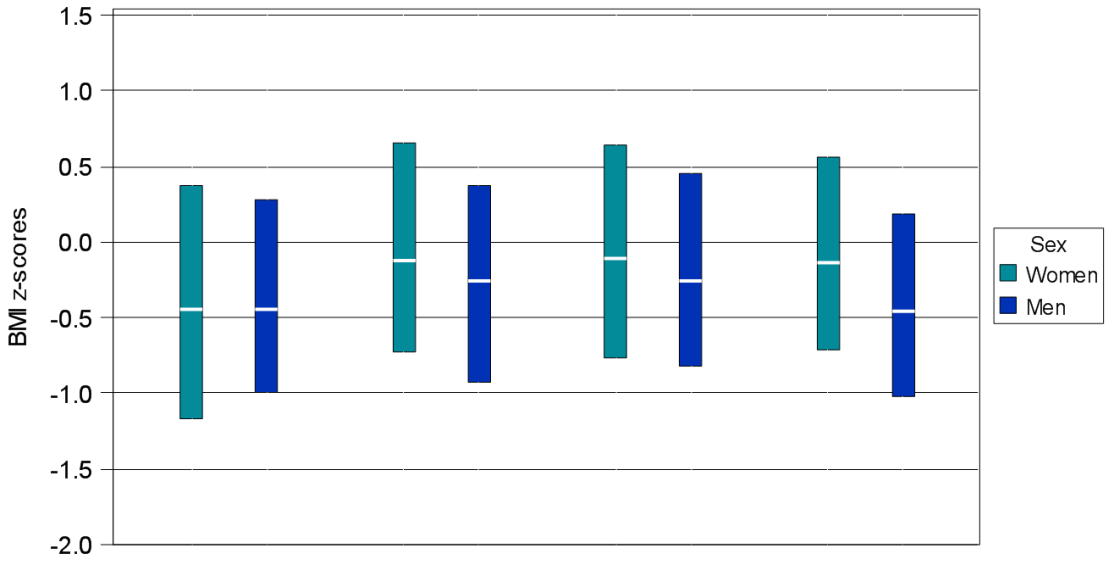
*See explicative note p 22.

5. Anthropometry

Body Mass Index (BMI)

Figure 5.3. BMI z-scores in children, by age group and sex



Age groups (years)		00-04	05-09	10-14	15-19	Total
Mean BMI z-score	Women	-0.34	0.02	0.04	-0.01	-0.05
	Men	-0.38	-0.20	-0.09	-0.38	-0.26
Median BMI z-score	Women	-0.45	-0.12	-0.11	-0.13	-0.17
	Men	-0.45	-0.26	-0.26	-0.46	-0.35
BMI z-score >=0 (% of patients)	Women	36.7%	44.7%	46.6%	45.3%	43.8%
	Men	32.1%	37.3%	38.4%	30.9%	34.8%

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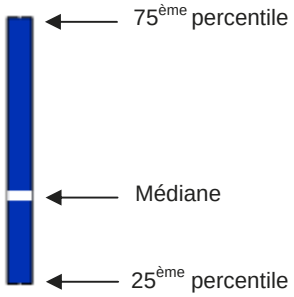
The z-score is a anthropometric reduced centered variable (Z = [measure-mean]/standard deviation), ajusted for gender and age; the mean and standard deviation are taken from the French reference population with the same gender and age as the patient. This index measures the difference with population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

- 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.).

- 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).

Explanation for figures pages 21 to 24

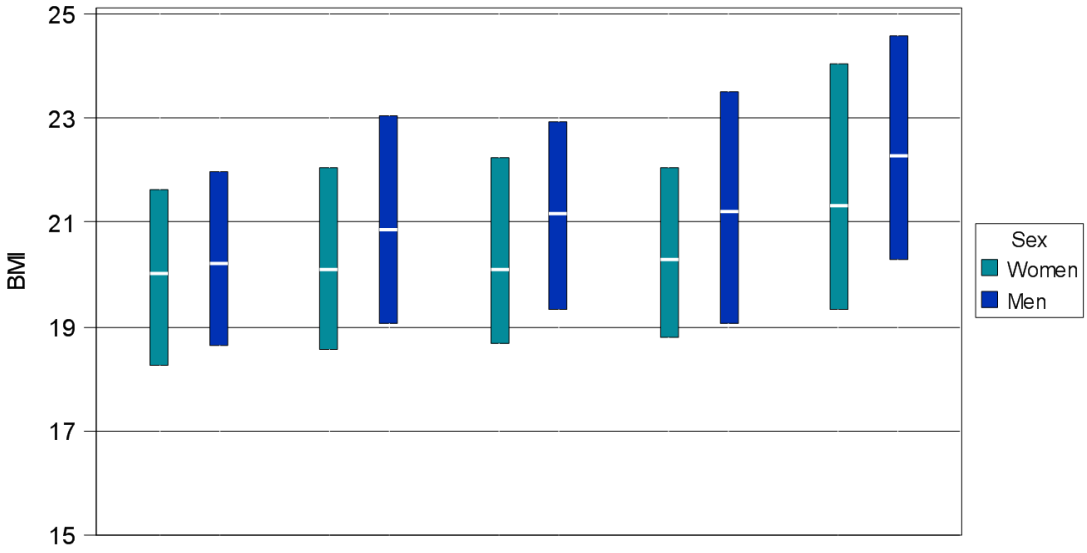
Those figures represent z-scores of anthropométrie and spirometry values.
For each age and sex group, median values are the white lines, extremes are the 25th and 75th percentiles.



5. Anthropometry

Body Mass Index (BMI)

Figure 5.4. BMI in adults, by age group and sex



Age groups (years)		20-24	25-29	30-34	35-39	40 +	Total
Mean BMI	Women	20.2	20.7	20.7	20.9	22.2	20.9
	Men	20.7	21.3	21.4	21.6	22.8	21.5
Median BMI	Women	20.0	20.1	20.1	20.3	21.3	20.3
	Men	20.2	20.9	21.2	21.2	22.3	21.1
BMI < 18.5 (% of patients)	Women	29.5%	23.9%	22.9%	18.6%	15.4%	22.7%
	Men	23.2%	19.1%	16.2%	16.7%	8.5%	17.1%
BMI ≥ 22 (% of patients)	Women	20.8%	25.1%	26.7%	25.7%	39.2%	27.3%
BMI ≥ 23 (% of patients)	Men	17.0%	26.2%	23.9%	30.6%	38.4%	26.7%

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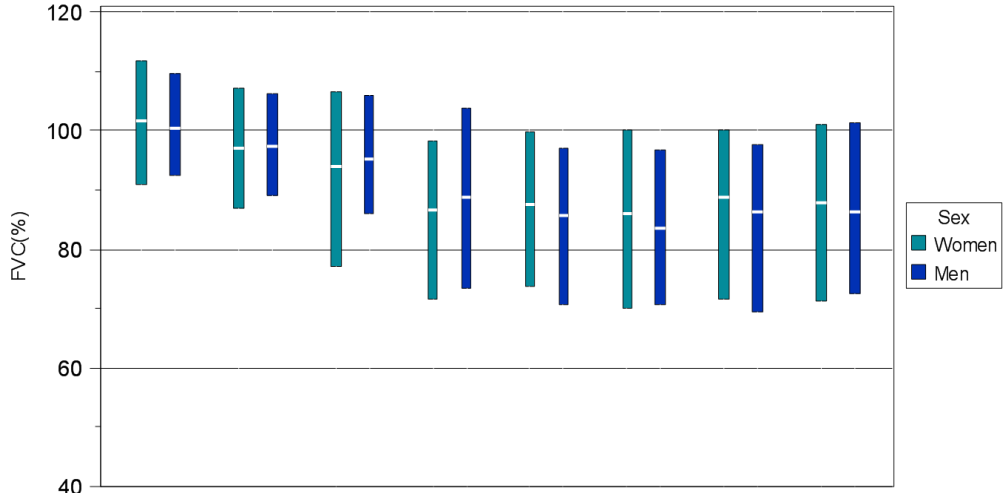
6. Spirometry

95.2% Patients aged 6 and over carried out spirometry

Figure 6.1. FVC (% predicted)*, by age group and sex



	Age groups (years)	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +	Total
Mean FVC	Women	100.5	95.4	91.3	84.8	86.3	84.8	86.4	85.4	89.7
	Men	100.3	96.9	95.1	87.6	82.9	82.9	83.7	85.6	89.9
	All patients	100.4	96.2	93.2	86.2	84.5	83.8	84.9	85.5	**89.8**
Median FVC	Women	101.6	97.1	93.8	86.7	87.4	85.7	88.7	87.8	87.8
	Men	100.3	97.4	95.3	88.8	85.6	83.6	86.3	86.4	92.5
	All patients	101.1	97.2	94.8	87.4	86.1	84.9	87.1	87.2	**92.5**

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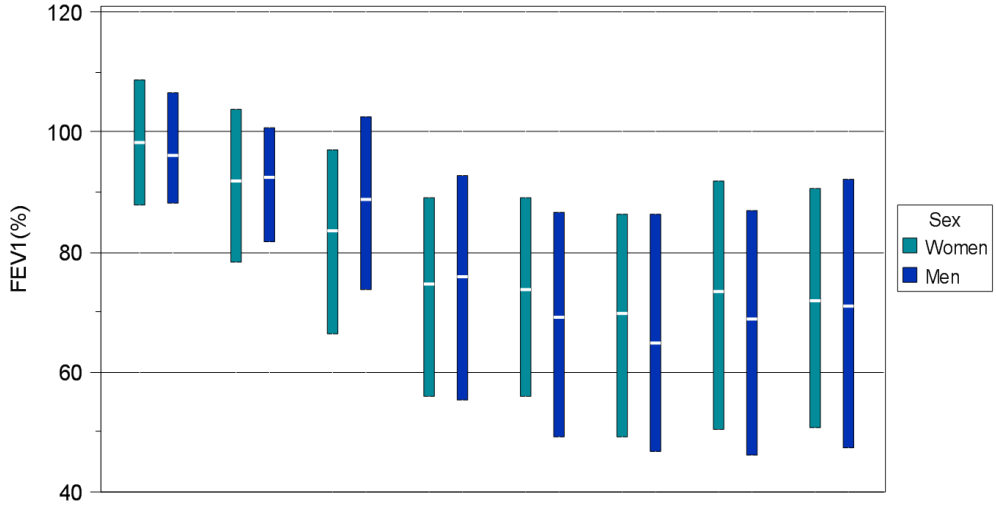
Figure 6.2. FEV_1 (% predicted)*, by age group and sex



	Age groups (years)	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +	Total
Mean FEV_1	Women	97.4	97.4	80.6	72.0	72.5	68.7	71.6	70.8	78.7
	Men	96.2	90.2	86.2	73.3	67.7	66.4	66.8	70.5	78.1
	All patients	96.8	90.0	83.5	72.7	70.0	67.5	68.9	70.7	**78.4**
Median FEV_1	Women	98.1	91.8	83.5	74.7	73.7	69.6	73.5	71.7	81.3
	Men	96.0	92.5	88.8	75.8	69.2	64.8	69.0	71.0	82.2
	All patients	97.3	92.5	86.3	74.9	71.2	67.0	71.1	71.3	**81.8**

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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.

*See explicative note p 22.

6. Spirometry

Figure 6.3. FEV_1 (% predicted) classes

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

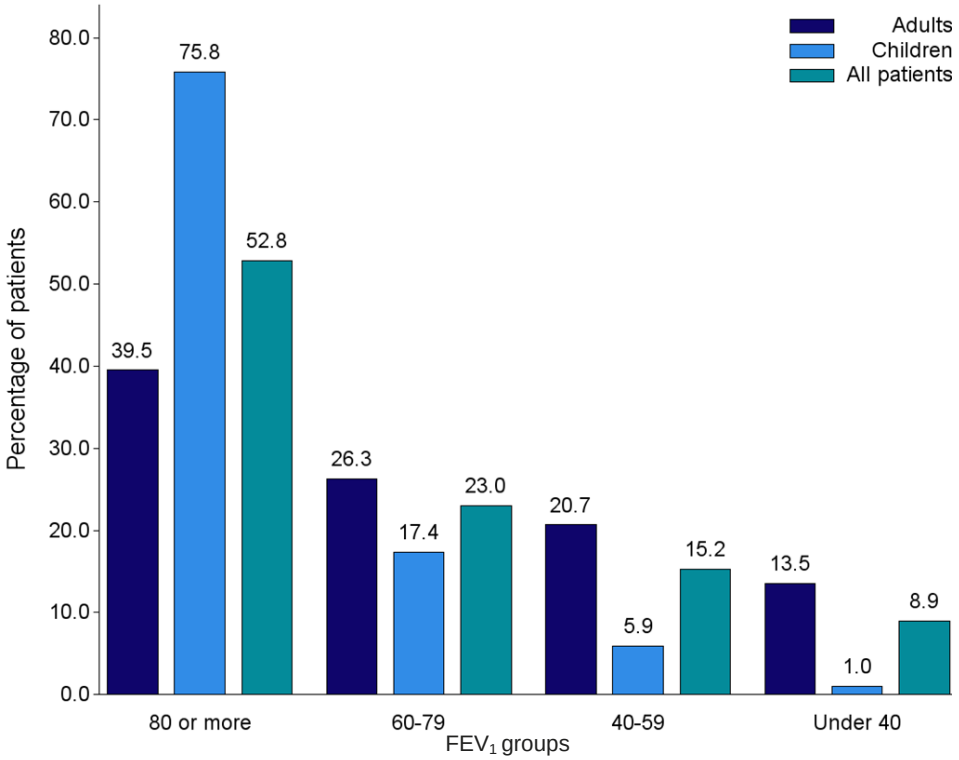

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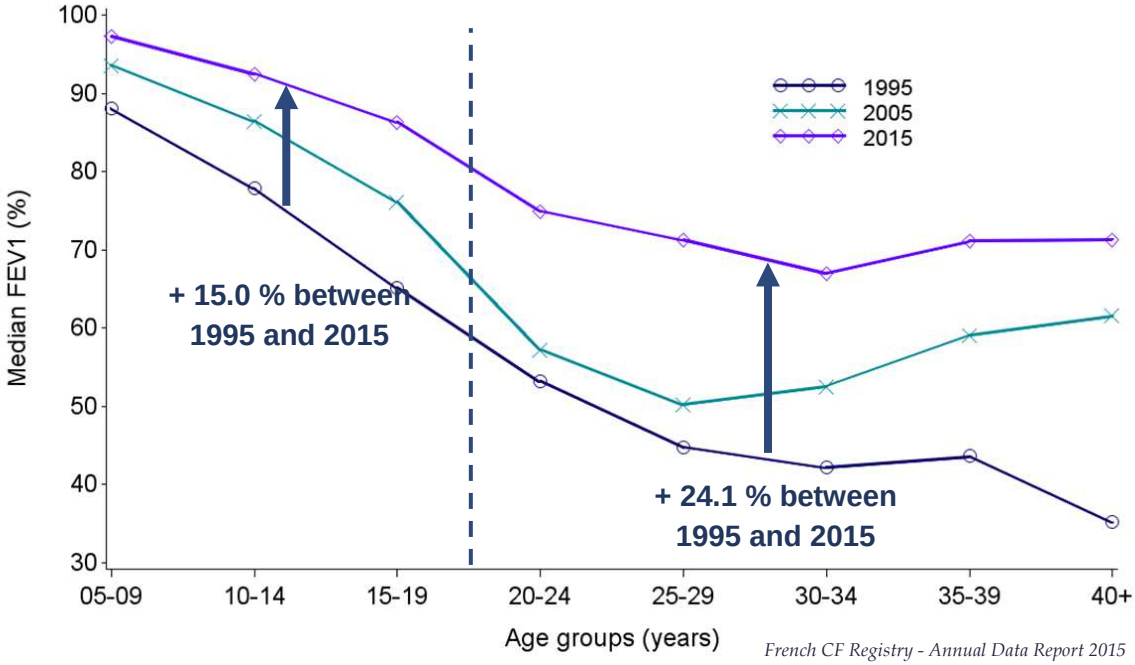
Figure 6.4. Median FEV_1 (% predicted) in 2015 compared with 1995 and 2005



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The last FEV1 (%) value of the year was collected from 1992 to 2010, and the best value of the year since 2011. The median FEV1 was 77.1% for patients aged 6 to 19 years in 1995, and 92.1% in 2015. It was 47.7% in 1995 and 71.8% in 2015 for patients aged 20 years or more.

See appendix 2 for additional information on spirometry and transplantation

7. Microbiology

Table 7.1. Sputum cultures

Patients with at least one sputum	N	*Proportion (%)*
All patients	5768	*88.1 %*
Children	2966	*98.0 %*
Adults	2802	*79.6 %*

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In 2015, 88.1% of the patients had at least one sputum culture; this proportion slightly decreases as it was 88.8% % in 2014 and 90.4 % in 2013. Among the patients without sputum culture (N=779), 59.8 % of them were transplanted.

Table 7.2. Distribution of the respiratory germs, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%*
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Patients with at least one sputum	**690**	**860**	**897**	**826**	**684**	**613**	**429**	**287**	**482**	**5768**	**88.1 %**
Normal culture	418	465	381	209	79	43	49	32	75	1751	26.7 %
Achromobacter xylosoxidans	14	33	70	87	54	67	37	18	29	409	6.2 %
Aspergillus	39	129	206	279	250	201	138	91	123	1456	22.2 %
Burkholderia cepacia, including:	1	6	11	14	34	15	16	9	9	115	1.8 %
- chronic B. cepacia	*.*	*1*	*6*	*6*	*18*	*12*	*12*	*6*	*5*	*66*	*1.0 %*
Haemophilus influenzae	241	321	225	156	106	68	44	32	43	1236	18.9 %
Atypical mycobacteria	1	8	16	26	26	34	17	3	12	143	2.2 %
Pneumococcus	69	65	34	17	9	7	8	8	9	226	3.5 %
Pseudomonas aeruginosa, including:	140	184	292	360	419	390	295	187	286	2553	39.0 %
- Chronic P. aeruginosa	*4*	*31*	*83*	*179*	*275*	*273*	*195*	*140*	*204*	*1384*	*21.1 %*
- Multidrug resistant P. aeruginosa	*2*	*3*	*10*	*32*	*68*	*94*	*83*	*47*	*75*	*414*	*6.3 %*
Staphylococcus, including:	409	636	718	676	505	418	257	164	215	3998	61.1 %
- MSSA	*384*	*611*	*667*	*606*	*431*	*342*	*210*	*127*	*171*	*3549*	*54.2 %*
- MRSA	*13*	*40*	*74*	*104*	*79*	*85*	*48*	*34*	*33*	*510*	*7.8 %*
Stenotrophomonas maltophilia	52	86	117	153	90	71	39	25	41	674	10.3 %
Streptococcus (non *pneumoniae*)	32	55	28	15	25	21	27	7	16	226	3.5 %

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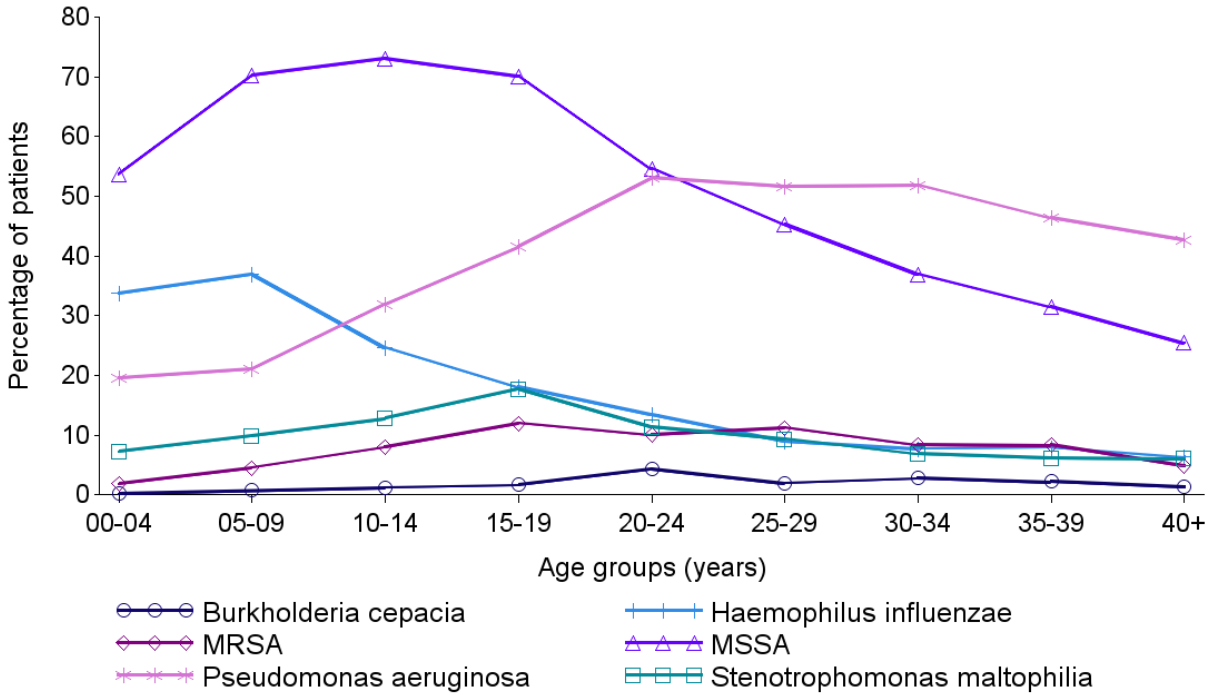
* Percentage with respect to the entire population.

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.

7. Microbiology

Figure 7.1. Clinically important bacteria, by age group



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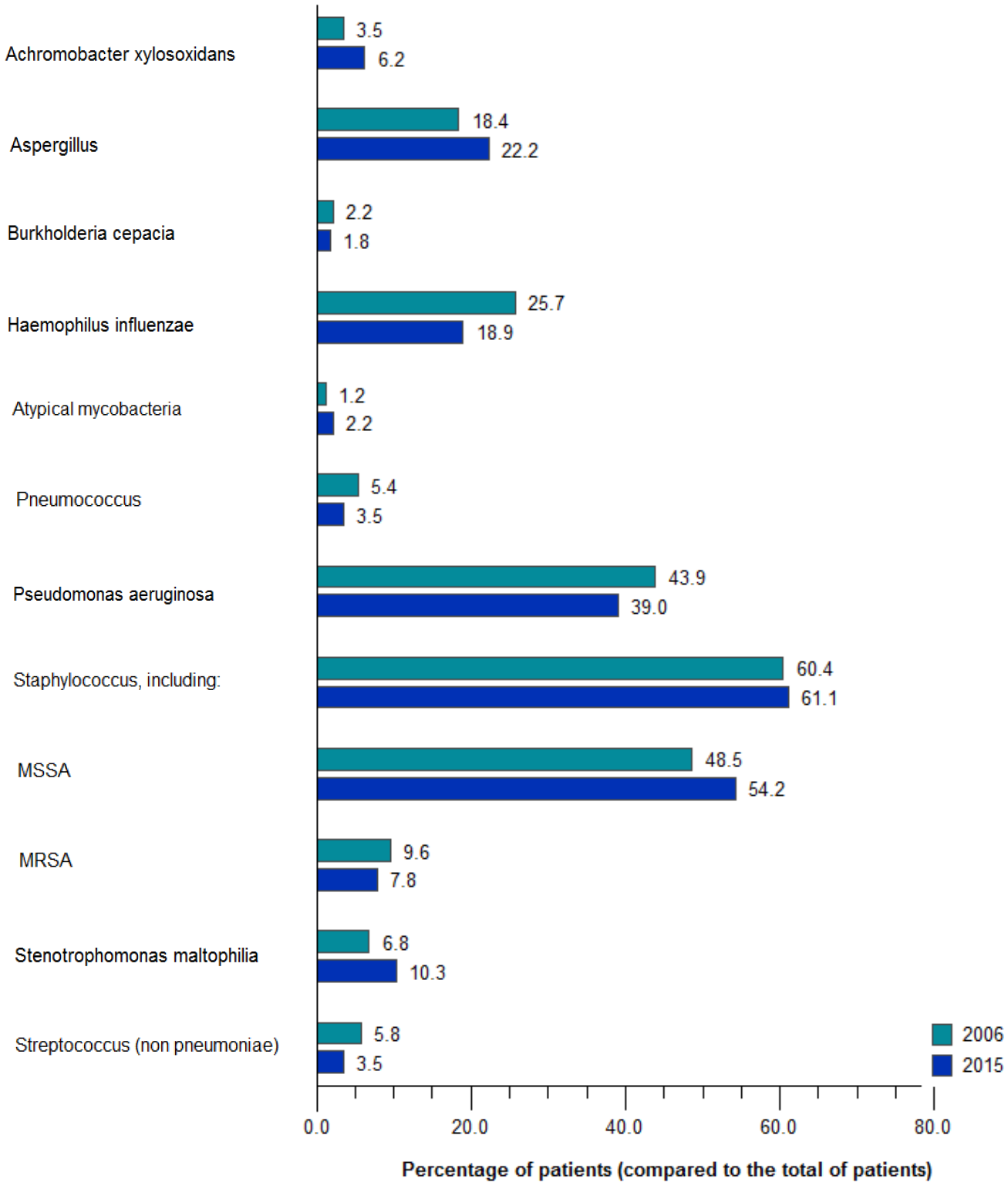
7. Microbiology

Figure 7.2. Comparison of germs in 2015 and in 2006



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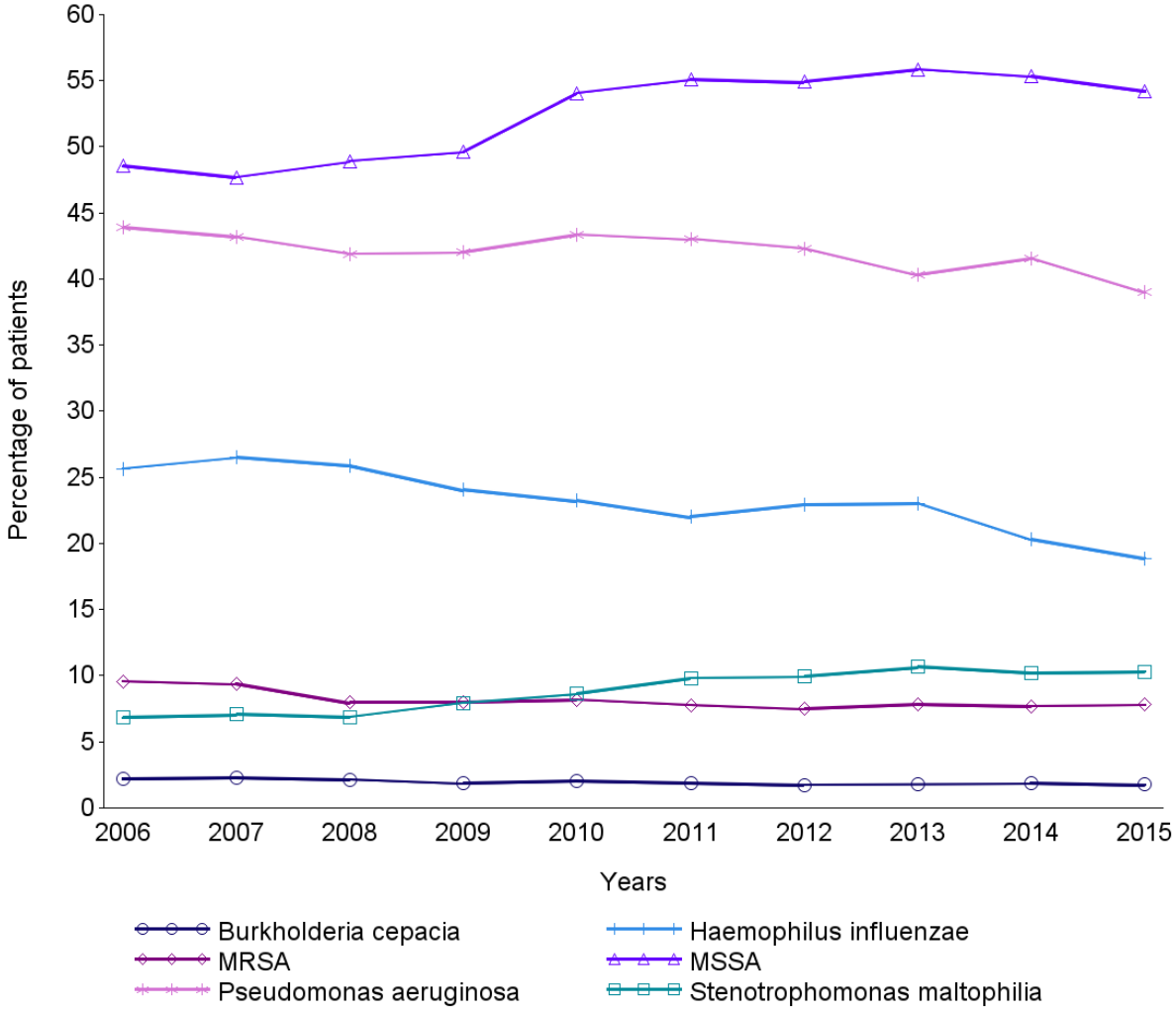
7. Microbiology

Figure 7.3. Evolution of respiratory germs since 2006



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8. Complications

Respiratory

Table 8.1. Respiratory complications, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Treated aspergillosis	6	41	86	128	126	78	66	39	57	627	9.6 %
Asthma	113	193	224	184	118	115	77	52	96	1172	17.9 %
Haemoptysis	.	2	15	55	74	69	50	17	32	314	4.8 %
Pneumothorax	.	1	.	10	17	8	10	5	6	57	0.9 %
Nasal polyps	18	118	146	148	149	116	112	53	99	959	14.6 %

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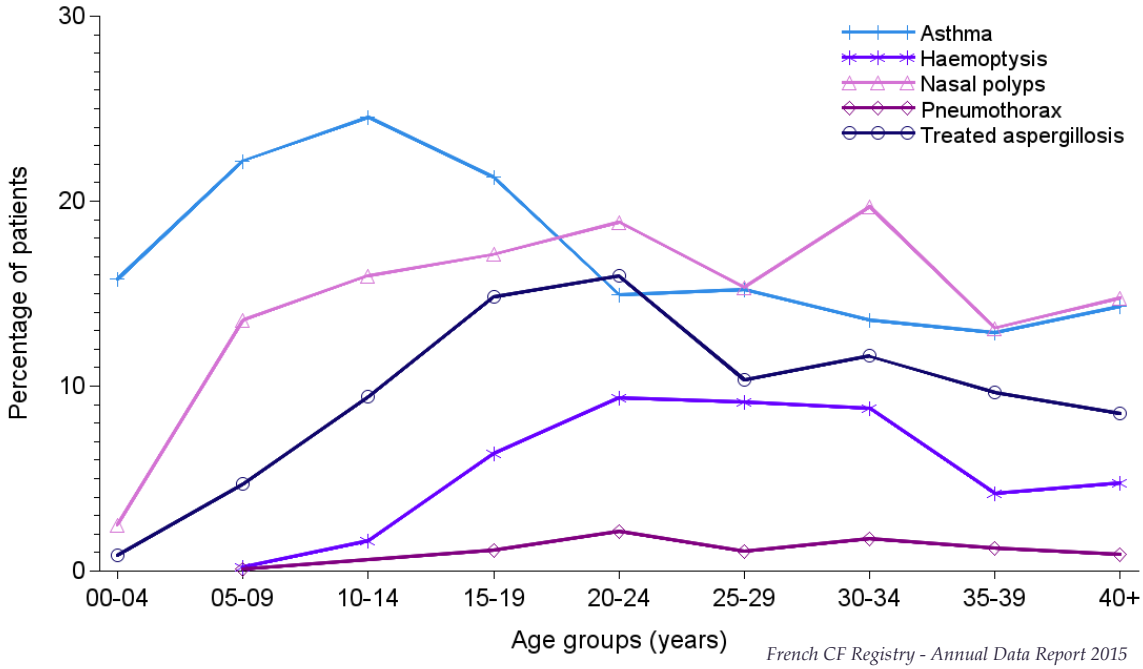
Figure 8.1. Respiratory complications, by age group

Percentage of age groups reporting complications.



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8. Complications

Gastro-intestinal

Table 8.2. Gastro-intestinal complications, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Gallstones	4	12	19	7	24	44	38	21	31	200	3.1 %
Cirrhosis/Portal hypertension	1	16	38	68	44	37	27	11	17	259	4.0 %
Elevated liver enzymes	32	47	74	68	62	77	42	18	36	456	7.0 %
Abnormal exocrine pancrea-tic function	571	713	742	745	669	623	478	317	422	5280	80.6 %
Intestinal obstruction	12	26	23	22	42	48	43	27	35	278	4.2 %
Acute pancreatitis	.	2	4	11	13	15	11	4	14	74	1.1 %
Treated gastro-oesophageal reflux disease	92	81	81	108	153	186	154	111	195	1161	17.7 %

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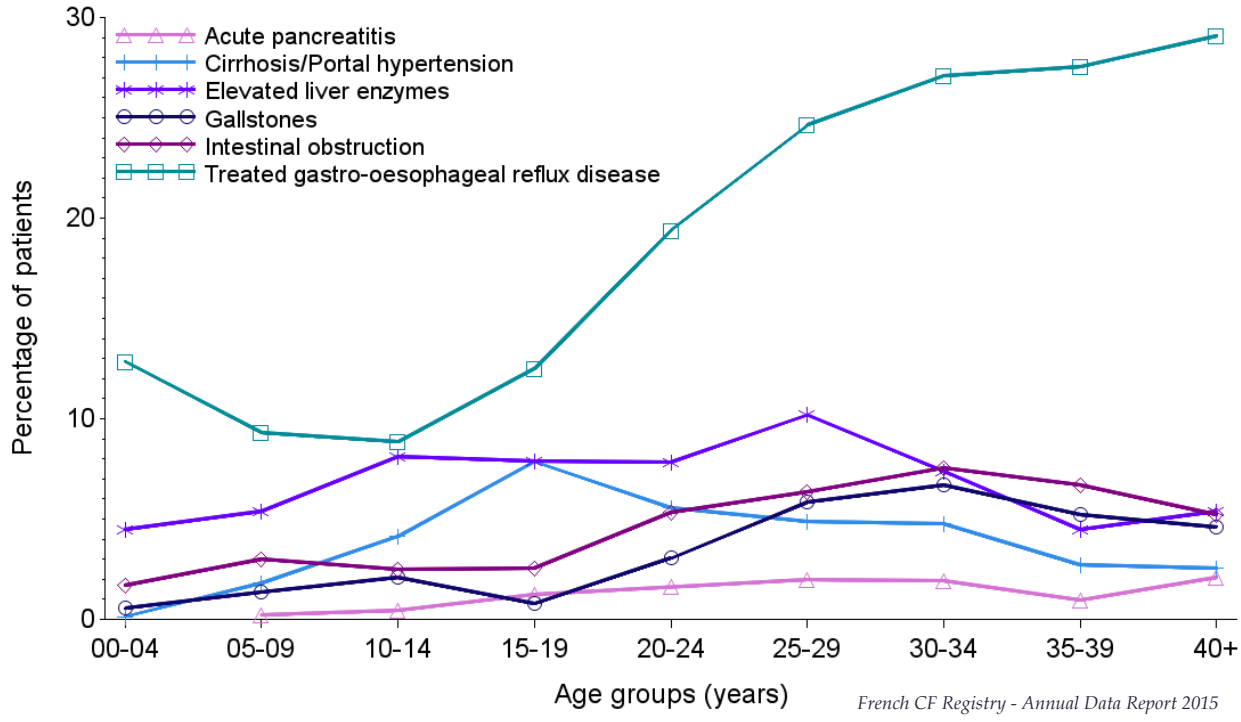
Figure 8.2. Gastro-intestinal complications, by age group

Percentage of age groups reporting complications.



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8. Complications

Diabetes mellitus

35% of adult patients are with diabetes mellitus

Table 8.3. Diabetes mellitus and degenerative complications of diabetes, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Total diabetes (ID and non ID diabetes)	.	22	40	131	193	228	203	152	225	1194	18.2 %
Non insulin-dependent diabetes	.	1	7	25	36	37	23	27	39	195	3.0 %
Insulin-dependent diabetes	.	21	34	109	160	193	180	126	186	1009	15.4 %
Degenerative complications of diabetes	.	.	.	.	4	7	15	7	11	44	0.7 %

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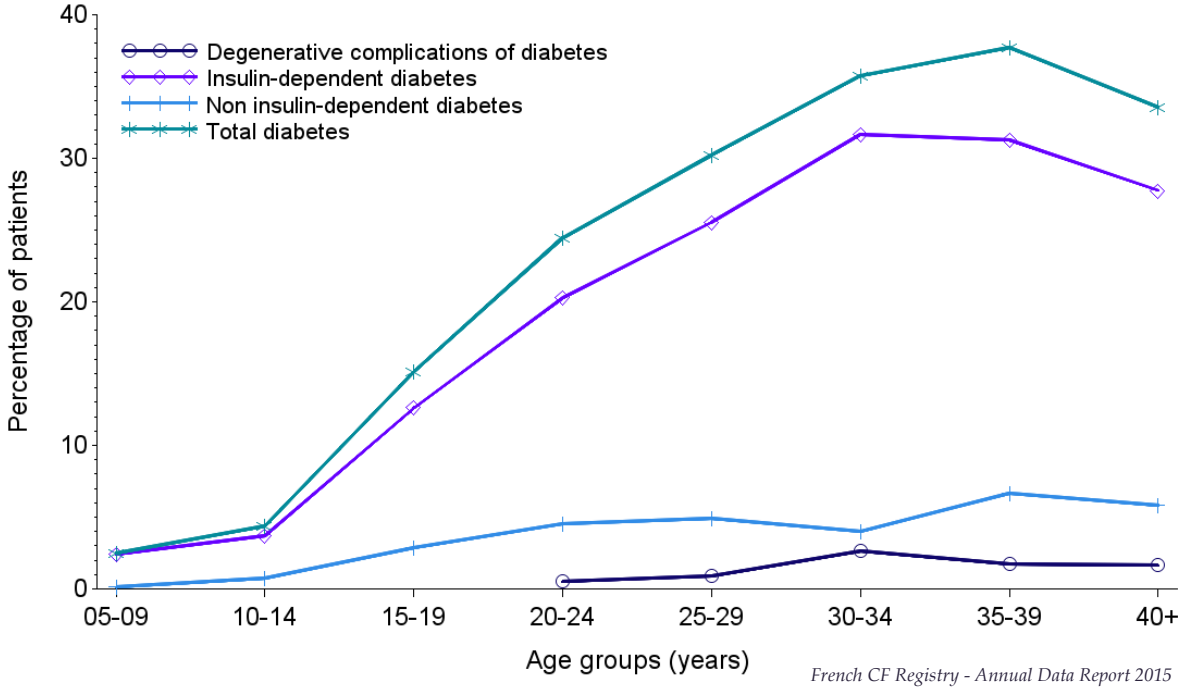
The line « Total diabetes » sums the number of patients having at least one type of diabetes. Among the 1194 patients, 10 patients presented with both types of diabetes during the year.

Figure 8.3. Diabetes mellitus and degenerative complications of diabetes, by age group

Percentage of age groups reporting complications.



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8. Complications

Other complications

Table 8.4. Other complications, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Arthropathy	.	4	7	14	17	21	24	11	37	135	2.1 %
Cancer	.	.	.	1	.	4	3	6	23	37	0.6 %
Depression (evaluated and followed)	.	.	2	11	21	31	34	28	58	185	2.8 %
Urinary incontinence	.	3	2	4	12	8	6	6	12	53	0.8 %
Terminal renal failure	1	.	.	.	3	4	7	10	24	49	0.7 %
Bone disease	.	2	16	22	62	63	64	53	107	389	5.9 %
Deafness/Hypoacusia	1	8	14	19	34	41	50	30	68	265	4.0 %

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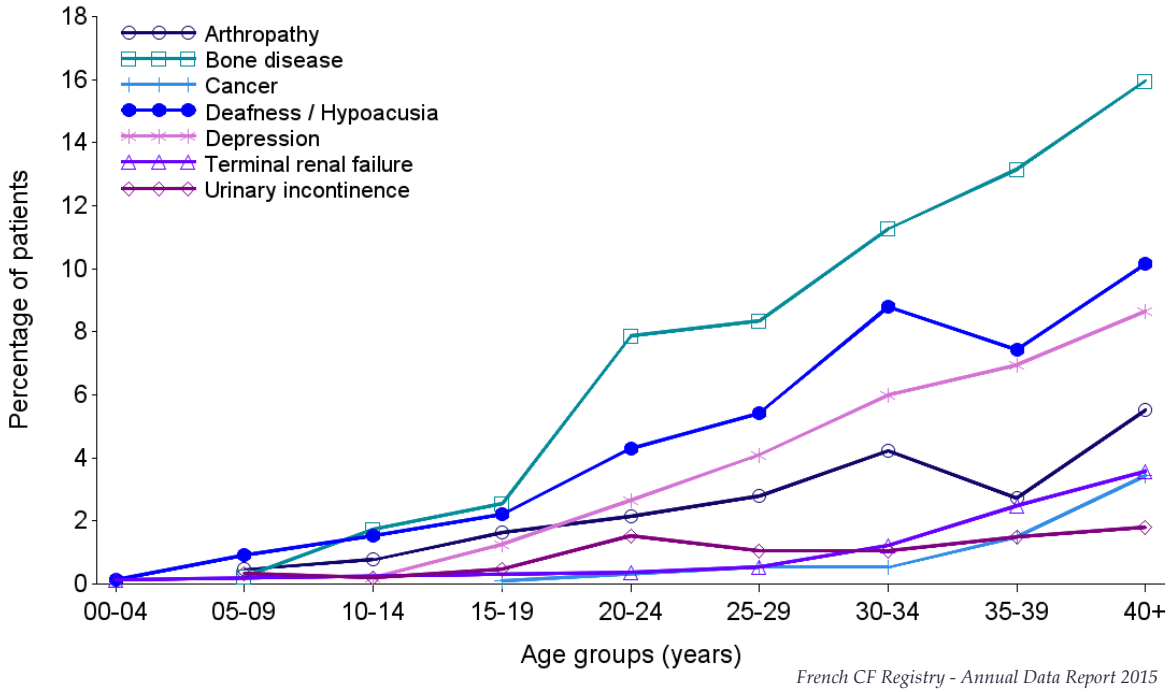
Figure 8.4. Other complications, by age group

Percentage of age groups reporting complications.



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9. Transplantation

Were included in this table all the patients seen and/or dead in 2015.

Table 9.1. Characteristics of the patients on waiting list and of transplant recipients

	All years	2015
WAITING LIST	All waiting patients	Listed in 2015
Nb of patients	**141**	**96**
Mean age (years) and standard deviation (SD)	29.7 ± 11.3	31.2 ± 10.8
Extremes of age (years)	7.2-61.1	10.9-61.1
Deaths on waiting list	3	1
TRANSPLANTATION	All transplanted*	Transplanted in 2015
Nb of patients	**739**	**88**
Transplant type:		
- bilateral lung - N (%)	676 (91.5 %)	76 (86.4 %)
- liver - N (%)	24 (3.2 %)	3 (3.4 %)
- kidney - N (%)	40 (5.4 %)	2 (2.3 %)
- other organ - N (%)**	5 (0.7 %)	
Combined transplantations:		
- heart / lung - N (%)	31 (4.2 %)	1 (1.1 %)
- heart / lung / liver - N (%)	2 (0.3 %)	
- bilateral lung / liver - N (%)	18 (2.4 %)	1 (1.1 %)
- bilateral lung / kidney - N (%)	7 (0.9 %)	2 (2.3 %)
- liver / kidney - N (%)	2 (0.3 %)	
- other combined transplant - N (%)***	10 (1.4 %)	3 (3.4 %)
Mean age (years)	34.0	30.1
SD	9.61	10.7
Extremes of age (years)	10-63.8	10.6-61.1
Post-transplantation deaths	21	5

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*** 69 patients underwent two or more organ transplants.**

** 3 monopulmonary, 1 pancreatic and 1 bone marrow transplantations.

*** 6 bilateral lung / Islets of Langerhans (2 in 2015), 2 kidney / pancreas (1 in 2015), 1 liver / pancreas and 1 liver / lung transplantations.

9. Transplantation

Figure 9.1. Annual number of transplanted patients, since 1992

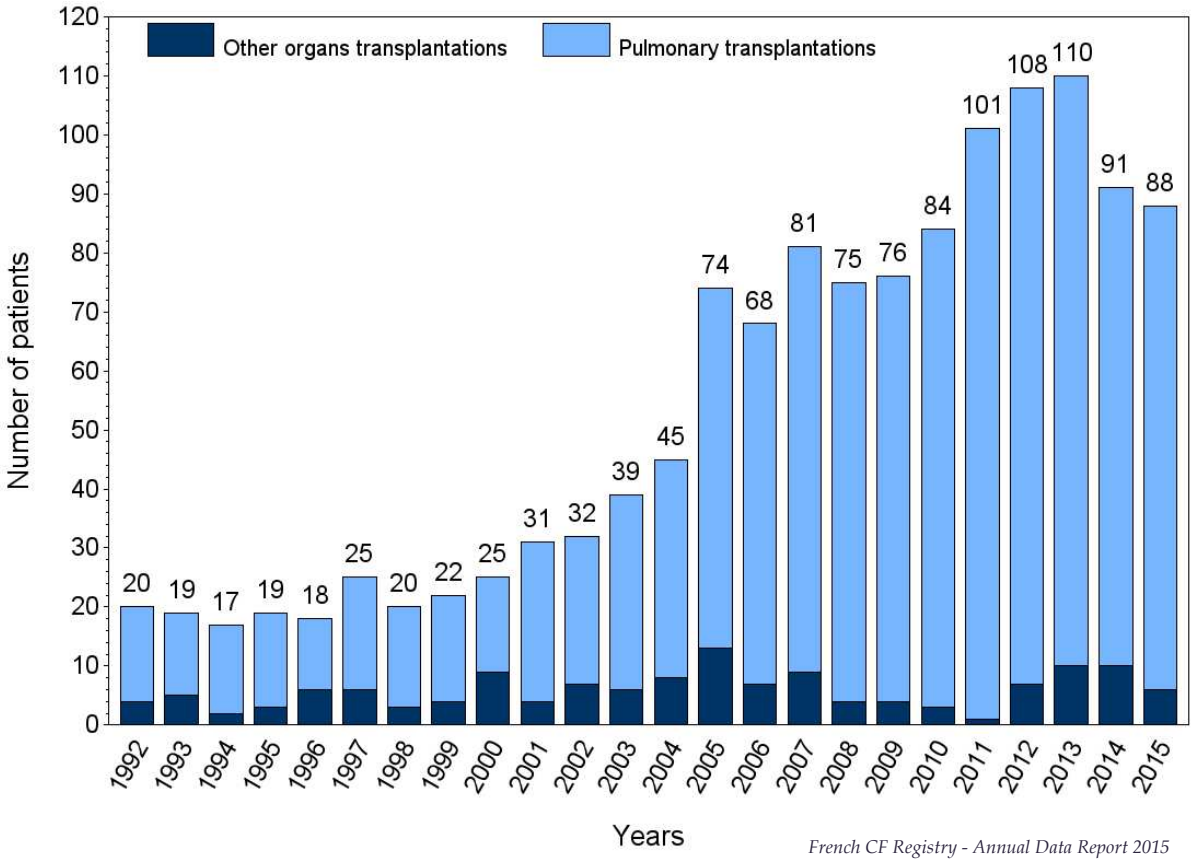

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Table 9.2. Annual number of transplanted patients, since 1992

	Years											
Greffes	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Pulmonary	16	14	15	16	12	19	17	18	16	27	25	33
Other organs	4	5	2	3	6	6	3	4	9	4	7	6

	Years											
Greffes	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Pulmonary	37	61	61	72	71	72	81	100	101	100	81	82
Other organs	8	13	7	9	4	4	3	1	7	10	10	6

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10. Outpatient and inpatient visits

Table 10.1. Characteristics of the visits, by age group

	Age groups (years)									
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*
< 4 visits per year	115	163	170	163	214	222	177	140	254	1618
≥ 4 visits per years	600	707	743	701	575	533	391	263	416	4929
Outpatient visits										
Number of patients with at least one outpatient visit	*487*	*575*	*600*	*563*	*604*	*560*	*415*	*299*	*470*	*4573*
Median number of visits	4	3	3	3	3	3	3	3	3	3
Mean number of visits	4.1	3.4	3.4	3.6	3.8	3.6	3.6	3.1	3.2	3.6
One-day hospitalizations										
Number of patients with at least one one-day visit	*641*	*819*	*857*	*793*	*665*	*615*	*484*	*333*	*523*	*5730*
Median number of visits	3	3	3	3	2	2	2	2	2	2
Mean number of visits	3.6	3.0	3.4	3.6	2.7	2.9	2.8	2.8	2.8	3.1
Inpatient visits										
Number of patients with at least one inpatient visit	*169*	*165*	*206*	*279*	*286*	*261*	*197*	*119*	*214*	*1896*
Median number of visits	1	1	1	1	1	1	1	2	2	1
Mean number of visits	1.8	1.6	2.0	2.2	2.2	2.2	2.1	2.2	2.4	2.1
Median duration (days)	9	5	6	10	10	9	11	10	12	9
Mean duration (days)	19.3	12.1	13.0	18.8	19.3	20.5	20.3	19.2	21.5	18.4

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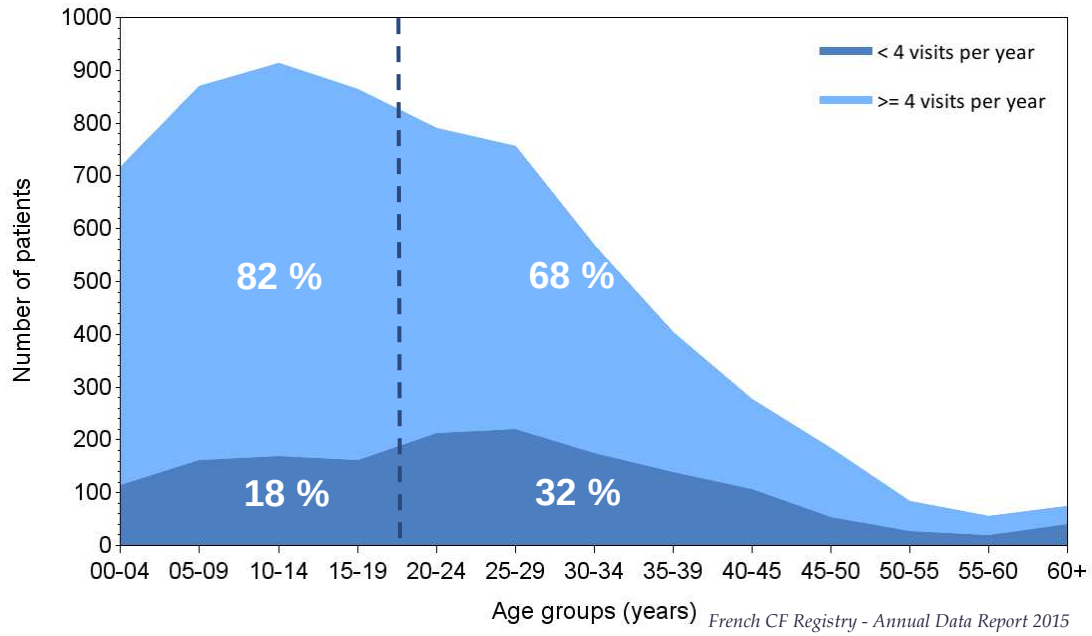
Notes:
- Visits include outpatient, one-day hospitalizations and inpatient visits.

Figure 10.1. Number of visits, by age group



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Among patients aged 0 to 19, 82% had at least 4 visits in 2015, compared with 68% for patients of 20 years and older.

11. Therapeutic management

Antibiotic courses – TIVAD

Table 11.1. IV antibiotic courses, by age group

	Age groups (years)									Total
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*
Nb of patients with at least one course	63	107	197	309	379	350	268	150	235	2058
- and with TIVAD*	9	29	69	137	189	193	144	74	110	954
Nb of courses	88	184	422	677	892	858	626	344	485	4576
Nb of days of courses including:	1495	2956	6949	11452	13804	14638	10519	5664	7788	75265
- at hospital	896	1165	1761	3322	3110	3496	2404	1577	2030	19761
- at home	285	1816	4566	8033	10373	10192	7828	3919	5388	52400
TIVAD* (with and without course)	11	41	85	158	215	241	181	109	156	1197

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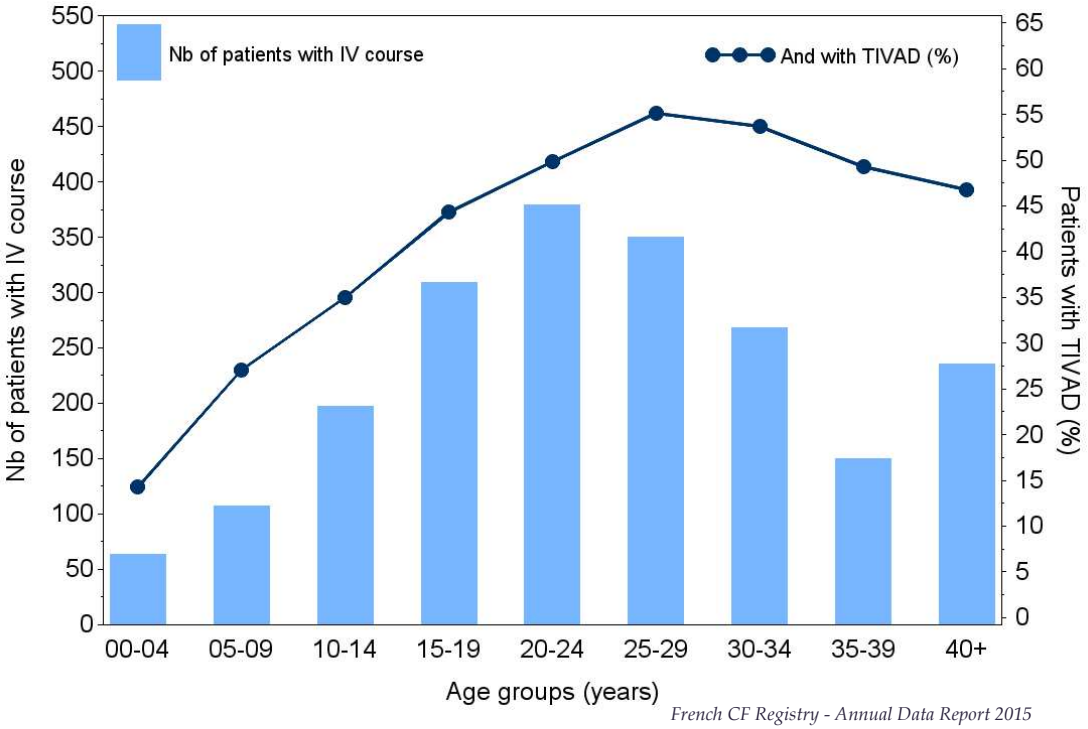
Figure 11.1. Patients with at least one IV antibiotic course and a TIVAD*, by age group



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* TIVAD: Totally Implantable Vascular Access Device

11. Therapeutic management

Antibiotic courses

Table 11.2. Repartition of courses

	Age groups (years)									Total
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	
Courses										
Mean number of courses	1.4	1.7	2.2	2.3	2.5	2.5	2.4	2.3	2.2	2.3
SD	0.9	1.1	1.4	1.6	1.9	1.9	1.8	1.9	1.6	1.7
Median number of courses	1	1	2	2	2	2	2	2	2	2
1st quartile (Q1)	1	1	1	1	1	1	1	1	1	1
3rd quartile (Q3)	2	2	3	3	3	3	3	3	3	3
Day of courses										
Mean duration of courses (days)	23.7	27.6	36.0	38.4	38.2	43.6	41.3	39.1	35.1	38.0
SD	40.1	27.3	37.6	43.5	34.3	48.9	44.8	41.9	35.3	40.9
Median duration of courses (days)	15	15	28	28	28	30	29	29	28	28
1st quartile (Q1)	14	14	15	15	15	15	15	15	15	15
3rd quartile (Q3)	20	30	45	45	49	49	52	45	42	45

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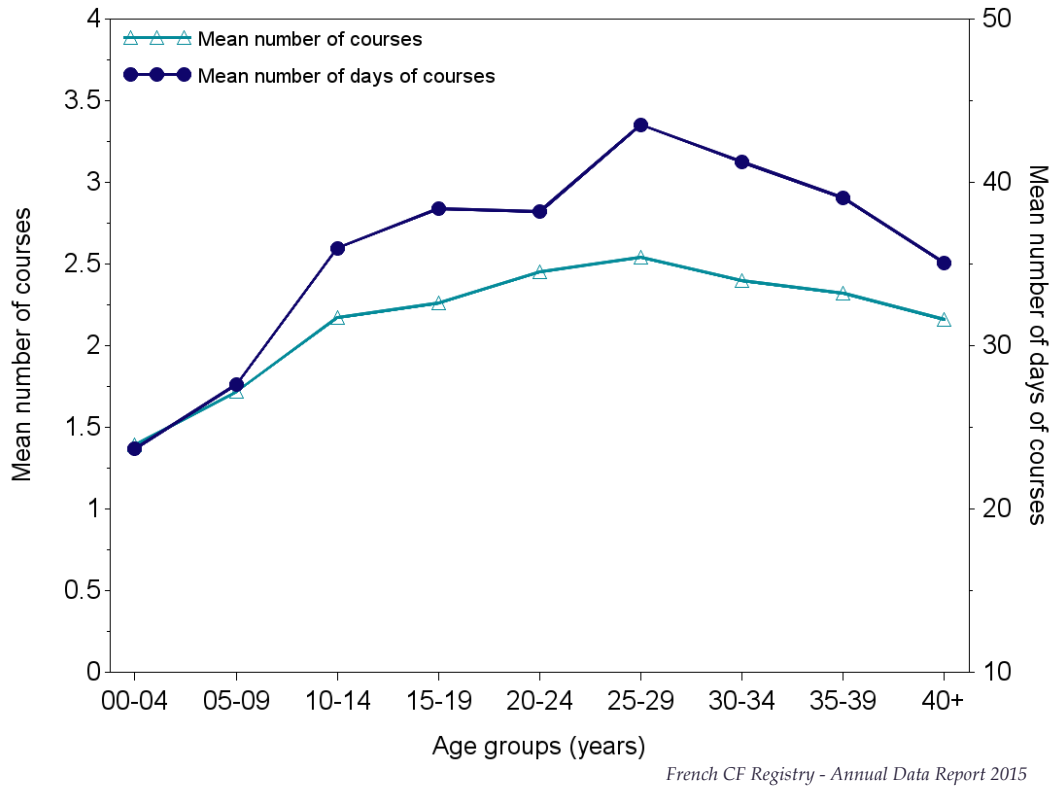
Figure 11.2. Mean number of courses and of days of courses, by age group



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11. Therapeutic management

Respiratory /CFTR gene modulators

Table 11.3. Respiratory therapeutics, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Aerosol therapy*	304	670	805	778	679	595	425	282	466	5004	76.4 %
NSAID	13	32	56	61	52	50	24	26	38	352	5.4 %
Azithromycin	60	204	333	430	424	435	341	236	349	2812	43.0 %
Oxygen therapy	.	9	16	29	52	50	55	33	75	319	4.9 %
Oral corticosteroids	20	43	65	94	158	186	170	136	208	1080	16.5 %
Nasal ventilation	1	4	16	30	39	42	37	26	52	247	3.8 %

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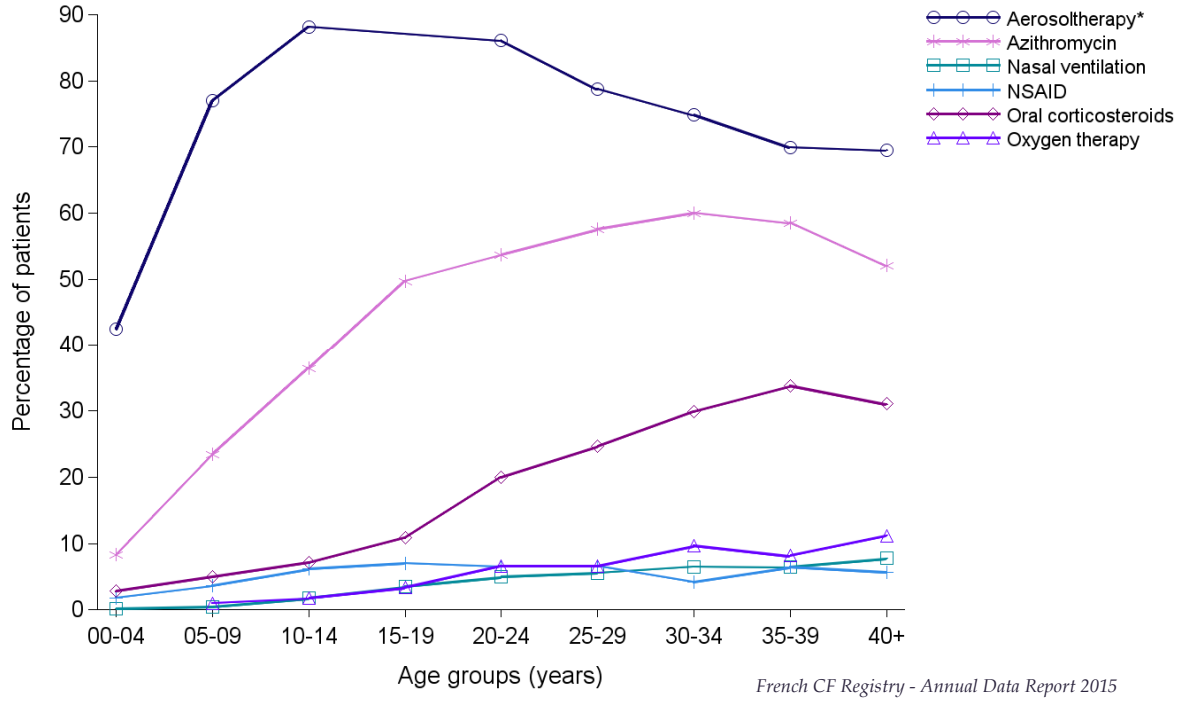
Figure 11.3. Respiratory therapeutics, by age group



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* By nebulization, spray or powder

Table 11.4. CFTR gene modulators

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Ivacaftor	.	21	22	21	14	10	9	5	22	124	1.9 %
Lumacaftor + Ivacaftor	.	.	7	16	13	6	7	3	2	54	0.8 %

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11. Therapeutic management

Aerosoltherapy

Table 11.5. Aerosoltherapy treatments, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Patients under aerosol therapy*	**304**	**670**	**805**	**778**	**679**	**595**	**425**	**282**	**466**	**5004**	**76.4 %**
Inhaled antibiotics, including:	95	180	308	388	371	312	264	155	219	2292	35.0 %
- Tobramycin	*54*	*100*	*180*	*245*	*191*	*146*	*119*	*62*	*75*	*1172*	*17.9 %*
- Colistin	*48*	*98*	*167*	*223*	*225*	*195*	*157*	*102*	*152*	*1367*	*20.9 %*
- Aztreonam	*.*	*1*	*14*	*13*	*25*	*26*	*39*	*19*	*31*	*168*	*2.6 %*
Inhaled bronchodilators	171	359	494	472	388	364	277	191	329	3045	46.5 %
Inhaled corticosteroids	152	310	435	380	299	257	200	146	261	2440	37.3 %
Inhaled hypertonic saline	36	77	106	87	41	31	25	16	24	443	6.8 %
RhDNase	82	471	608	544	407	300	197	120	190	2919	44.6 %

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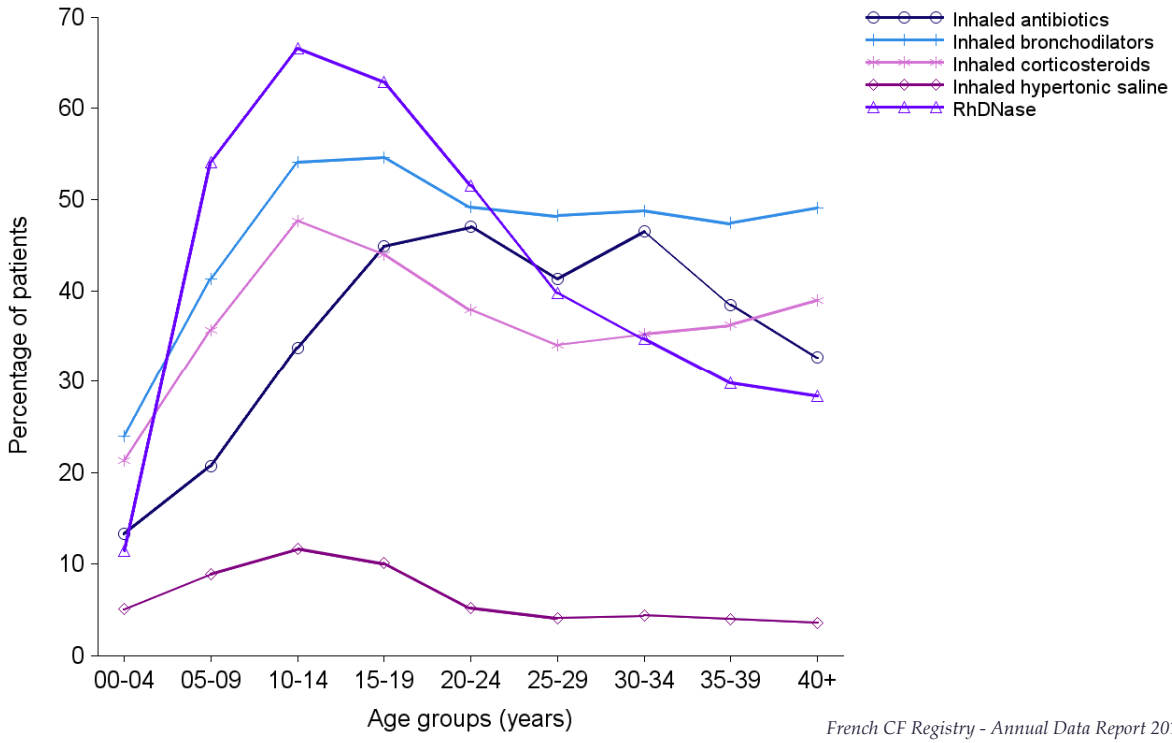
* By nebulization, spray or powder

Figure 11.4. Aerosoltherapy treatments, by age group



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11. Therapeutic management

Digestive and nutritional

Table 11.6. Hepatic, digestive and nutritional treatments, by age group

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*715*	*870*	*913*	*864*	*789*	*755*	*568*	*403*	*670*	*6547*	
Ursodeoxycholic acid	112	212	326	380	322	319	197	125	174	2167	33.1 %
Acid blockers	226	312	383	426	425	414	321	222	389	3118	47.6 %
Pancreatic enzymes	569	716	749	752	681	646	488	325	435	5361	81.9 %
Supplemental tube feeding	36	37	62	71	48	40	18	13	9	334	5.1 %
Oral supplemental feeding	176	265	318	294	314	253	211	115	156	2102	32.1 %
Fat-soluble vitamins	676	822	872	813	734	669	521	359	540	6006	91.7 %

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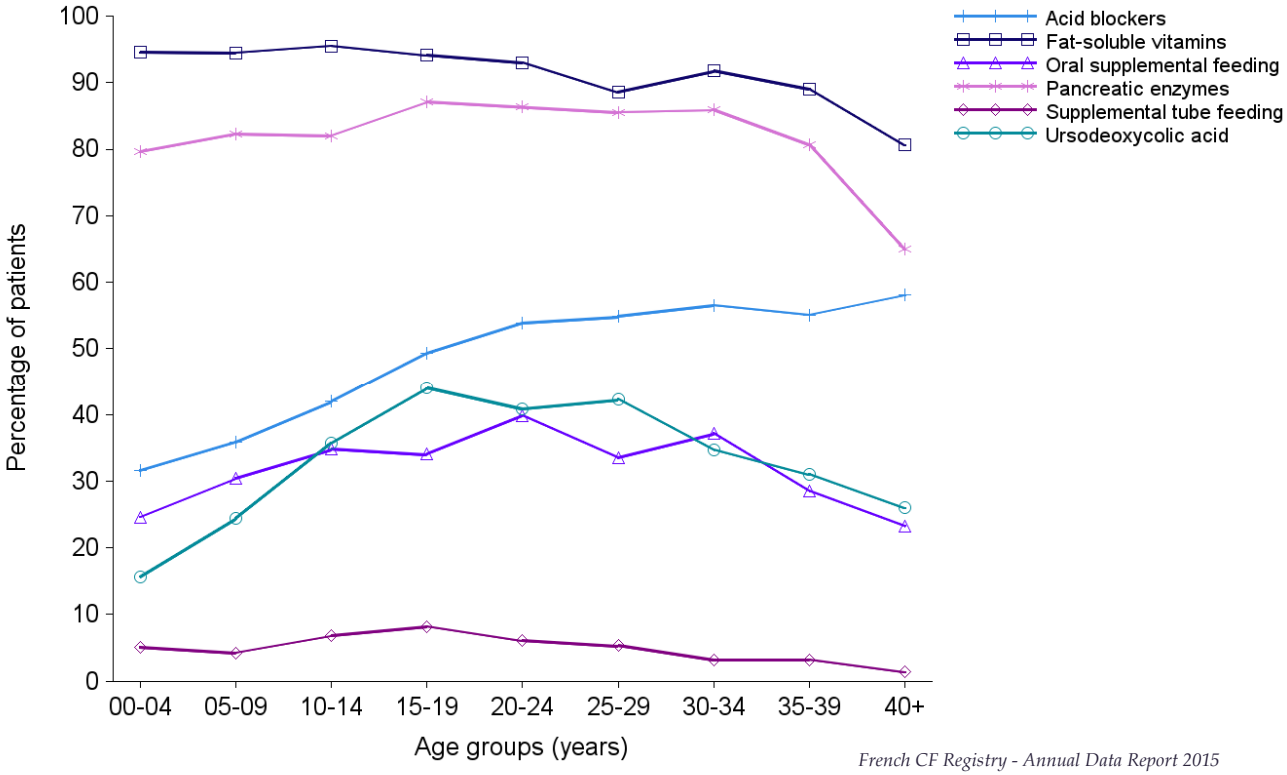
Figure 11.5. Hepatic, digestive and nutritional treatments, by age group



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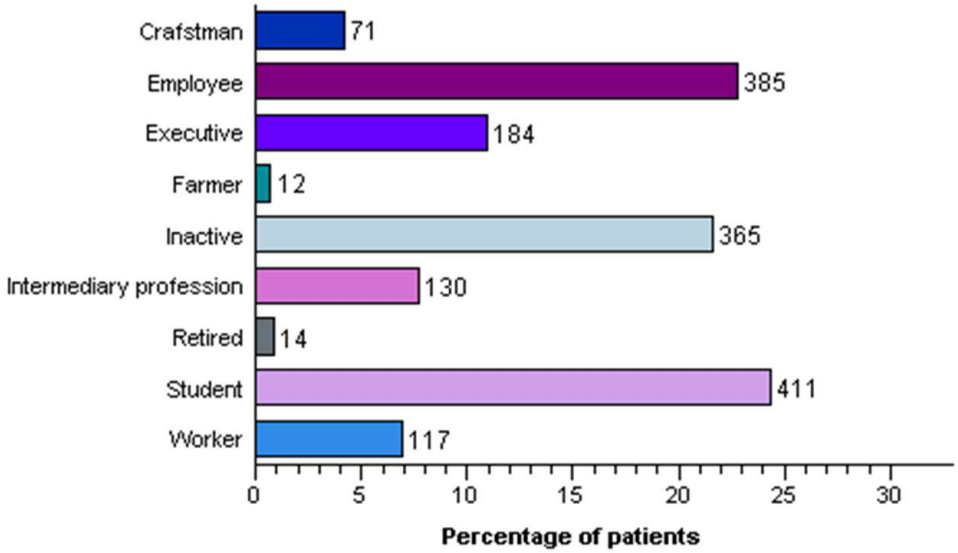
12. Social data

Employment

Figure 12.1. Employment of men ≥ 18 years

N = 1689 (number of men with a known employment situation, corresponding to 91.4 % of adults men).



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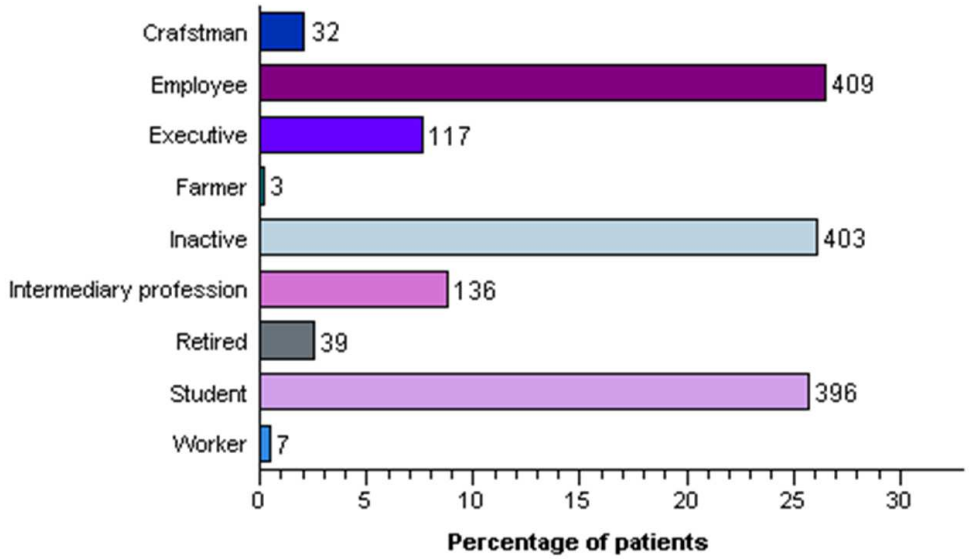
Among men aged 18 to 65, 48.8% are working.

Among men aged 18 to 25, 59.7% are studying.

Figure 12.2. Employment of women ≥ 18 years

N = 1542 (number of women with a known employment situation, corresponding to 92.4 % of adults women).



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Among women aged 18 to 65, 43.0% are working.

Among women aged 18 to 25, 60.7% are studying.

12. Social data

Marital status

Figure 12.3. Marital status of men ≥ 18 years

N = 1699 (number of men with a known marital status, corresponding to 91.9 % of adults men).

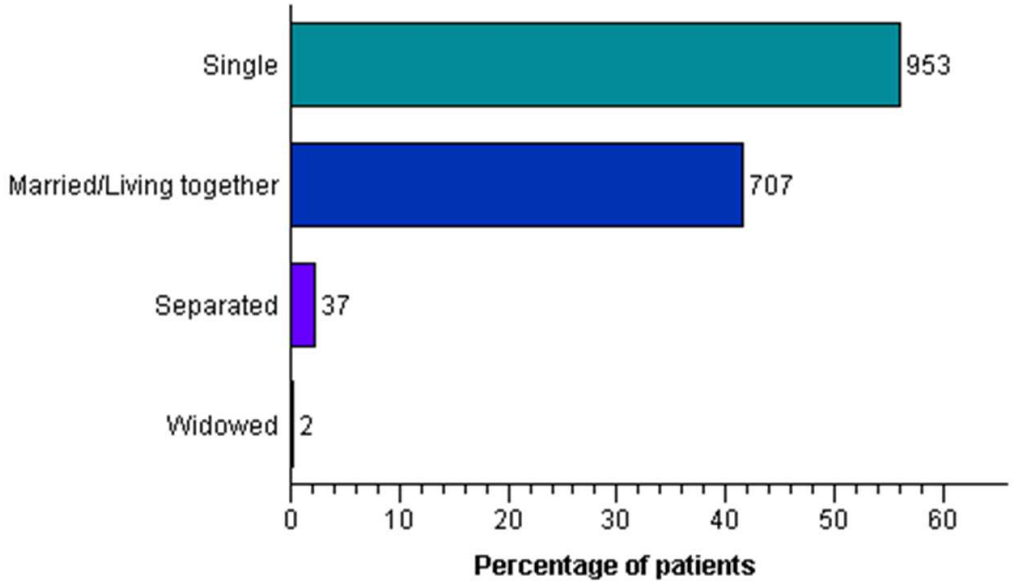

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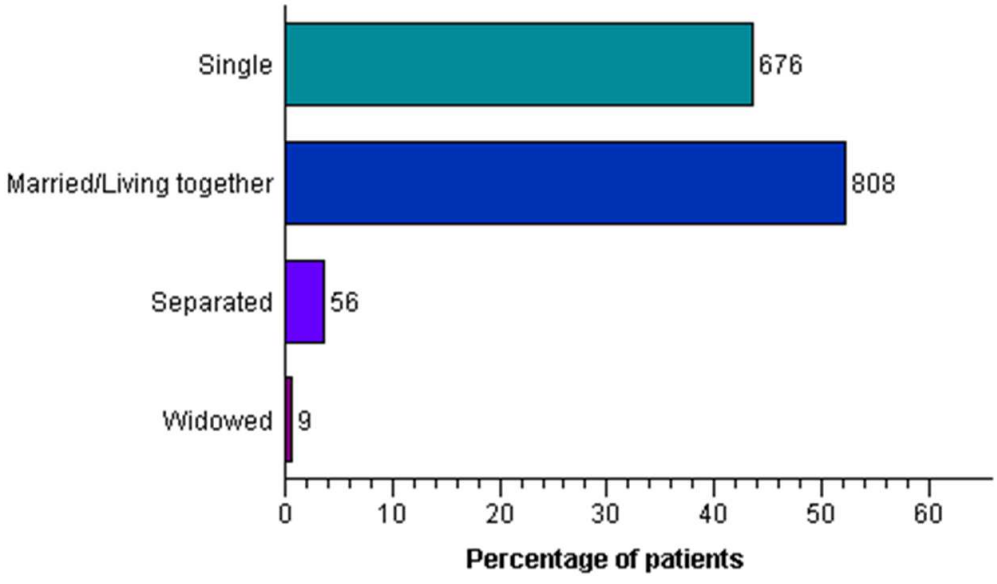
Figure 12.4. Marital status of women ≥ 18 years

N = 1549 (number of women with a known marital status, corresponding to 92.8 % of adults women).



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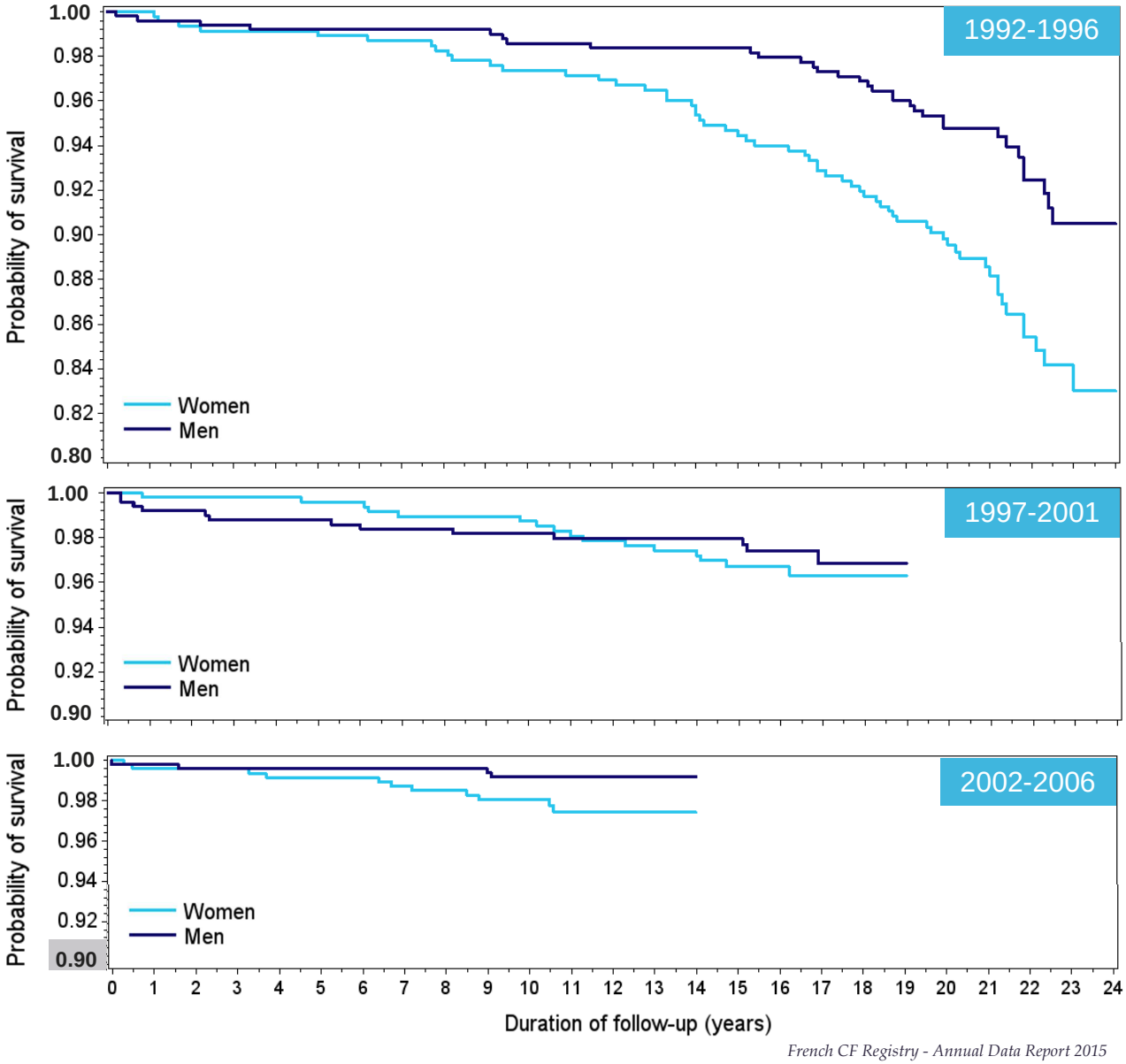
Annex 1

- Complement on survival analysis – stratification by sex

Figure A1.1. Survival curves by birth cohort and sex (Kaplan-Meier method)

Birth cohorts	Men		Women	
	Patients (N)	Deaths (N)	Patients (N)	Deaths (N)
1992-1996	505	32	466	59
1997-2001	500	13	485	16
2002-2006	525	4	489	11



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In the 1992-1996 cohort, women had a lower survival, from the age of 6 years compared with men gender group. This no longer appears in the 1997-2001 birth cohort, suggesting an improvement in the health status of women over time.

In the most recent cohort (2002-2006), a slight gender gap appears, but this cohort is followed for only 14 years.

Annex 2

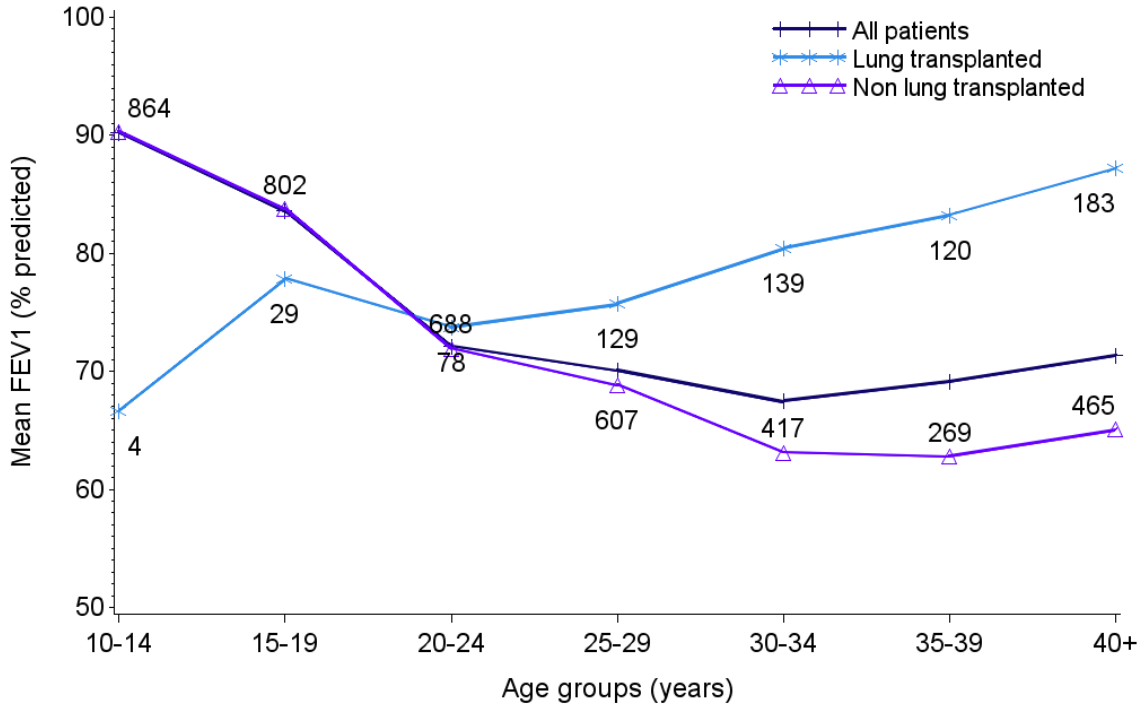
Spirometry and transplantation

This complementary analysis compares by age group the whole CF population to: 1) double lung or heart-lung transplant recipients and, 2) to non transplanted patients in terms of FEV_1(%).

The curves of the whole population and of non-transplanted patients are identical up to age 20-24, as the number of patients transplanted before 20 is low. Above 25 years, FEV_1 (%) of non-transplanted patients drops more sharply, with a difference of almost 5% at ages 35-39.

Among patients aged 35 or above, an upward trend is observed in all groups, suggesting a selection bias of patients with the mildest forms of CF at these ages. Among transplanted patients, the explanatory factors for this increase are probably different.

Figure A2.1. Mean FEV_1 (% predicted) and transplantation, by age group



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Curve « Lung transplant recipients »:

- The values below the curve represent the number of lung transplant recipients with a FEV1 value (eg: 78 patients in the 20-24 age group).
- No pulmonary transplantation has been reported in patients under 10.

Curve « Non lung transplant recipients »:

- The values above the curve represent the number of non lung transplant recipients with a FEV1 value (eg: 688 patients in the 20-24 age group).

Annex 3 (1/2)

Participating centres

Table A3.1. List of the participating CF care centres

CF care centres	Number of patients*
Paediatric CF care centres	
AMIENS Picardie CHU Sud	97
BORDEAUX Groupe Pellegrin Hôpital d'Enfants	148
GRENOBLE Hôpital de la Tronche Pédiatrie	117
LILLE Hôpital Jeanne de Flandres Pédiatrie	174
LYON Hôpital Mère-Enfant / Groupt Hosp. Est	292
MARSEILLE Hôpital La Timone Pédiatrie	129
NANCY Hôpital d'enfants	120
NANTES Hôpital Mère-Enfant	102
PARIS Hôpital Armand Trousseau	68
PARIS Hôpital Necker	211
PARIS Hôpital Robert Debré	168
RENNES-ST BRIEUC Pédiatrie	135
ST DENIS DE LA REUNION Hôpital d'Enfants	47
TOULOUSE Hôpital des Enfants	128
TOURS Hôpital de Clocheville Pédiatrie	122
VERSAILLES Hôpital Mignot Pédiatrie	70
Adults CF care centres	
BORDEAUX-PESSAC Groupe Sud Hospitalier	130
GRENOBLE Hopital de la Tronche Pneumologie	98
LILLE Hôpital Calmette Pneumologie	232
LYON SUD Centre Hospitalier	340
MARSEILLE CHU Nord	230
NANCY Hôpital de Brabois Pneumologie	89
NANTES Hôpital Laënnec	208
PARIS Hôpital Cochin	414
RENNES Hôpital Pontchaillou Pneumologie	103
SURESNES Hôpital Foch	428
TOULOUSE Hôpital Larrey Pneumologie	168
TOURS Hôpital Bretonneau Pneumologie	64
Paediatric and Adults CF care centres	
ANGERS - LE MANS	124
BESANCON	129
CAEN	95
CLERMONT FERRAND CHU d'Estaing Pédiatrie	110
CRETEIL Centre Hospitalier Intercommunal	119
DIJON Hôpital d'Enfants du Bocage	119
DUNKERQUE Centre Hospitalier	78
GIENS Hôpital Renée Sabran	220
LIMOGES Hôpital Mère/Enfant	62
MONTPELLIER Hôpital Arnaud de Villeneuve	205
NICE CHU Lenval-Hôpital Pasteur	111
REIMS American Memorial Hospital	129
ROSCOFF Centre de Perharidy	153
ROUEN	195
ST PIERRE DE LA REUNION Groupe Hosp. Sud	75
STRASBOURG	254
VANNES-LORIENT	83

Annex 3 (2/2)

Participating centres

Table A3.2. List of the participating centres (CF care centres excepted)

Centres	Number of patients*
Paediatric local centres	
BREST Hôpital Augustin Morvan	2
COLMAR CHG Louis Pasteur Pédiatrie	4
DAX Centre Hospitalier	10
LE HAVRE Hôpital Flaubert	24
MONTLUCON Centre Hospitalier	8
POINTE A PITRE CHU	5
Adults local centres	
MULHOUSE Centre Hospitalier Pneumologie	3
Paediatric and Adults local centres	
BRIVE Centre Hospitalier	5
LENS Centre Hospitalier	40
POITIERS Hôpital La Milétrie	36
ST NAZAIRE Centre Hospitalier	16
Other centres	
PARIS Hôp. Européen G.Pompidou	59

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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 2015 were excluded from those statistics.

Annex 4 (1/2)

Table A4.1. Summary of data

	2013	2014	2015
Patients seen during the year and centres participating to the registry			
- Patients registered* (N):	6235	6405	6585
- Patients seen during the year in a centre** (N):	6186	6354	6547
- Centres (N) :			
Paediatric CRCMs:	19	16	16
Adult CRCMs:	12	12	12
Paediatric and Adult CRCMs:	18	17	17
Other centres:	13	16	12
Demographics			
- Male patients (%):	51.8	51.7	52.1
- Age of patients, in years (mean):	20.2	20.8	21.3
- Age of patients, in years (median):	18.4	18.9	19.4
- Age of patients. in years (min-max):	0-83	0-83	0-83
- Patients aged 18 years and over (%):	51.2	52.5	53.7
- Age of patients, in years (mean):	50	52	40
- Age of patients, in years (median):	31.1	30.9	22.7
- Age of patients. in years (min-max):	28.4	28.8	30.6
- Deaths (N):	53	71	40
Including death of patients not seen during the year:	11	13	6
- Crude death rate (for 1 000):	8.6	11.3	6.2
- Age at death, in years (mean):	34	29	34
- Age at death, in years (median):	31	27	31
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	2.5	2.3	2.2
- New patients diagnosed during the year (N):	156	185	226
Including by neonatal screening:	84	124	136
- Age at diagnosis of the new patients, in years (median):	1.7	1.3	1.3
- Age at diagnosis of the new patients, in years (min-max):	0-72	0-77	0-66
- Full genotypes identified (%):	96.5	96.2	96.2
F508del / F508del:	42.8	42.5	41.9
F508del / Other:	40	39.8	40
Other / Other:	13.8	13.9	14.3
F508del / Missing:	1.4	1.5	1.4
Other / Missing:	0.9	1.1	1.1
Missing / Missing:	1.2	1.2	1.4
Anthropometry			
- Height z-score, patients aged 17 years and less (mean):	-0.04	-0.03	-0.01
- Height z-score, patients aged 18 years and over (mean):	-0.51	-0.51	-0.49
- Weight z-score, patients aged 17 years and less (mean):	-0.24	-0.24	-0.23
- Weight z-score, patients aged 18 years and over (mean):	-0.31	-0.23	-0.20

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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.

Annex 4 (2/2)

Table A4.1. Summary of data

	2013	2014	2015
Spirometry			
- FEV_1 (% predicted) - Knudson, patients aged 17 years and less (mean):	90.4	90.8	90.9
- FEV_1 (% predicted) - Knudson, patients aged 18 years and over (mean):	69.5	70.1	71.1
Microbiology			
- Patients with at least one sputum during the year (%):	90.6	88.8	88.1
H. influenzae:	23.0	20.3	18.9
MSSA:	55.9	55.3	54.2
MRSA:	7.8	7.7	7.8
P. aeruginosa:	40.3	41.6	39.0
S. maltophilia:	10.7	10.2	10.3
B. cepacia:	1.8	1.9	1.8
Aspergillus:	23.5	24.6	22.2
Complications and transplantations			
- Aspergillus (%) :	10.0	10.2	9.6
- Abnormal exocrine pancreatic function (%) :	82.8	83.2	80.6
- Treated gastro-oesophageal reflux (%) :	16.1	16.6	17.7
- Bone disease (%) :	4.5	5.6	5.9
- Haemoptysis (%):	4.4	5.0	4.8
- Cirrhosis / portal hypertension (%):	4.2	4.3	4.0
- Insulin-dependent and non insulin-dependant diabetes (%):	17.3	18.2	18.2
- Transplanted patients (N):	702	692	739
Including patients transplanted during the year:	106	89	88
- Patients on waiting list (N):	161	132	141
Including patients listed during the year:	71	66	96
Deaths on waiting list:	2	3	1
Therapeutic management			
- IV courses (%):	32.5	32.1	31.4
- Oxygenotherapy (%):	4.6	4.7	4.9
- Nasal ventilation (%):	3.3	3.7	3.8
- Azithromycin (%):	43.6	44.2	43.0
- Inhaled antibiotics (%):	39.0	40.7	35.0
- rhDNase (%):	47.3	48.9	44.6
- Inhaled bronchodilatators (%):	50.6	50.1	46.5
- Inhaled corticosteroids (%):	39.9	39.4	37.3
- Pancreatic enzymes (%):	83.0	82.9	81.9

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Annex 5

Table A5.1. Summary of data - Transplanted vs non transplanted patients

	Transplanted patients	Non transplanted patients	2015 data
- Patients seen during the year in a centre* (N):	736	5811	6547
Demographics			
- Age of patients, in years (mean):	34	19.6	21.3
- Age of patients, in years (median):	33.4	17.3	19.4
- Patients aged 18 years and over (%):	96.6	48.3	53.7
- Early pregnancies during the year (N):	2	38	40
- Deaths (N):	21	19	40
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	6.3	2.0	2.2
- Full genotypes identified (%):	96.1	96.2	96.2
F508del / F508del:	54.3	40.3	41.9
F508del / Other:	33.4	40.9	40
Other / Other:	8.3	15.0	14.3
F508del / Missing:	1.4	1.4	1.4
Other / Missing:	0.7	1.1	1.1
Missing / Missing:	1.9	1.3	1.4
Anthropometry and spirometry			
- Height z-score, patients aged 17 years and less (mean):	-1.74	0	-0.01
- Height z-score, patients aged 18 years and over (mean):	-0.71	-0.43	-0.49
- Weight z-score, patients aged 17 years and less (mean):	-1.85	-0.21	-0.23
- Weight z-score, patients aged 18 years and over (mean):	-0.7	-0.08	-0.2
- BMI z-score, patients aged 17 years and less (mean):	-0.76	-0.15	-0.15
- BMI, patients aged 18 years and over (mean):	20.0	21.4	21.1
Spirometry			
- FEV_1 (% predicted) - Knudson, patients aged 17 years and less (mean):	76.8	91.1	90.9
- FEV_1 (% predicted) - Knudson, patients aged 18 years and over (mean):	80.0	68.9	71.1
Complications			
- Treated aspergillosis (%)	7.3	9.9	9.6
- Abnormal exocrine pancreatic function (%) :	86.0	80.0	80.6
- Treated gastro-oesophageal reflux disease (%) :	40.4	14.9	17.7
- Bone disease (%) :	19.6	4.2	5.9
- Haemoptysis (%):	1.8	5.2	4.8
- Cirrhosis / portal hypertension (%):	3.7	4.0	4.0
- Insulin-dependent and non insulin-dependant diabetes (%):	61.1	12.8	18.2
Therapeutic management			
- Pancreatic enzymes (%) :	94.8	80.2	81.9
- Oral steroids (%) :	77.6	8.8	16.5

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** The difference between the number of transplanted patients page 34 (739) and the number of patients shown in this table (736) are the patients who died and were not seen in 2015.*

FRENCH CYSTIC FIBROSIS

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