FRENCH CYSTIC FIBROSIS REGISTRY

ANNUAL DATA REPORT 2018

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VAINCRE LA MUCOVISCIDOSE

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Editorial

2018, a "picture" of patients that will make a milestone in the history of cystic fibrosis

This report appears at a time when the marketing authorization for Kaftrio® was issued by the European Medicines Agency concomitantly with the completion of the evaluation process by the French National Authority for Health. This triple therapy is expected by nearly 80% of people with cystic fibrosis. We can hope that the 2018 indicators will have nothing to do with the ones in 5 years, just like the 2008 data compared to 2018 data. This is why this report mentions 2008 data for some main indicators.

In 2018, 18.7% of CF patients have been prescribed a CFTR modulator. Nearly 1,200 patients aged 12 and over were on Orkambi® and its effects could be evaluated in real life thanks to the study conducted by Prof. Pierre-Régis Burgel (AJRCCM, 2020) in collaboration with the Registry. With access to Orkambi® finally made possible for children under 12 at the end of 2019, other studies are underway with Prof. Isabelle Sermet in close collaboration with the Registry team.

The Register, a mine of information serving the Muco-CFTR community

The French Cystic Fibrosis Registry is managed by Vaincre la Mucoviscidose, a patient organization that for 55 years has tirelessly pursued its fight to overcome cystic fibrosis. Without the dedication of the 47 CF centers, the Registry would not exist. We would like to thank them for their immense work which has made the Registry a true "mine" for the Muco-CFTR community of researchers and clinicians. Many studies are carried out using the Registry data, thus enabling the exploration of new therapeutic options. There are still many to discover. Vaincre la Mucoviscidose encourages the entire scientific and medical community to promote the Registry and use it.

Several major studies currently underway closely associate the Registry. Prof. Harriet Corvol who from the start of the Covid-19 epidemic launched a cohort study evaluating the clinical expression of coronavirus infection and risk factors of severe forms in patients with cystic fibrosis. There is also the study by Prof. Isabelle Durieu on the healthcare expenditure for patients with cystic fibrosis carried out by linking the Registry data with the Health Insurance's. These studies are a great source of information on patient care.

In 2020, a strategic committee was set up to bring together the community people and anticipate major developments in the coming years for the Registry.

The main lessons from the 2018 data: the trends of the previous year are confirmed

The number of patients registered in the Registry is 7,180, an increase of 1.5% *, mainly due to the increase in the adult population currently of 4,060 (+ 5%). Adults thus represent 57.4% of the total patient population (+ 1.6% compared to 2017). The increase in the proportion of adults can be explained by the improvement in care but also by the decrease in the number of children since 2012-2013 (- 3%).

A young population that continues to grow older, and that's good news! The mean age in 2018 was 22.5 years, an average increase of 6 months per year since 2008. When superimposing the 2008 and 2018 age pyramids, the observation is clear: the top is thickening, CF population is aging. The annual number of deaths is relatively stable, 56 in 2018, a figure that is still too high. However, this year the median age is falling: 31.3 years in 2018 against 33.8 years in 2017.

* erratum : see annual report 2017

Editorial

Patients health is stabilizing but remains precarious. From 2008 to 2018, the median FEV1 increased by an average of 11.7%. This increase is more significant for the older age group categories (+ 8.4% for 5-19 year old and + 15.1% for 20 years and over; + 16.3% for 40 and over). With regard to infections with respiratory germs, the trend is towards stabilization, as with respiratory, hepatic and digestive pathologies, IV antibiotic cures and hospitalizations.

A social life that pursues its quest for the ordinary. While almost all children have access to regular schooling for several years, the rate of adult patients with a professional activity is increasing: 47.6% for men (compared to 46.5% in 2017) and 40.2% for women (against 39.1% in 2017). Half of them live as a couple (52%).

Organ transplantation continues to decline. The 886 transplant recipients (+ 2.4% compared to 2017) represent more than 12% of all patients. A decrease of 22% is observed in the number of transplanted patients in 2018 (76) compared to 2017. This confirms the previously observed trend of a decrease of transplantations since 2013. The average age at transplant has fallen by one year: 31.5 years. The average age of transplant recipients is stable (35.8 years) and is slightly higher than the overall CF population.

It is difficult to convey in a few words all the information contained in the Registry. Registry data publication is also an opportunity for the centers to situate themselves in relation to the national data and to question themselves about possible differences. With the sole objective of improving the health of all patients.

Enjoy Your Reading!

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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, called *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) 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 2,000 mutations have been identified, the most common (about 80% of patients) being F508del.

Before implementation of the systematic newborn screening program, the most common context for diagnosis was as follows: clinical symptoms (meconium ileus, steatorrhoea, bronchial obstruction, recurrent respiratory infections), confirmed by an elevated sweat chloride ions concentration. This would be followed by molecular analysis of the *CFTR* gene and identification of the disease causing mutations.

Newborn screening has been systematic in France and the French overseas territories since 2002. 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 then 29 up to 01/01/2015). 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.

In CF, 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
- 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 institutional partners in strategic decisions
- helping research by facilitating pre-selection of patients eligible for clinical trials
- evaluating the impact of therapeutics and 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. This initiative was approved in July 2006 by the Committee for Protection of Personal Data in Medical Research and in March 2007 by the Data Protection Agency. At the end of 2008 and then in 2011 and 2015, the registry was certified by the National Committee of Rare Disease Registries.

Population and data

The population is composed of people with cystic fibrosis followed in the French CF care centres (metropolitan France, Reunion Island and Guadeloupe). Data are collected once a year by means of an e-CRF, paper questionnaire or export from electronic medical records. They refer to the previous year and include semi-anonymous patient identification, diagnosis, medical follow-up, treatments, anthropometry, respiratory function, microbiology, evolution of the condition and social and family situation. Thematic questionnaires collect data on pregnancies, *Burkholderia Cepacia* complex and related, and inclusion in clinical trials.

Data use

Statistical analysis is performed on anonymized data. Unless otherwise indicated, the results presented hereafter relate to the population seen during the year 2018.

Data from different centers are now entered in one file per patient, thus allowing better data exhaustiveness and quality.

Missing data were considered an absence of event, some percentages can therefore be underestimated.

Data analysis

Ad hoc studies on various themes are conducted on the Registry data. Some are the subject of publications and communications at international congresses.

The French Registry sends anonymised data to the European Cystic Fibrosis Patient Registry in order to allow a wider use of the data along with other countries. Comparisons between indicators from national registries must be made with caution due to numerous biases linked in particular to the impact of neonatal screening, transplantation, socio-economic status but also to compliance with the measurement guidelines, population references and statistical limits, in particular in the event of an insufficient number of patients in an age group.

1. Demographics

Characteristics of the population

Figure 1.1. Evolution of the number of patients since 1992

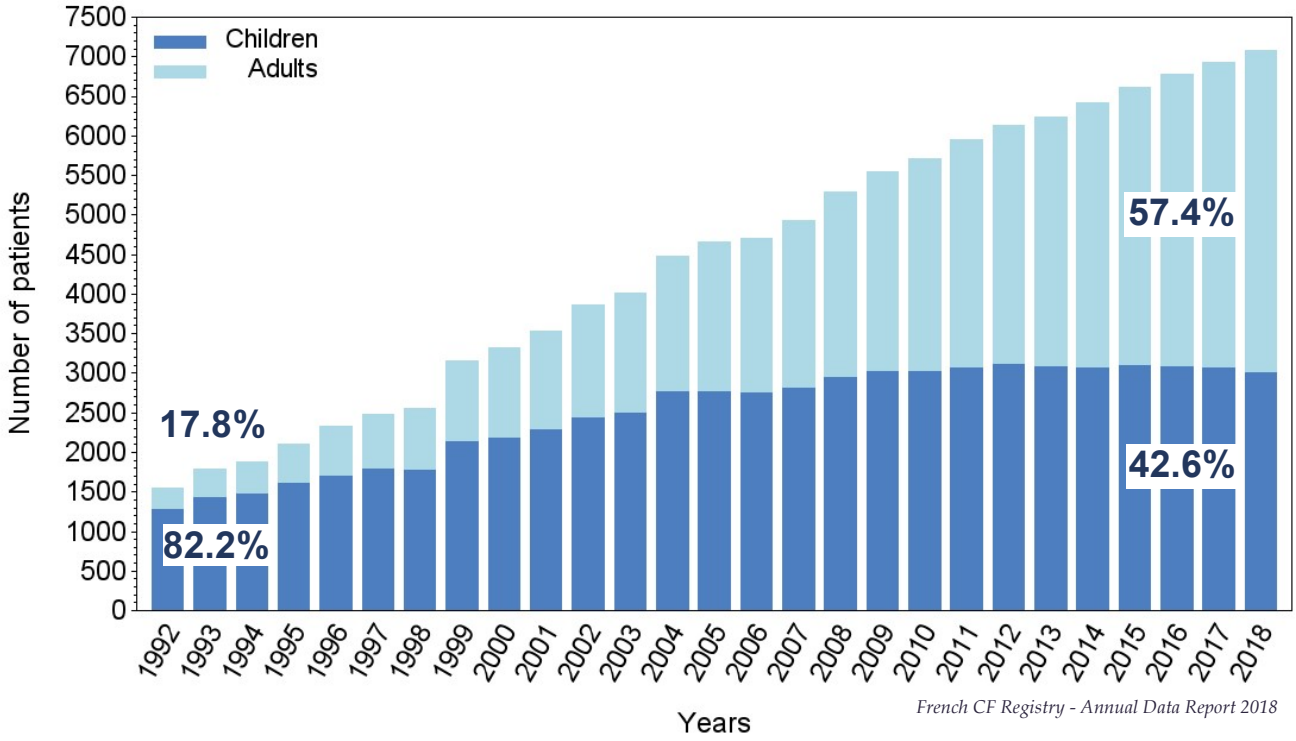

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Table 1.1. Annual evolution of the main indicators

	Years of follow-up										
Indicators	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
All patients*	5308	5569	5714	5968	6139	6250	6427	6630	6786	7076	7180
Patients seen during the	5297	5550	5705	5956	6127	6239	6413	6620	6779	6933	7072
Children	2946	3016	3018	3068	3108	3084	3069	3096	3079	3062	3012 (42.6 %)
Adults	2351	2534	2687	2888	3019	3155	3344	3524	3700	3871	4060 (57.4 %)
Over 40 years	250	309	338	398	452	508	585	667	757	824	910 (12.9 %)
Men	2764	2889	2940	3085	3167	3223	3314	3442	3547	3615	3680 (52.0 %)
Women	2533	2661	2765	2871	2960	3016	3099	3178	3232	3318	3392 (48.0 %)
Mean age (years)	17.6	18.1	18.5	19	19.5	20.1	20.7	21.1	21.8	22.3	22.9
Median age (years)	16.2	16.5	16.9	17.4	17.8	18.2	18.9	19.3	19.9	20.3	20.9
Minimum age (years)	0	0	0.1	0	0.1	0.1	0	0	0.1	0.1	0.1
Maximum age (years)	76.8	77.8	80	88	86.8	82.5	82.8	83.2	84.1	85.1	86.1

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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 for survival.

This table is updated each year with the corrections made to previous year's data. Patients with unconfirmed or withdrawn diagnosis (N=20) were excluded from the analysis.
Due to incorrect entry, the 2017 data report initially published contained an error in the number of patients identified.

1. Demographics

Characteristics of the population

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

Characteristics	2016		2017		2018	
	Men	Women	Men	Women	**Men**	**Women**
Patients seen during the year	3547	3232	3615	3318	**3680**	**3392**
Children	1593	1486	1583	1479	**1540**	**1472**
Adults	1954	1746	2032	1839	**2140**	**1920**
Mean age (years)	21.8	21.8	22.2	22.3	**22.9**	**23**
Median age (years)	20.1	19.6	20.5	20.1	**21.3**	**20.5**

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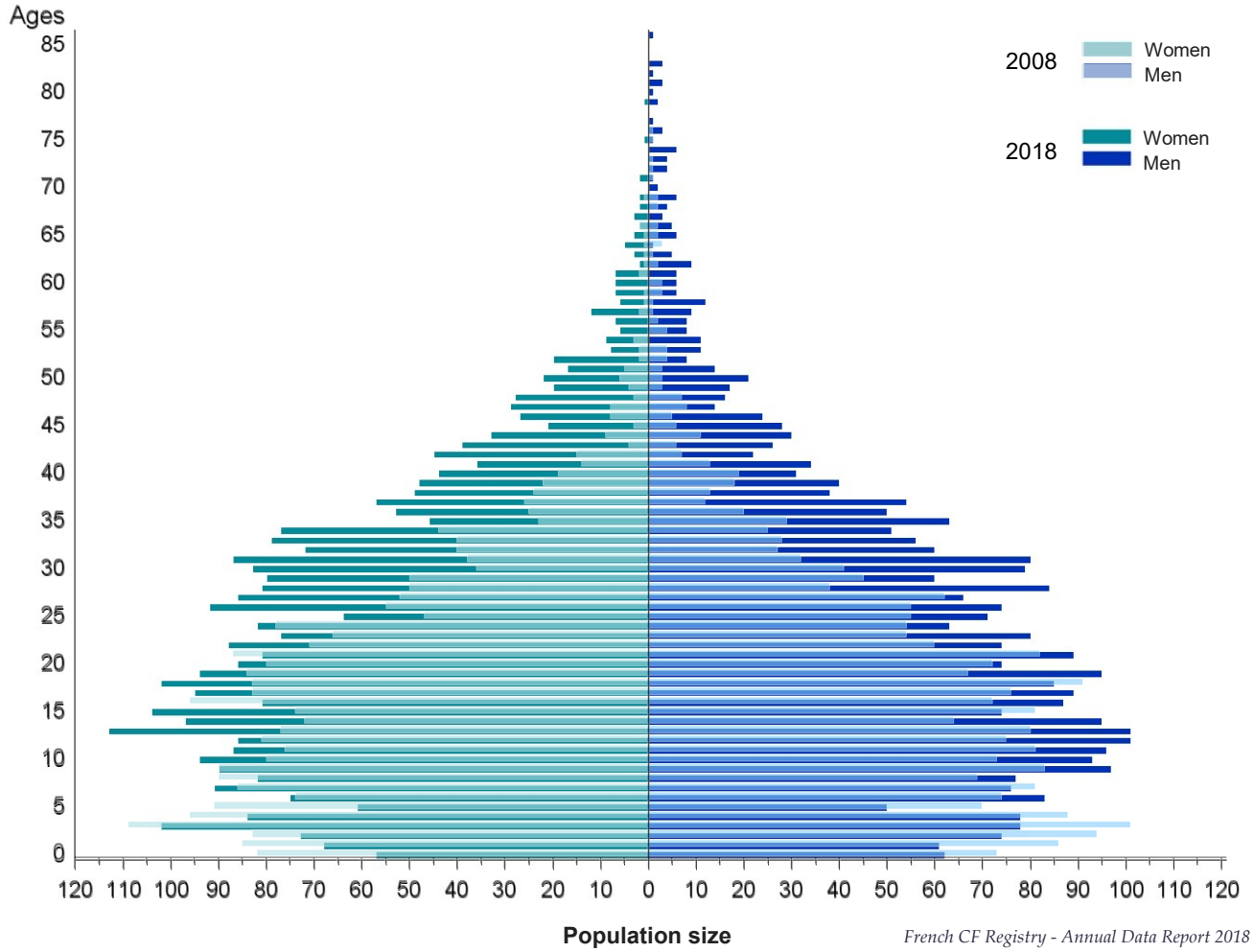
Figure 1.2. Population pyramid



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The short bar corresponding to children born in 2013 has been validated with the newborn screening program 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	17	2184	30.9	128	0.1	62.9	10.4	10.7	9.2
Adult	14	2824	39.9	202	17.4	83.9	34.2	31.8	14.0
Paediatric/Adult	16	1978	28.0	124	0.2	86.1	21	18.2	18.8
Subtotal	47	6986	98.8	149	0.1	86.1	23.0	21.0	20.9
Other centres									
Paediatric	2	15 (b)	0.2	7	2.6	18.4	10.1	9.0	9.7
Paediatric/Adult	1	36 (c)	0.5	36	5.3	18.6	11.2	10.9	6.4
Other Centres	1	35 (d)	0.5	35	17.4	50.2	29.1	28.8	14.0
Subtotal	4	86	1.2	21	2.6	50.2	18.3	16.1	15.4
Total	51	7072	100	139	0.1	86.1	22.9	20.9	20.9

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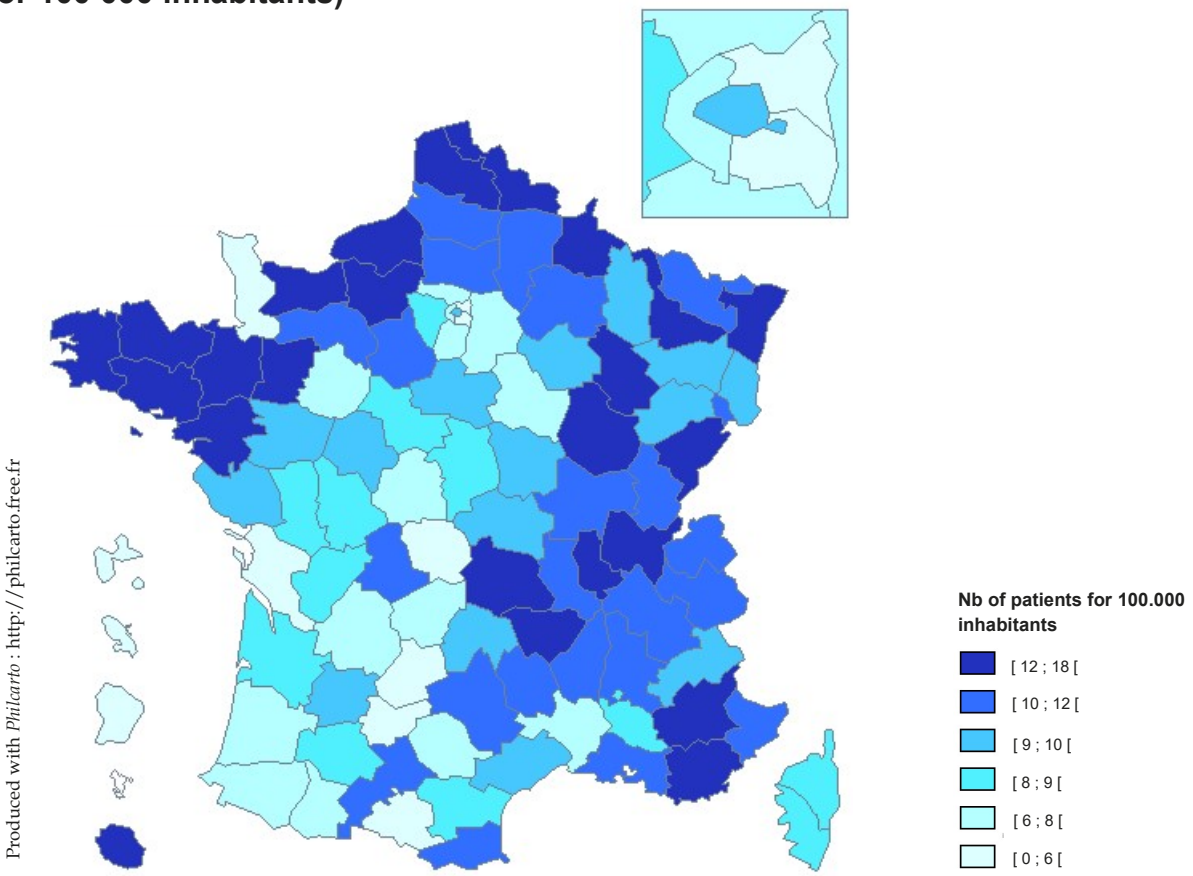
Notes : (a) Patients visiting at least 2 CF centres during the year were only counted in the one with the highest number of visits
(b) Including 3 patients also seen by a CF centre
(c) Including 6 patients also seen by a CF centre
(d) Including 7 patients also seen by a CF centre

* Cases when a child's follow up is made by an adult centre or 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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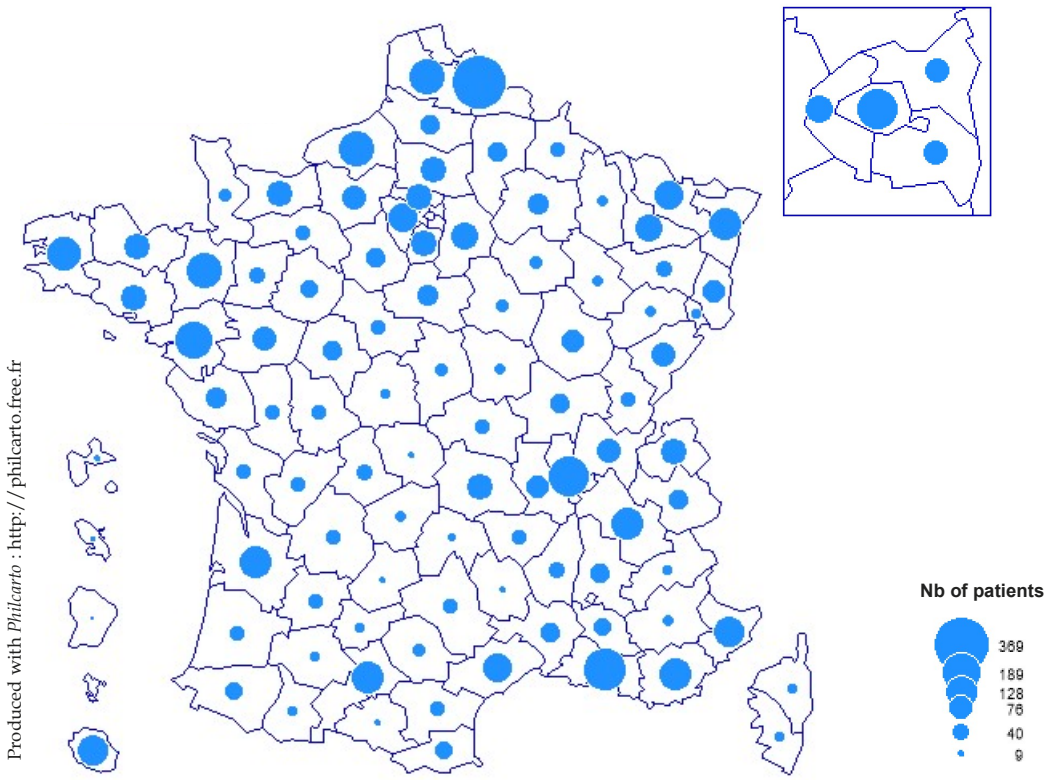
Map 1.2. Localisation of the patients by « département » of residence (absolute numbers)



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2. Mortality

Characteristics

Figure 2.1. Annual number of deaths since 1992

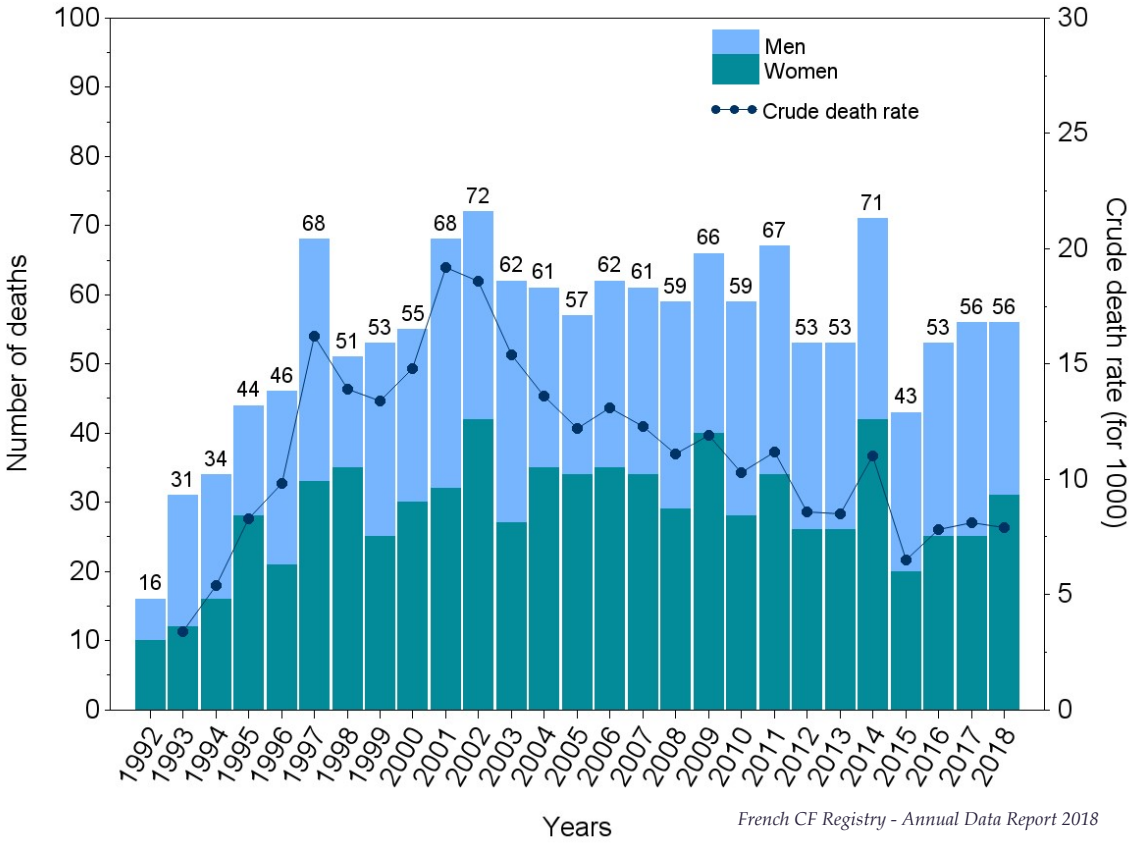

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Table 2.1. Mortality characteristics

Indicators	Years of follow-up										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of deaths	59	66	59	67	53	53	71	43	53	56	56*
- including transplanted patients	27	34	32	33	27	29	41	22	37	33	35
Crude death rate (per 1000)	11.1	11.9	10.3	11.2	8.6	8.5	11.0	6.5	7.8	8.1	7.9
Mean age (years)	29.1	25.1	29.3	26.4	32.3	34.4	29.0	34.1	31.9	35.0	33.7
Median age (years)	27.9	24.0	27.6	24.9	27.8	30.7	27.1	31.8	28.0	33.8	31.3
Minimum age (years)	0.1	0.4	0.2	1.9	2.2	1.1	0.1	9.0	1.6	5.9	7.3
Maximum age (years)	66.1	73.4	68.9	55.5	88.4	82.5	71.2	83.2	76.0	74.3	80.9

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* 8 out of the 56 were not seen by a CF center in 2018.

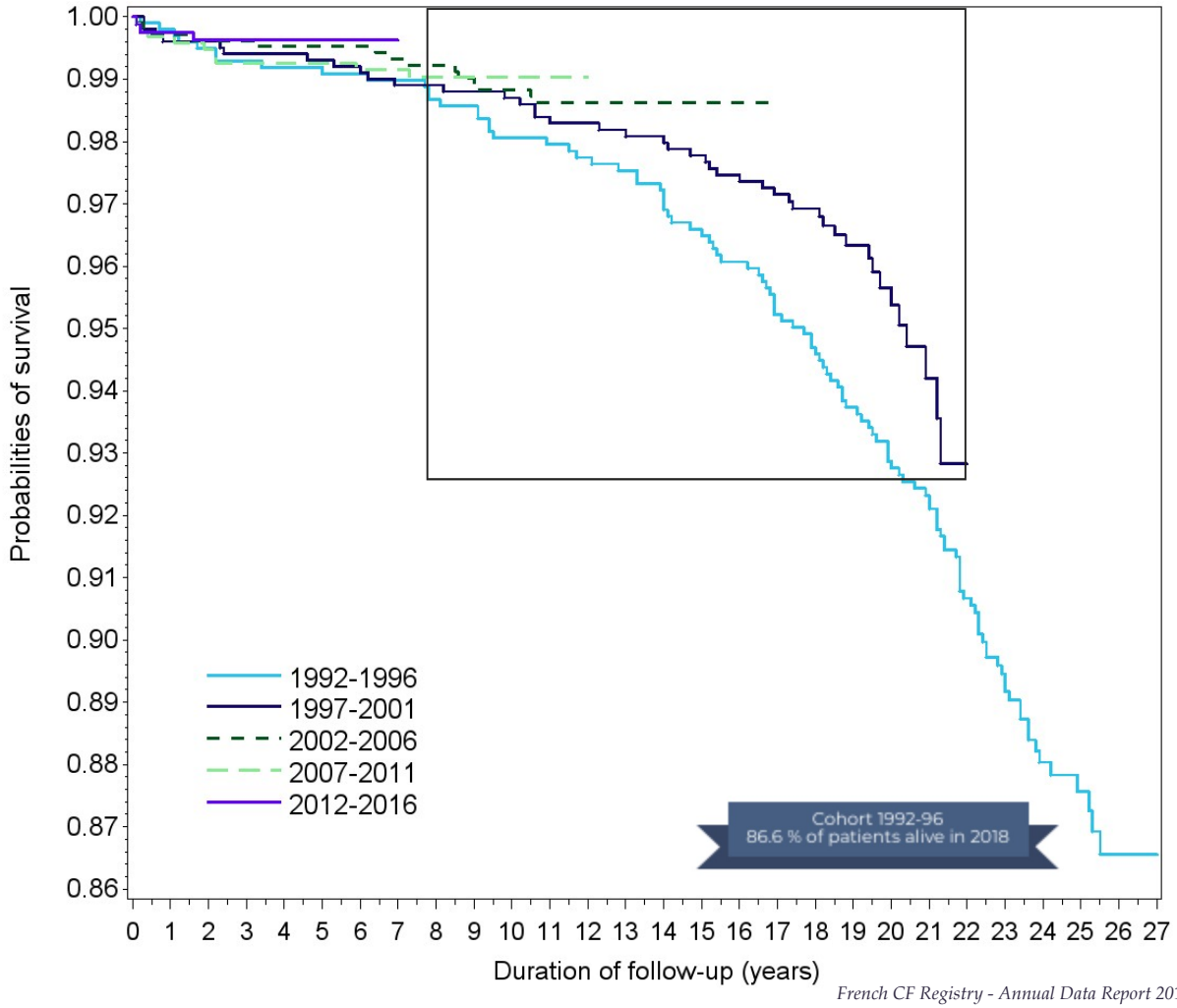
2. Mortality

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 5 birth cohorts; the numbers of patients and of deaths are:

- Births from 1992 to 1996 (in 2018 this cohort was followed during 27 years maximum): 984 patients, 112 deaths
- Births from 1997 to 2001 (maximum 22 years of follow up): 1008 patients, 43 deaths
- Births from 2002 to 2006 (maximum 17 years of follow up): 1054 patients, 15 deaths
- Births from 2007 to 2011 (maximum 12 years of follow up): 953 patients, 9 deaths
- Births from 2012 to 2016 (maximum 7 years of follow up): 800 patients, 3 deaths



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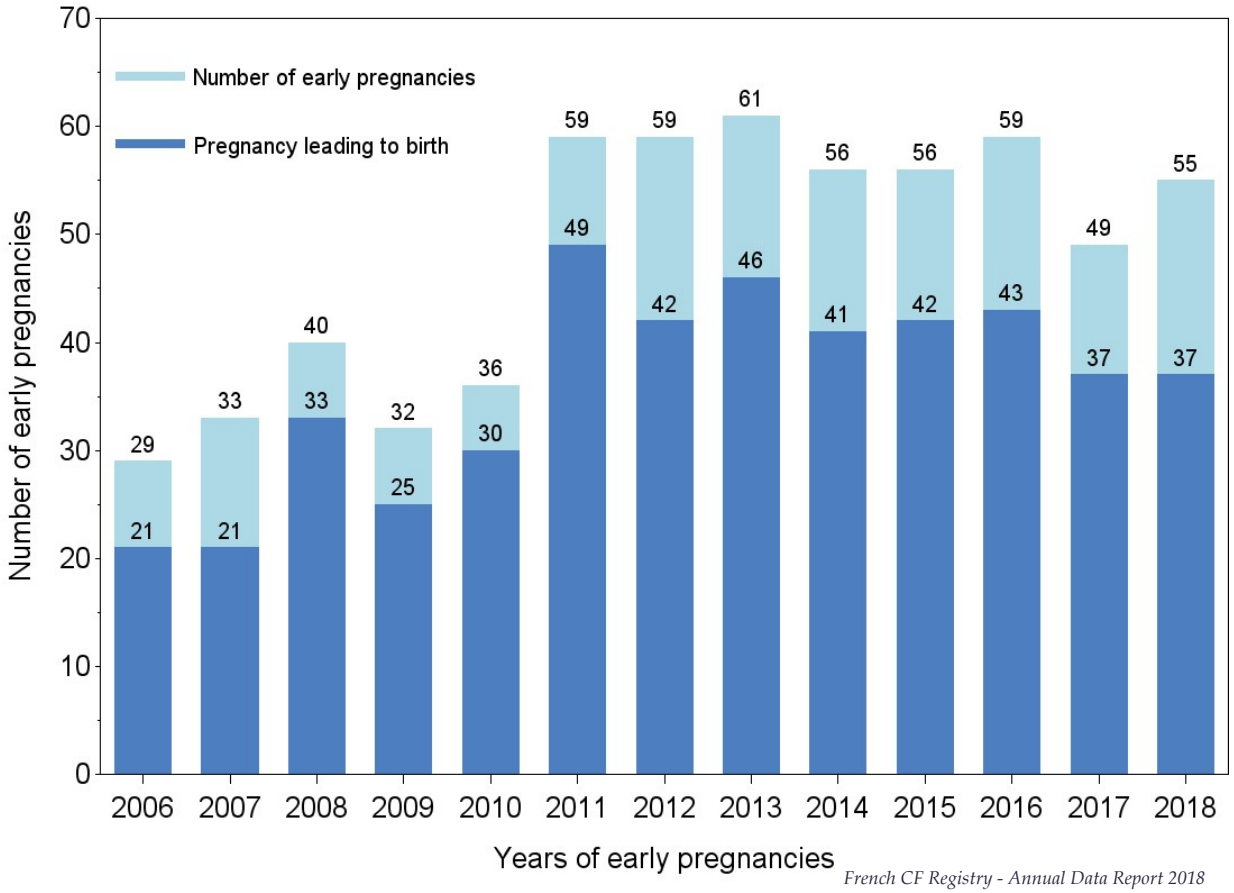
Until the age of 8, there is no difference in survival between the different birth cohorts.

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 = 4.09, p = 0.04).

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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Of the 55 early pregnancies in 2018, 37 resulted in a birth (in 2018 or 2019).

Table 3.1. Early pregnancy characteristics

Characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Number of early pregnancies	29	33	40	32	36	59	59	61	56	56	59	49	55
Pregnancy rates in women aged 15 to 49 years (for 1000)	26.1	28.5	32.4	24.2	25.9	40.1	38.2	37.8	33.1	31.6	32.2	25.9	28.4
Mean age at 31st December of the year of early pregancy	27.2	27	26.7	27.5	28.8	28.4	28.3	28.5	28.6	30.9	28.2	29.9	30.1
Number of lung transplanted women starting a pregnancy	1	2	1	3	3	3	7	4	1	3	4	4	9

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3. Pregnancy – Paternity

Table 3.2. Paternities

Characteristics	N	Proportion (%)
Number of paternities, including:	36	
- Natural father	3	8.3
- Medically assisted reproduction, including:	28	77.8
+ Intracytoplasmic Sperm Injection / in vitro fertilization	24	85.7
+ Artificial insemination with sperm donor	1	3.6

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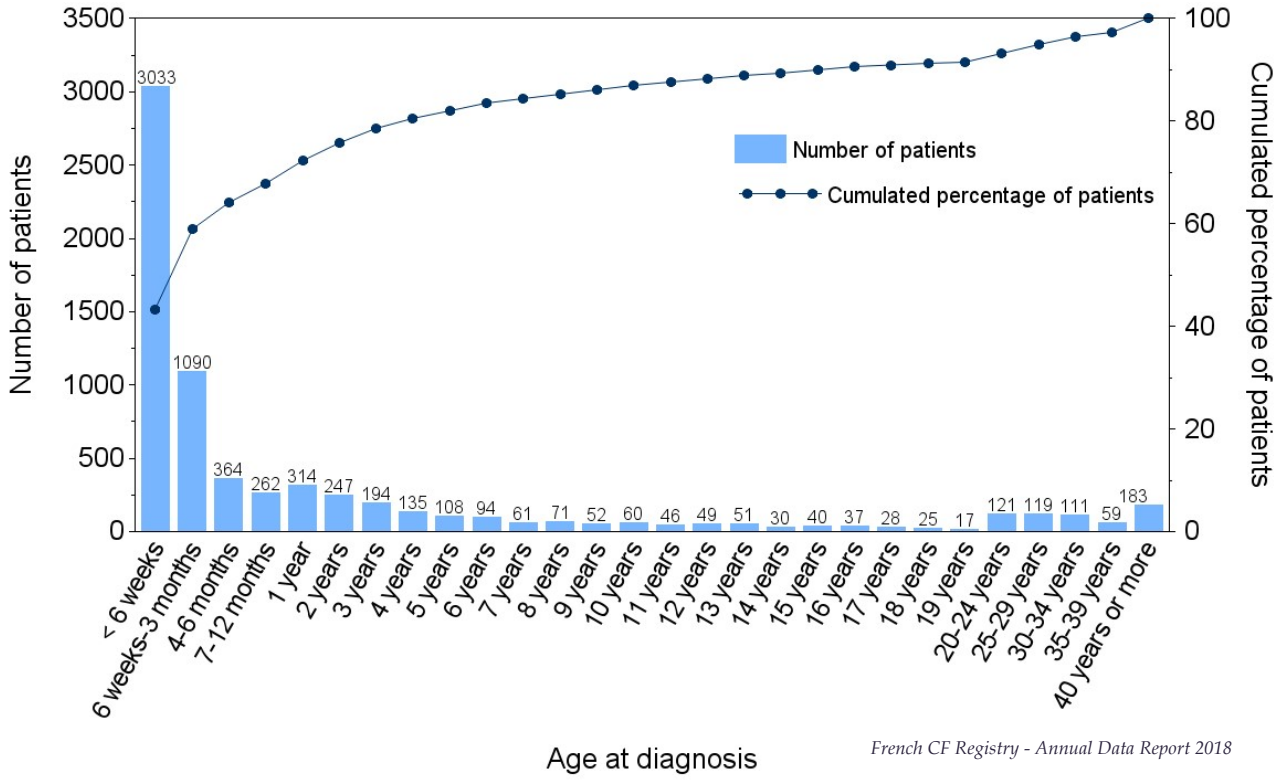
Note: precision on paternity was missing for 5 patients.

4. Diagnosis

Main characteristics

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

N = 7001 (number of patients whose age at diagnosis is known).



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4. Diagnosis

Main characteristics

Table 4.1. Diagnosis characteristics

Characteristics	**2018**
ALL PATIENTS	
Patients whose age at diagnosis is known - N (%) *	7001 (99 %)
Age at diagnosis	
- Median age (months)	2.0
- Mean age (years)	4.7
- Minimum age (years)	0
- Maximum age (years)	81
NEW PATIENTS DIAGNOSED DURING THE YEAR	
Number of patients	
New patients - N (%)	172 (2.4 %)
- Including 2016 newborn patients - N	119
Age at diagnosis	
- Median age (months)	1.1
- Mean age (years)	6.8
- Minimum age (years)	0
- Maximum age (years)	81
Context of diagnosis	
1. Screened positive newborns (NBS)	**129**
- including Prenatal diagnosis - N (%)	9 (7.0 %)
- including Meconium ileus - N (%)	12 (9.3 %)
2. Diagnosis on symptoms (NBS excluded)	**43**
- including Meconium ileus - N (%)	2 (4.7 %)
- including Symptoms (other than MI):- N (%)	41 (95.3 %)
- Mean age at diagnosis (years)	26.2

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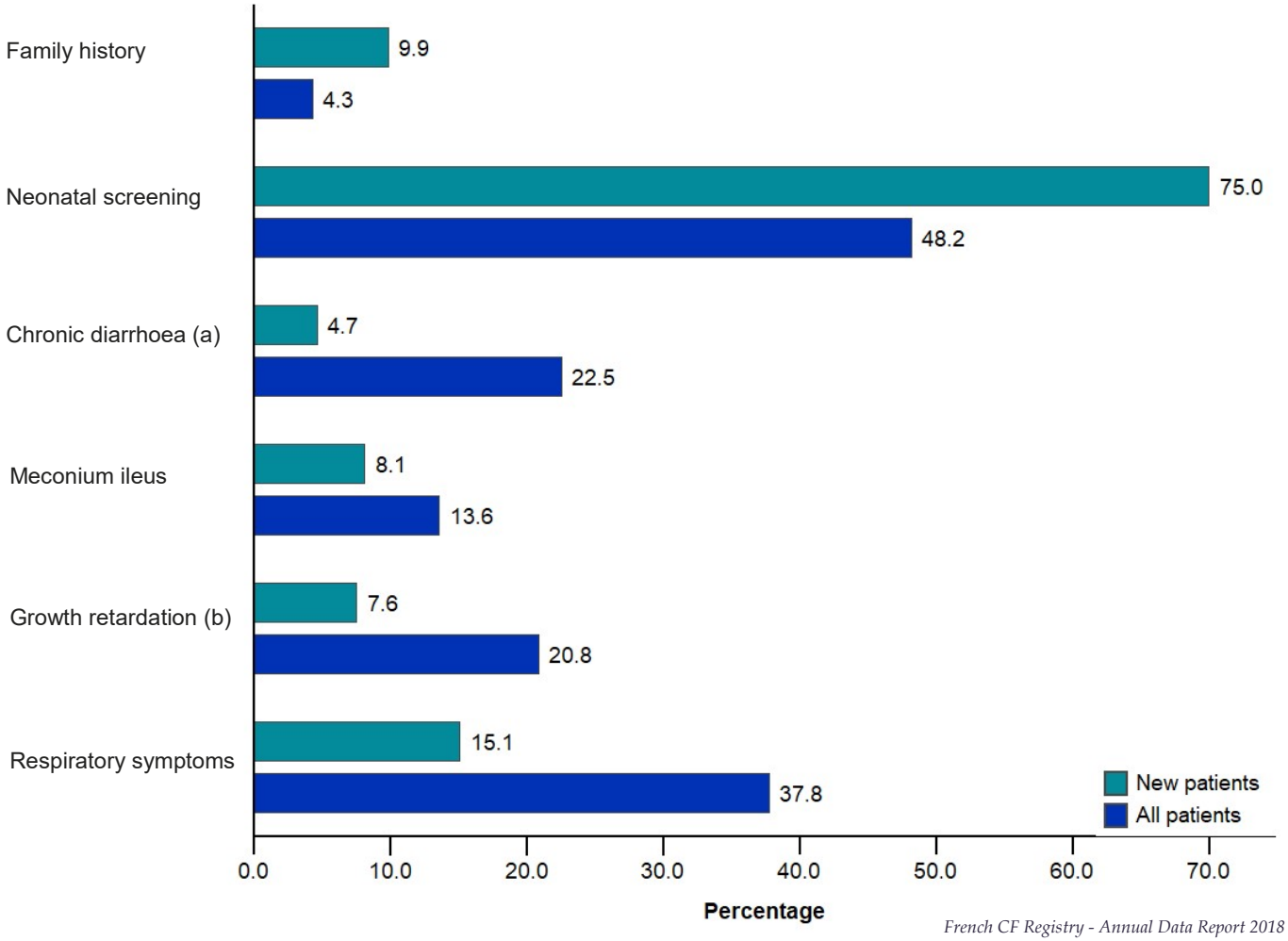
Among the 172 new patients, 119 were born in 2018. The method used to compile this report (patients seen in a care centre in 2018) means that infants born in 2018 and seen for the first time in 2019 are not included yet. For information purposes only, 12 newborns in 2017 were diagnosed in 2018 through neonatal screening. In the 2017 age pyramide, the number of patients aged 0 was 111 and should have been 111+12=123.

The number of patients diagnosed by neonatal screening (129) given in this report is not the actual number for France during the year, but represents the patients for whom screening resulted in diagnosis. It excludes patients for whom the diagnosis was made before the result of screening.

4. Diagnosis

Diagnosis signs

Figure 4.2. Diagnosis signs (most frequent ones)



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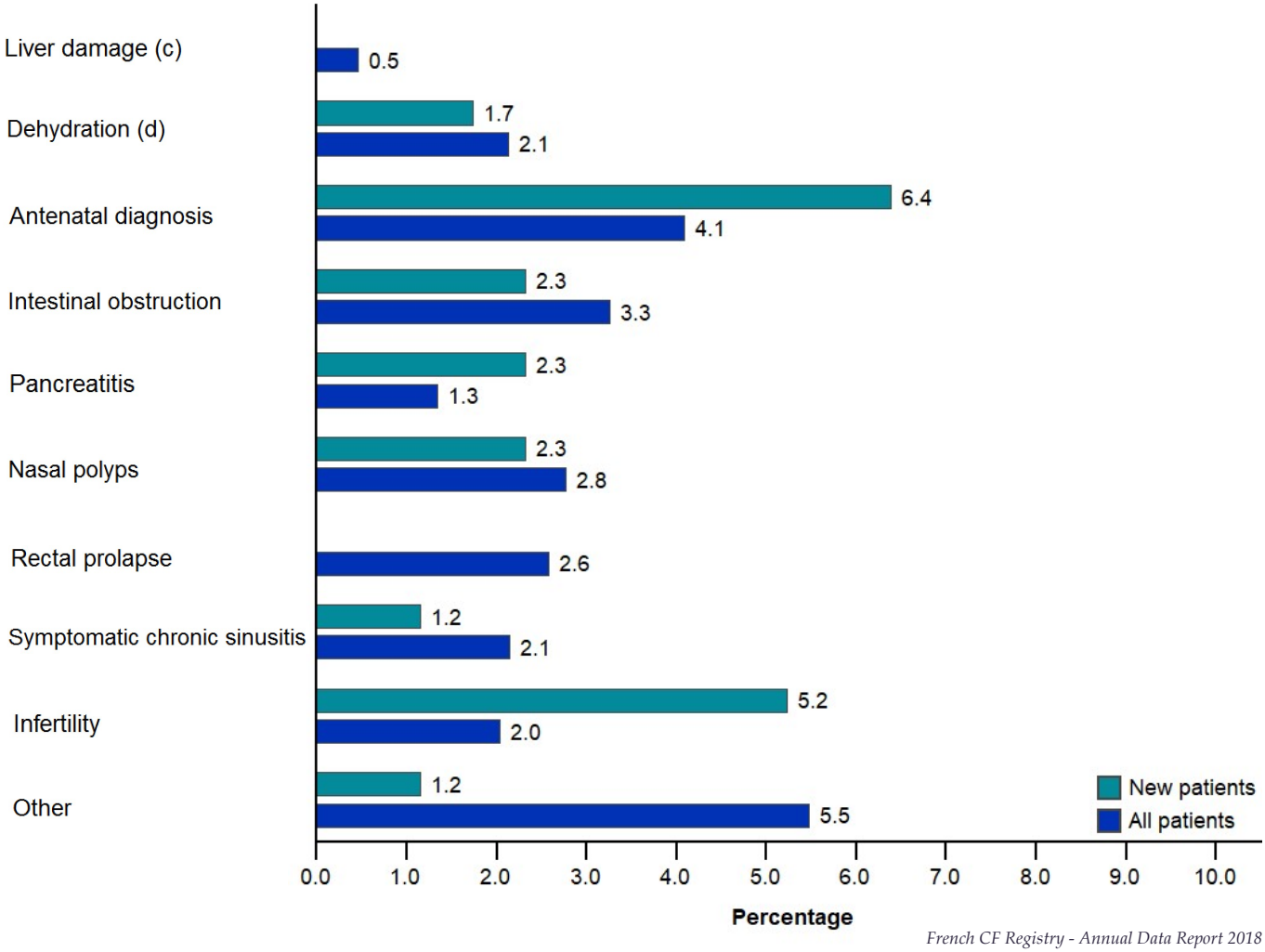
(a) Chronic diarrhoea / Steatorrhoea / Malabsorption
(b) Growth retardation / Malnutrition

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	5865	82.9
G542X	393	5.6
N1303K	296	4.2
2789+5G>A	184	2.6
R117H	152	2.1
1717-1G>A	149	2.1
R553X	129	1.8
G551D	122	1.7
W1282X	104	1.5
L206W	102	1.4
3849+10kbC>T	99	1.4
I507del	83	1.2
3272-26A>G	82	1.2
Y122X	80	1.1
711+1G>T	79	1.1
D1152H	78	1.1
2183AA>G	71	1.0
R347P	71	1.0
R1162X	60	0.8
3120+1G>A	59	0.8
G85E	53	0.7
R334W	53	0.7
Y1092X	51	0.7
A455E	49	0.7
3659delC	42	0.6
R347H	41	0.6
1078delT	40	0.6
S945L	40	0.6
1811+1.6kbA>G	37	0.5
394delTT	36	0.5
R1066C	33	0.5
W846X	32	0.5
E60X	31	0.4
621+1G>T	30	0.4
S1251N	27	0.4
1677delTA	24	0.3
L997F	21	0.3
4005+1G>A	19	0.3
E585X	19	0.3
Q220X	19	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	2898	41.0	21.7	20.7	64.1
F508del / Other	2927	41.4	23.2	20.6	83.9
Other/ Other	1084	15.3	23.3	20.1	86.1
Subtotal (non missing genotypes)	6909	97.7	22.6	20.6	86.1
F508del / Missing	40	0.6	40.7	38.5	83.6
Other/ Missing	52	0.7	36.9	35.2	77.5
Missing/ Missing	71	1.0	36.9	34.7	83.2
Subtotal (partial genotypes / missing)	163	2.3	37.8	35.8	83.6
Total	7072	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	202	2.9	24.3	21.3	68.0
At least one nonsense mutation	1109	15.7	21.4	19.2	76.8
At least one R117H mutation	152	2.1	19.1	14.1	83.0

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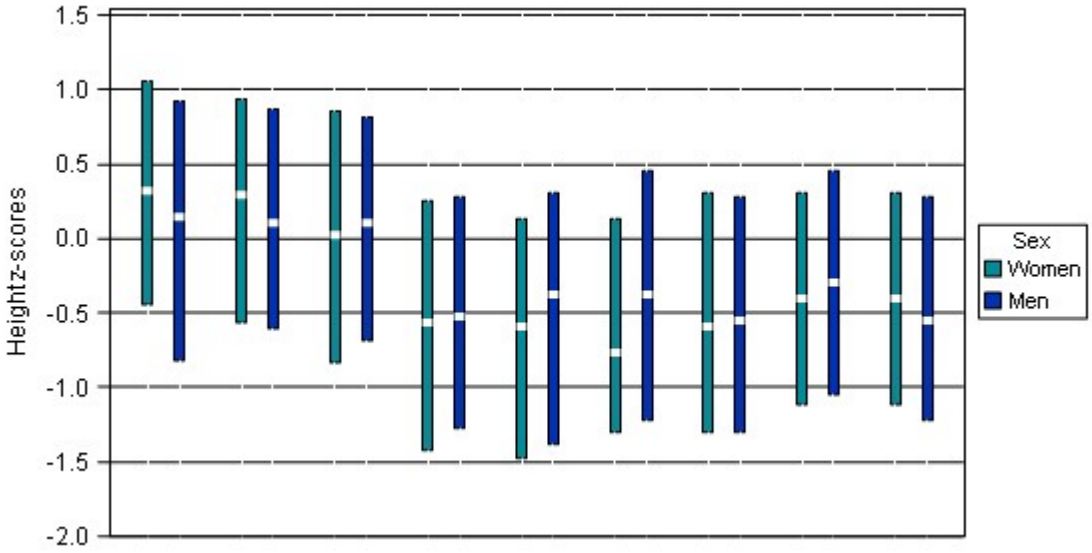
Gating mutations doesn't prevent the CFTR protein from reaching the cell membrane but alter choride transport.

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	0.30	0.19	0.05	-0.63	-0.68	-0.62	-0.50	-0.44	-0.42	-0.29
	Men	0.07	0.16	0.07	-0.48	-0.47	-0.45	-0.56	-0.32	-0.44	-0.27
Median height z-score	Women	0.32	0.30	0.03	-0.57	-0.59	-0.77	-0.59	-0.41	-0.41	-0.33
	Men	0.15	0.10	0.11	-0.52	-0.38	-0.38	-0.55	-0.30	-0.55	-0.28

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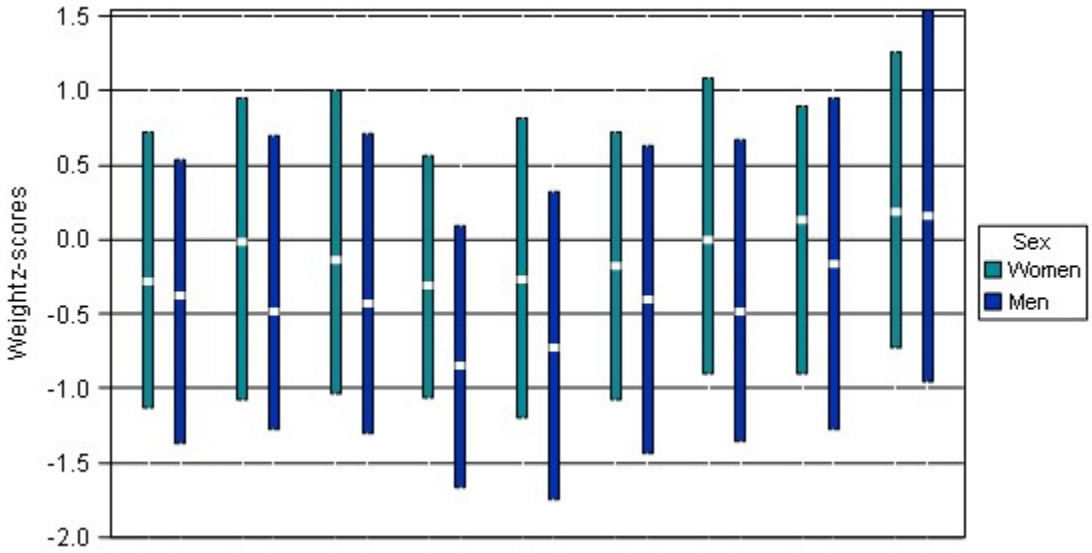
Figure 5.2. Weight z-scores*, by age group and sex



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	-0.15	0.06	0.06	-0.21	-0.18	-0.10	0.13	0.09	0.34	0.00
	Men	-0.36	-0.23	-0.28	-0.71	-0.55	-0.28	-0.26	-0.11	0.28	-0.29
Median weight z-score	Women	-0.28	-0.01	-0.13	-0.31	-0.27	-0.18	0.00	0.14	0.18	-0.13
	Men	-0.38	-0.49	-0.43	-0.85	-0.73	-0.40	-0.48	-0.16	0.16	-0.48

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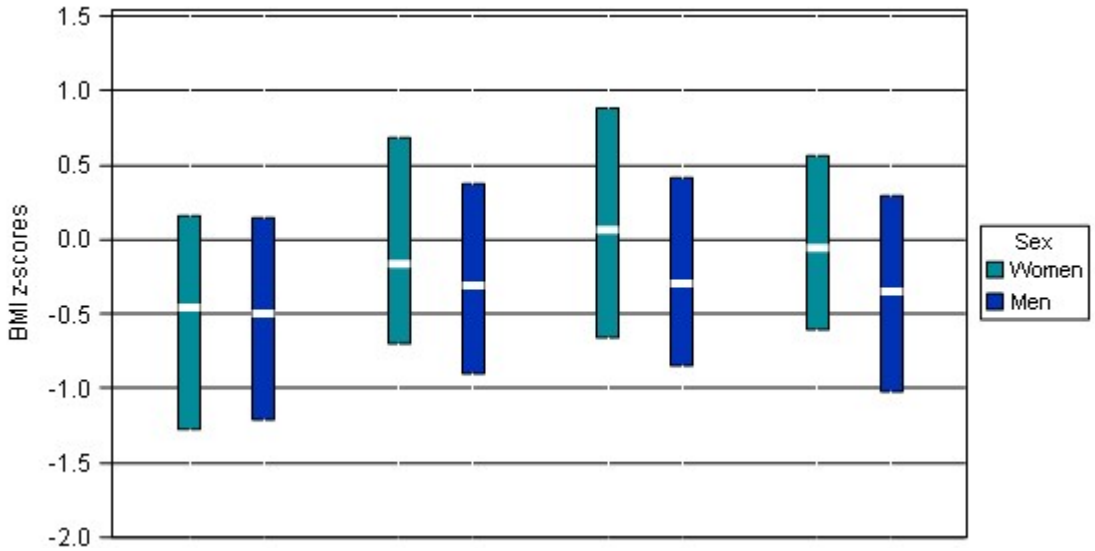
*See explicative note p 23

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	-0.45	0.09	0.20	0.06	0.01
	Men	-0.46	-0.16	-0.13	-0.31	-0.25
Median BMI z-score	Women	-0.46	-0.16	0.06	-0.05	-0.12
	Men	-0.50	-0.31	-0.30	-0.35	-0.36
BMI z-score >=0 (% of patients)	Women	31.4	44.4	53.5	49.4	45.9
	Men	29.9	39.0	39.8	36.1	36.5

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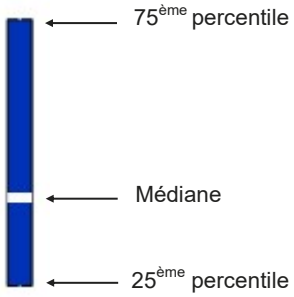
The z-score is a anthropometric reduced centered variable (Z = [measure-mean]/standard deviation), ajusted for gender and age; the mean and standard deviation are taken from the French reference population with the same gender and age as the patient. This index measures the difference with population 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 22 to 25

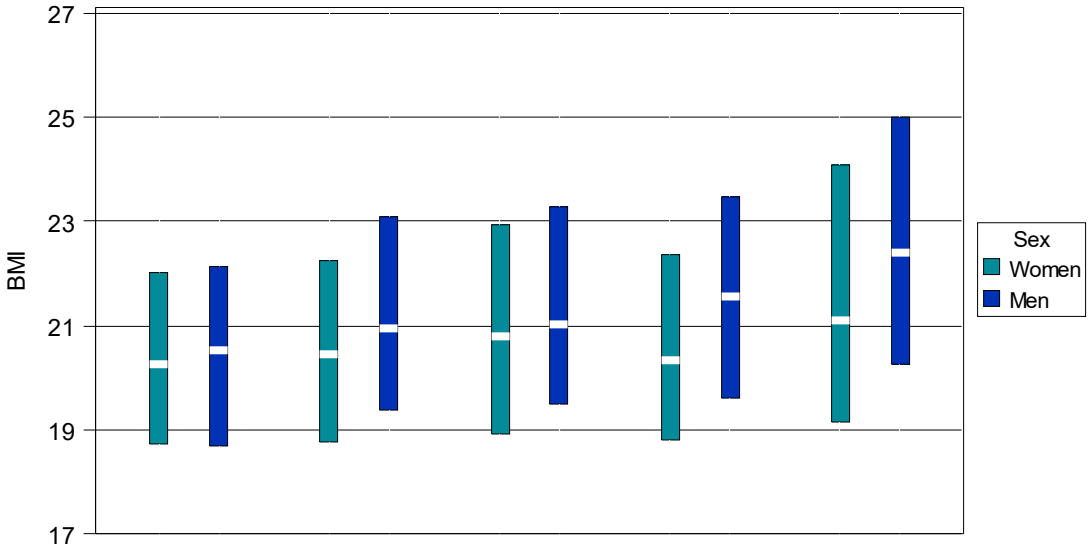
Those figures represent z-scores of anthropométrie and spirometry values.
For each age and sex group, median values are the white lines, extremes are the 25th and 75th percentiles.



5. Anthropometry

Body Mass Index (BMI)

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

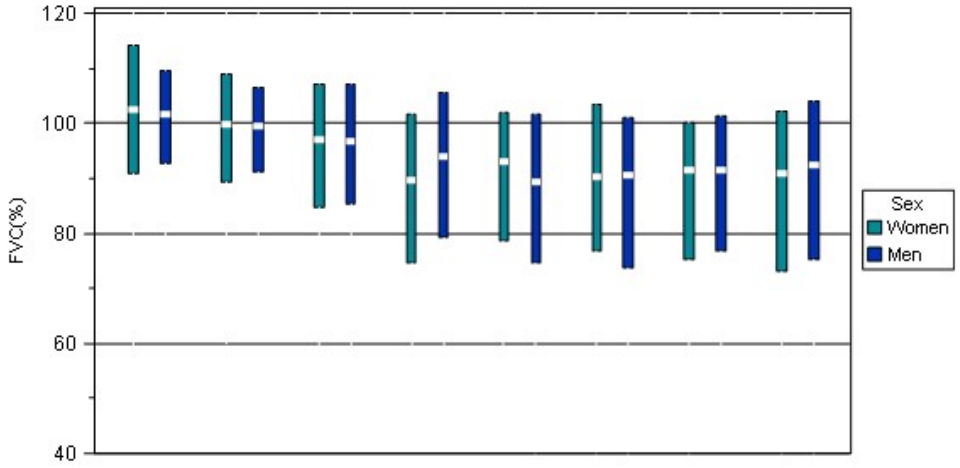


Age groups (years)		20-24	25-29	30-34	35-39	40 +	Total
Mean BMI	Women	20.6	20.8	21.3	20.9	22.1	21.2
	Men	20.7	21.5	21.6	21.7	22.9	21.7
Median BMI	Women	20.3	20.4	20.8	20.3	21.1	20.6
	Men	20.5	21.0	21.0	21.5	22.4	21.1
BMI ≥ 22 (%)	Women	25.3	27.1	34.3	29.3	38.8	31.3
BMI ≥ 23 (%)	Men	18.8	26.1	27.6	30.0	44.3	29.6
BMI < 18.5 (%)	Women	22.6	20.5	21.0	21.8	16.2	20.2
	Men	22.0	15.4	13.8	12.9	11.5	15.3

6. Spirometry

93.2% 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	102.2	98.2	93.8	87.6	89.8	89.5	87.9	88.1	92.2
	Men	100.9	98.3	95.8	91.1	87.3	87.4	88.6	88.8	92.4
	All patients	101.6	98.3	94.9	89.4	88.5	88.4	88.2	88.5	**92.3**
Median FVC	Women	102.5	99.8	96.9	89.7	93.0	90.3	91.4	90.8	95.0
	Men	101.6	99.6	96.8	94.1	89.3	90.5	91.4	92.3	95.3
	All patients	102.0	99.6	96.8	92.0	91.3	90.5	91.4	91.5	**95.2**

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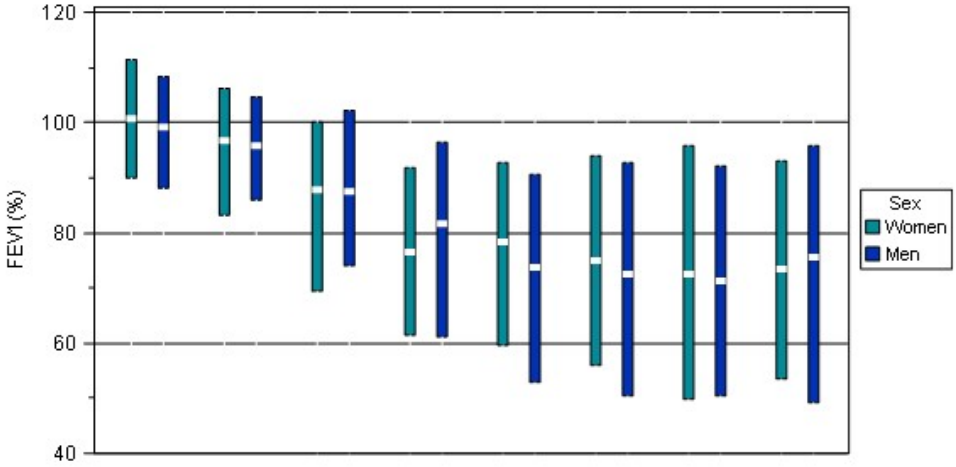
Figure 6.2. FEV_1 (% predicted)*, by age group and sex



Age groups (years)		05-09	10-14	15-19	20-24	25-29	30-34	35-39	40 +	Total
Mean FEV_1	Women	98.9	93.6	84.3	75.4	76.1	74.7	72.2	72.8	81.4
	Men	97.1	93.8	86.9	77.8	71.8	70.8	71.1	72.8	80.6
	All patients	97.9	93.7	85.6	76.6	73.8	72.6	71.6	72.8	**81.0**
Median FEV_1	Women	100.7	96.6	87.8	76.6	78.4	74.9	72.5	73.4	84.6
	Men	99.2	95.7	87.6	81.7	73.8	72.5	71.3	75.7	85.1
	All patients	100.1	96.3	87.7	79.4	76.1	73.9	71.6	74.6	**84.9**

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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 23.

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.

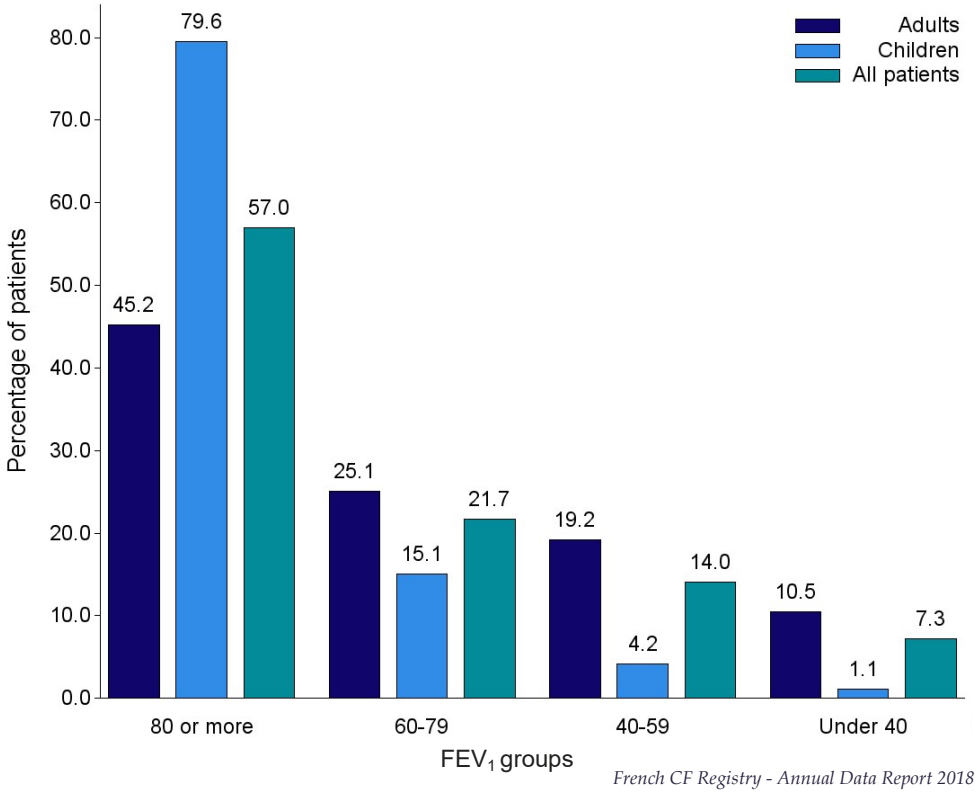
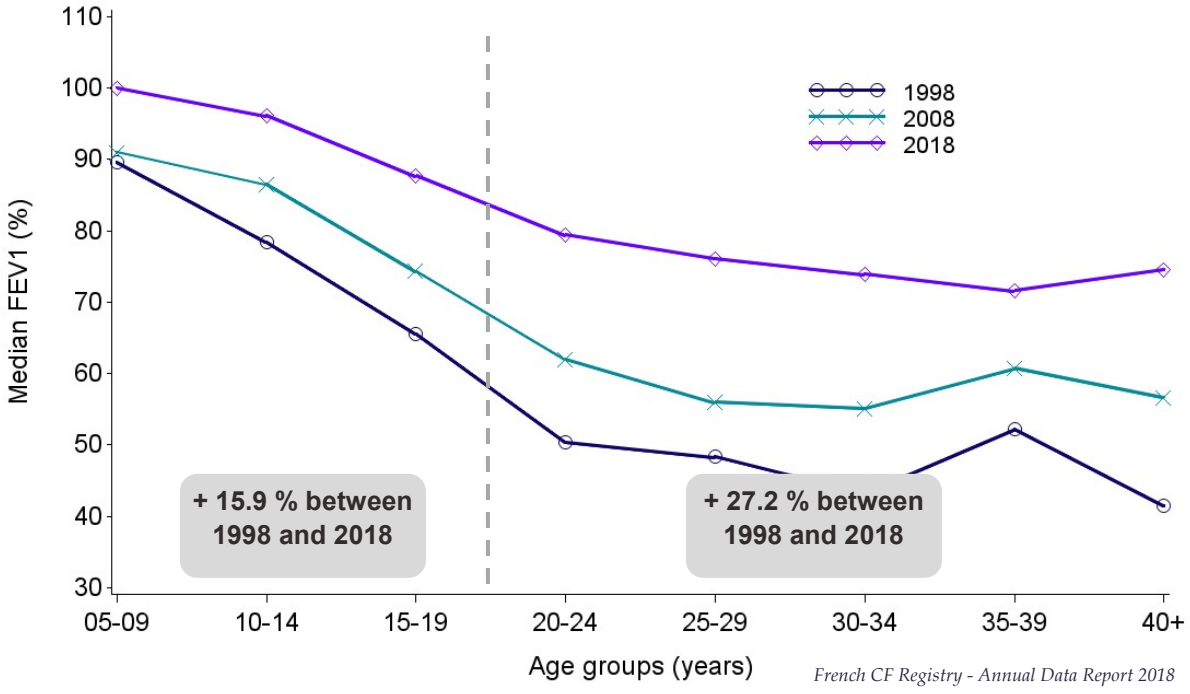


Figure 6.4. Median FEV_1 (% predicted) in 2018 compared with 1998 and 2008



Last FEV1 (%) value of the year was collected from 1992 to 2010, and best value since 2011.

The median FEV1 was 78.3 % for patients aged 6 to 19 years in 1998, and 94.2 % in 2018. It was 48.3 % in 1998 and 75.6 % in 2018 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	6076	*85.9 %*
Children	2920	*96.9 %*
Adults	3156	*77.7 %*

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In 2018, 85.9 % of the patients had at least one sputum culture. Among the patients without sputum culture (N=996), 69.7 % of them were transplanted.

Table 7.2. Distribution of the respiratory germs

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%*
All patients	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Patients with at least one sputum	**710**	**759**	**930**	**874**	**692**	**604**	**536**	**347**	**624**	**6076**	**85.9 %**
Normal culture	305	299	335	258	137	137	118	93	186	1868	26.4 %
Achromobacter xylosoxidans	17	29	82	77	75	77	54	27	35	473	6.7 %
Aspergillus	36	111	255	316	334	285	226	155	242	1960	27.7 %
Burkholderia cepacia, including:	2	8	9	27	33	22	19	12	14	146	2.1 %
- chronic B. cepacia	*1*	*3*	*3*	*15*	*22*	*20*	*14*	*7*	*8*	*93*	*1.3 %*
Haemophilus influenzae	188	268	166	169	140	109	88	44	76	1248	17.6 %
Atypical mycobacteria	1	5	28	33	43	46	22	12	28	218	3.1 %
Pneumococcus	57	52	20	11	6	7	4	8	19	184	2.6 %
Pseudomonas aeruginosa, including:	131	161	296	346	364	391	340	241	357	2627	37.1 %
- Chronic P. aeruginosa	*8*	*22*	*97*	*184*	*240*	*257*	*246*	*179*	*251*	*1484*	*21.0 %*
Staphylococcus, including:	465	582	763	716	546	432	358	203	316	4381	61.9 %
- MSSA	*449*	*567*	*740*	*679*	*500*	*388*	*305*	*180*	*272*	*4080*	*57.7 %*
- MRSA	*19*	*21*	*43*	*79*	*63*	*56*	*64*	*34*	*51*	*430*	*6.1 %*
Stenotrophomonas maltophilia	59	73	119	134	103	83	56	39	60	726	10.3 %

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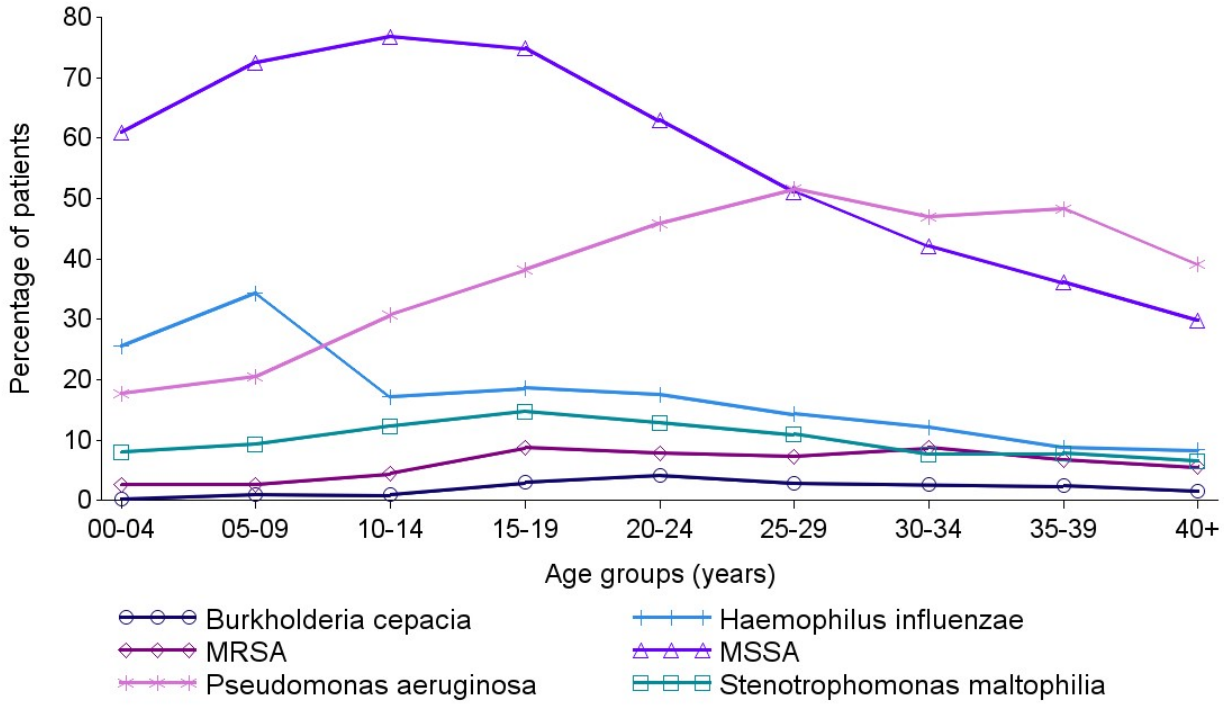
* Percentage with respect to the entire population.

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).

7. Microbiology

Figure 7.1. Clinically important bacteria



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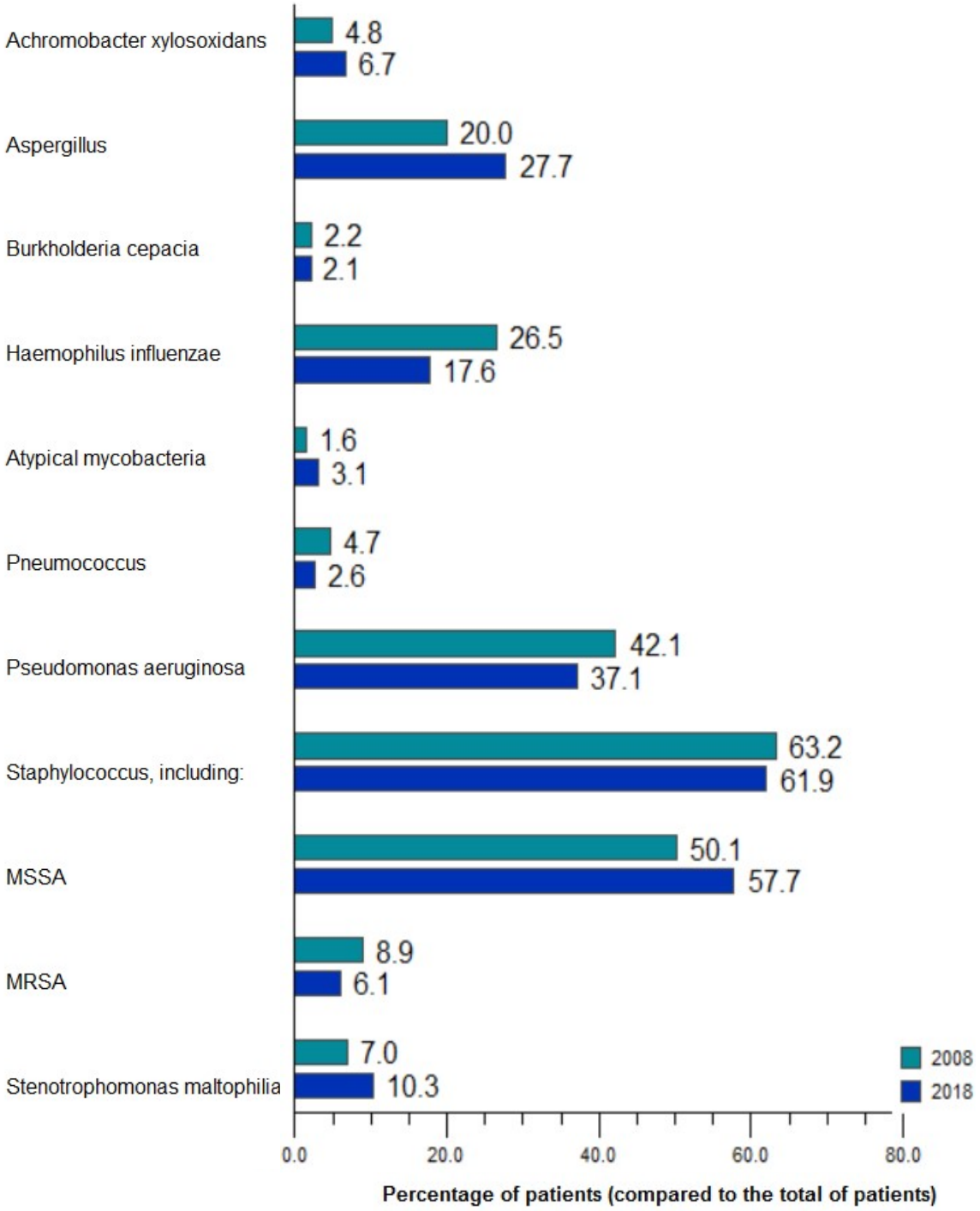
7. Microbiology

Figure 7.2. Comparison of germs in 2018 and in 2008



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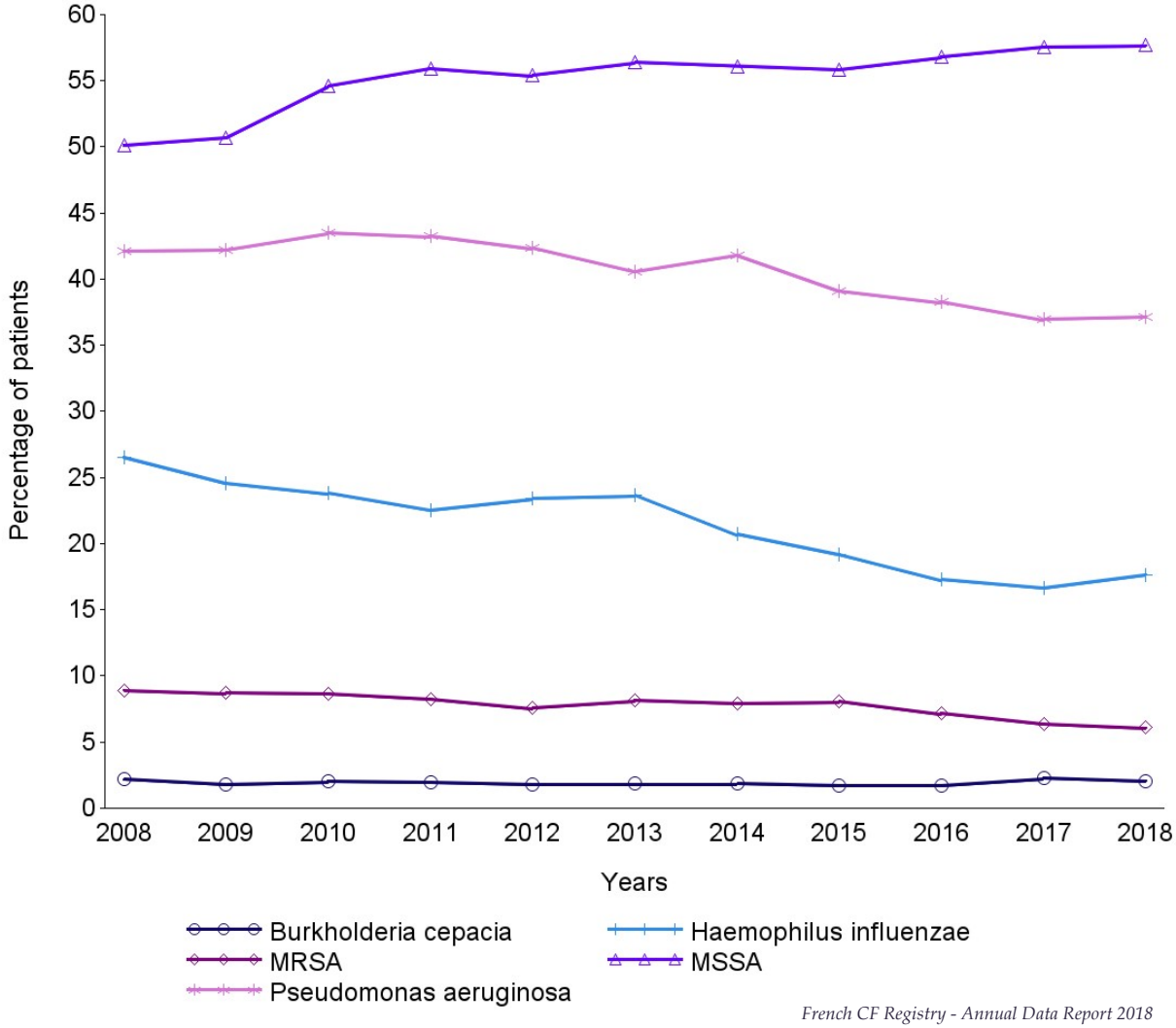
7. Microbiology

Figure 7.3. Evolution of respiratory germs since 2008



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8. Complications

Respiratory

Table 8.1. 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	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Treated aspergillosis	3	30	60	103	112	97	60	51	93	609	8.6 %
Asthma	128	173	220	208	192	180	186	124	198	1609	22.8 %
Haemoptysis	.	2	14	58	71	74	61	42	53	375	5.3 %
Pneumothorax	1	1	.	7	11	17	12	4	8	61	0.9 %
Nasal polyps	23	97	158	199	196	193	158	105	196	1325	18.7 %

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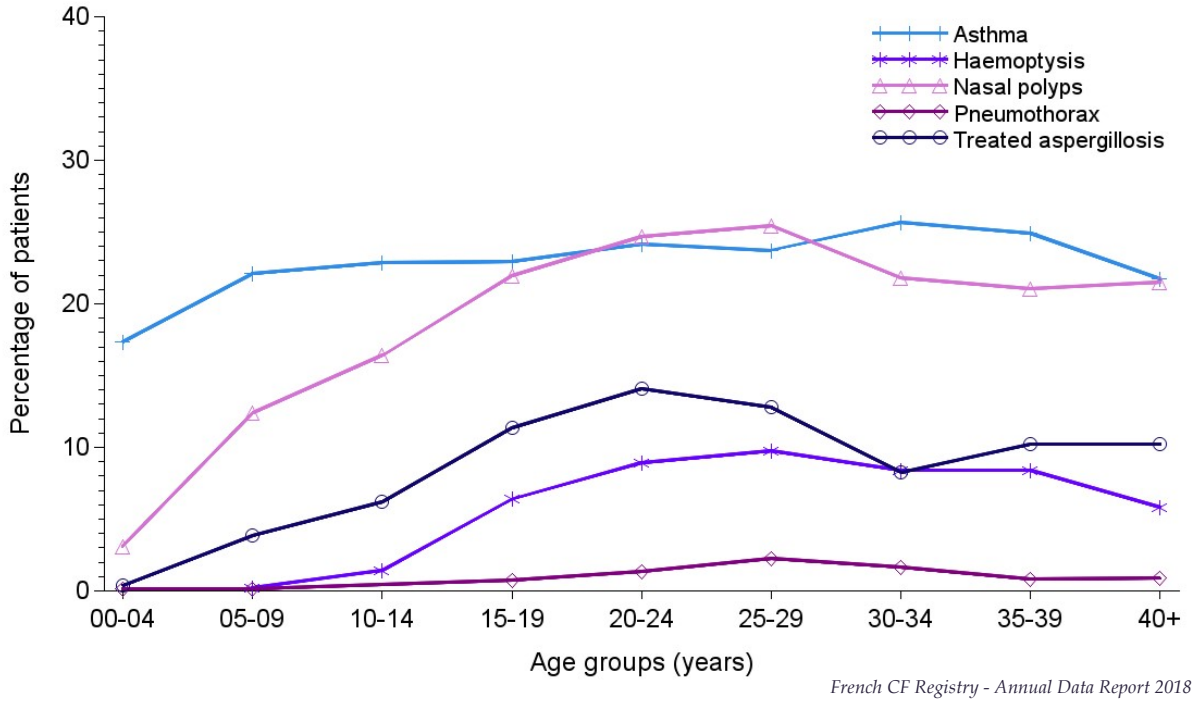
Figure 8.1. Respiratory complications

Percentage of age groups reporting complications.



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8. Complications

Gastro-intestinal

Table 8.2. 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	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Gallstones	6	6	17	19	22	37	42	28	52	229	3.2 %
Cirrhosis/Portal hypertension	2	6	37	42	46	35	28	12	26	234	3.3 %
Abnormal exocrine pancreatic function	561	595	747	744	690	663	610	421	616	5647	79.9 %
Intestinal obstruction	16	19	26	26	26	33	36	26	36	244	3.5 %
Acute pancreatitis	.	6	3	8	17	18	13	9	18	92	1.3 %
Treated gastro-oesophageal reflux disease	107	96	124	180	265	272	299	205	379	1927	27.2 %

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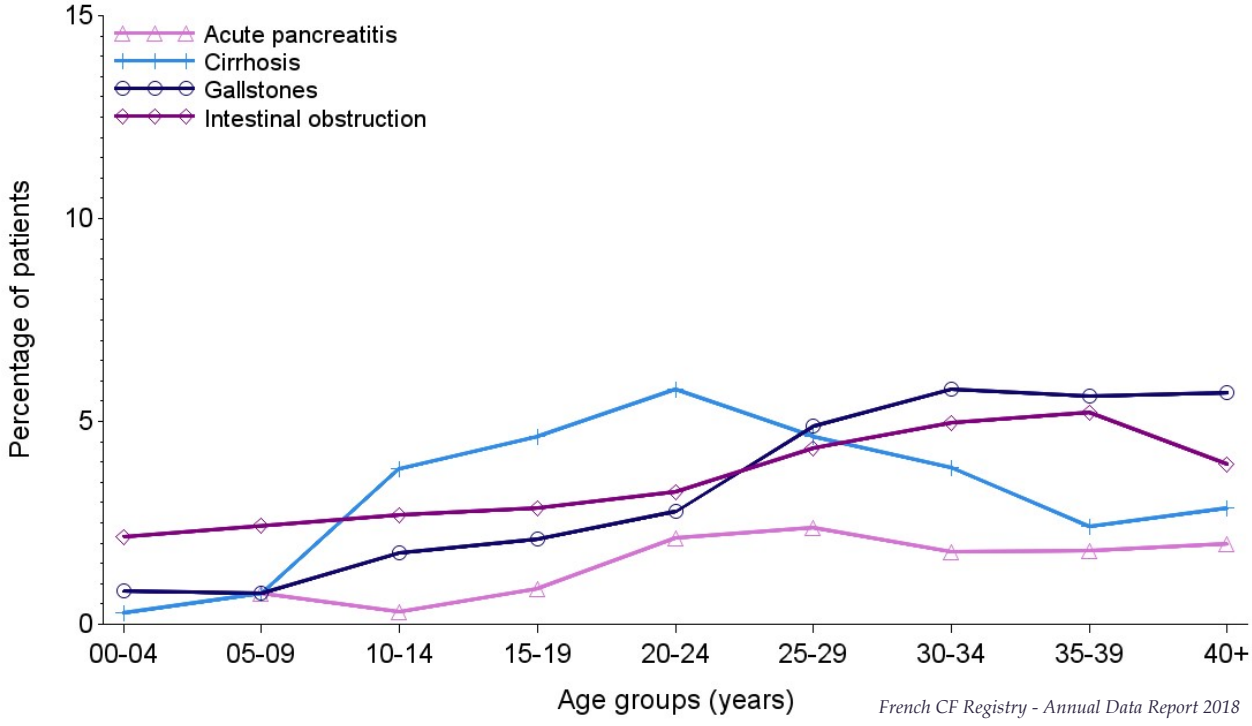
Figure 8.2. Gastro-intestinal complications

Percentage of age groups reporting complications.



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8. Complications

Diabetes mellitus

30.4% of adult patients are with diabetes mellitus

Table 8.3. 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	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Total diabetes (ID and non ID diabetes)	2	10	78	131	200	221	246	191	313	1392	19.7 %
Non insulin-dependent diabetes	1	1	19	25	33	24	23	21	29	176	2.5 %
Insulin-dependent	1	9	59	106	168	200	224	175	288	1230	17.4 %
Degenerative complications of diabetes	.	.	.	1	6	13	25	20	29	94	1.3 %

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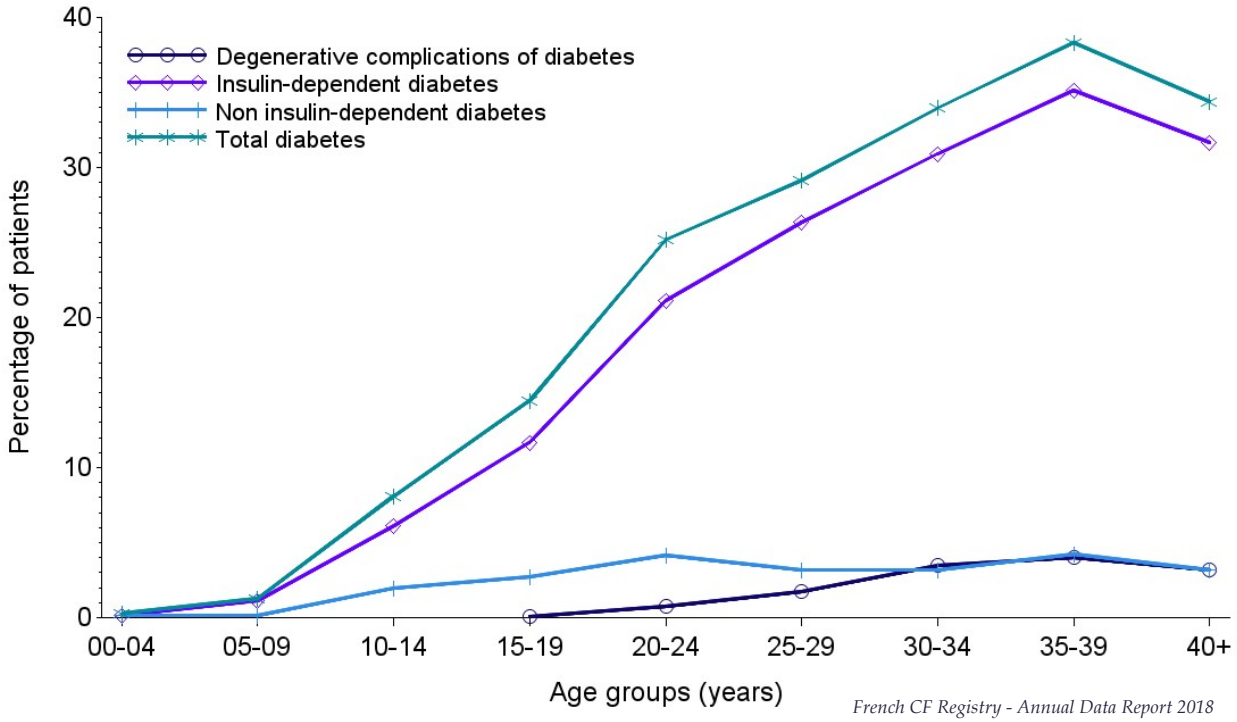
The line « Total diabetes » sums the number of patients having at least one type of diabetes. Among the 1392 patients, 14 patients presented with both types of diabetes during the year.

Figure 8.3. Diabetes mellitus and degenerative complications of diabetes

Percentage of age groups reporting complications.



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8. Complications

Other complications

Table 8.4. 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	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Arthropathy	.	4	8	7	13	23	31	29	53	168	2.4 %
Cancer	1	1	.	1	5	10	5	12	36	71	1.0 %
Depression (evaluated and followed)	1	6	15	32	62	99	84	69	169	537	7.6 %
Urinary incontinence	.	4	7	6	18	15	15	13	26	104	1.5 %
Terminal renal failure	.	.	.	.	.	6	5	7	12	30	0.4 %
Osteopenia/osteoporosis	.	.	26	63	136	185	176	169	309	1064	15.0 %
Deafness/Hypoacusia	2	4	9	24	69	122	121	94	182	627	8.9 %

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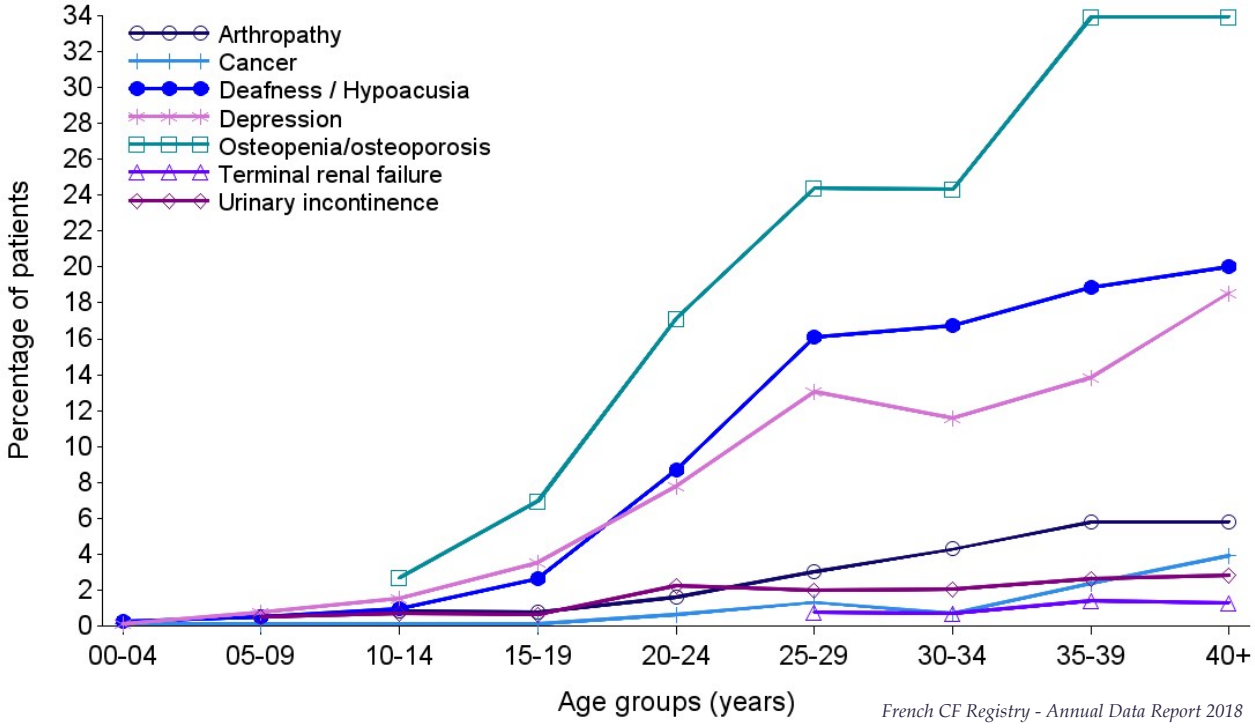
Figure 8.4. Other complications

Percentage of age groups reporting complications.



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9. Transplantation

21.3% of adult patients are living with a transplant

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

Were included in this table all the patients seen and/or dead in 2018.

	All years	2018
WAITING LIST	All waiting patients	Listed in 2018
Nb of patients	**124**	**74**
Mean age (years) and standard deviation (SD)	32.4 ± 11.6	30.4 ± 9.7
Extremes of age (years)	7.1-66.8	14.8-57.8
Deaths on waiting list	2	1
TRANSPLANTATION	All transplanted*	Transplanted in 2018
Nb of patients	**886**	**76**
Single organ transplant:		
- bilateral lung - N (%)	830 (93.7 %)	61 (80.3 %)
- liver - N (%)	28 (3.2 %)	1 (1.3 %)
- kidney - N (%)	58 (6.5 %)	7 (9.2 %)
- bilobar lung transplantation, N(%)	1 (0.1 %)	
- single lung - N (%)	9 (1.0 %)	
- pancreatic islets, N(%)	1 (0.1 %)	
- bone marrow - N (%)	1 (0.1 %)	
Multiple organ transplant:		
- heart-lung - N (%)	28 (3.2 %)	
- heart-lung / liver - N (%)	2 (0.2 %)	
- bilateral lung / liver - N (%)	25 (2.8 %)	3 (3.9 %)
- bilateral lung / kidney - N (%)	6 (0.7 %)	3 (3.9 %)
- bilateral lung / islet of Langerhans - N (%)	9 (1.0 %)	1 (1.3 %)
- liver / single lung - N (%)	1 (0.1 %)	
- liver / kidney - N (%)	1 (0.1 %)	
- liver / pancreas - N (%)	1 (0.1 %)	
- liver / pancreatic islets - N (%)	1 (0.1 %)	
- kidney / pancreas - N (%)	3 (0.3 %)	
Mean age (years)	35.8	31.5
SD	10.1	11.6
Extremes of age (years)	4.5-69.3	11.7-58.6
Post-transplantation deaths	35	9

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

9. Transplantation

Figure 9.1. Annual number of transplanted patients, since 1992

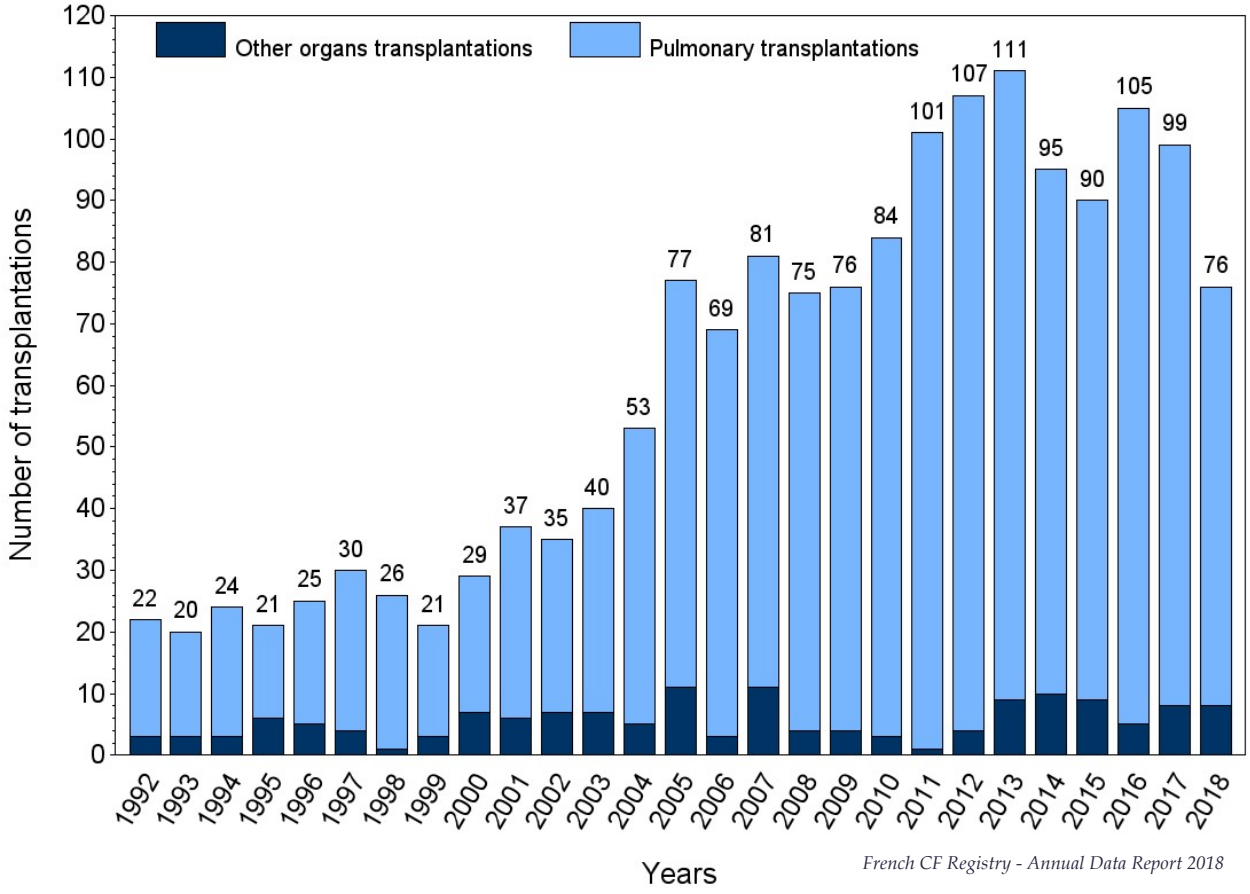

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Table 9.2. Annual number of transplanted patients, since 1992

	Years													
Transplant type	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Pulmonary*	19	17	21	15	20	26	25	18	22	31	28	33	48	11
Other organs	3	3	3	6	5	4	1	3	7	6	7	7	5	66

	Years												
Greffes	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Pulmonaires *	66	70	71	72	81	100	103	102	85	81	100	91	68
Autres organes	3	11	4	4	3	1	4	9	10	9	5	8	8

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* single lung, bilobar lung transplantation, bilateral lung or heart-lung (alone or combined with another organ).

10. Outpatient and inpatient visits

Table 10.1. Characteristics of the visits

	Age groups (years)									Total
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	
All patients	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*
< 4 visits per year	132	184	183	194	200	213	231	161	366	1864 (26.4 %)
≥ 4 visits per years	605	598	780	712	594	545	493	337	544	5208 (73.6 %)
Outpatient visits										
Number of patients with at least one outpatient visit	*479*	*469*	*614*	*574*	*527*	*525*	*491*	*332*	*633*	*4644*
Median number of visits	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Mean number of visits	3.8	3.2	3.5	3.7	4.1	4.2	3.6	3.7	3.4	3.7
One-day hospitalizations										
Number of patients with at least one one-day visit	*642*	*727*	*892*	*818*	*663*	*613*	*593*	*403*	*671*	*6022*
Median number of visits	3.0	3.0	3.0	3.0	2.0	2.0	2.0	2.0	2.0	2.0
Mean number of visits	3.6	3.0	3.2	3.4	2.8	2.8	2.8	2.7	2.6	3.0
Inpatient visits										
Number of patients with at least one inpatient visit	*175*	*129*	*233*	*262*	*245*	*249*	*224*	*162*	*277*	*1956*
Median number of visits	1.0	1.0	1.0	2.0	2.0	1.0	2.0	1.0	1.0	1.0
Mean number of visits	1.6	1.6	1.9	2.2	2.5	2.4	2.3	2.1	2.3	2.2
Median duration (days)	10.0	5.0	7.0	9.0	11.0	10.0	10.0	10.0	10.0	9.0
Mean duration (days)	15.8	13.1	13.3	20.3	23.0	23.5	19.2	15.9	19.8	18.8

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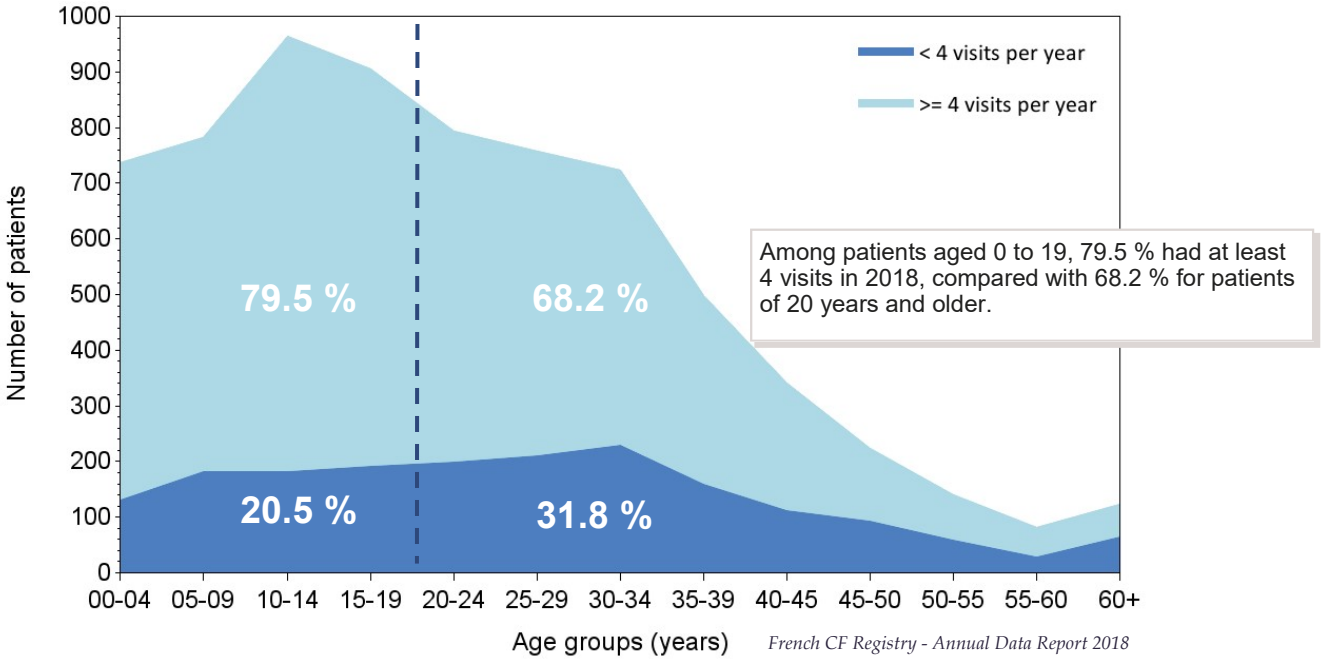
Figure 10.1. Number of visits



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Notes:
- Visits include outpatient, one-day hospitalizations and inpatient visits.
- Mean and median are calculated on patients with at least one visit (any type).

11. Therapeutic management

Antibiotic courses – TIVAD

Table 11.1. IV antibiotic courses

	Age groups (years)									Total
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	
All patients	737	782	963	906	794	758	724	498	910	7072
Nb of patients with at least one course	65	93	215	298	322	315	289	185	269	2051 (29.0 %)
- and with TIVAD*	7	27	66	113	124	129	111	74	96	747 (10.6 %)
Nb of courses	81	174	448	663	785	830	650	407	564	4602
Nb of days of courses including:	1107	2483	7185	10535	12111	11858	9779	6214	8023	69295
- at hospital	757	1019	2082	3297	3348	2872	2092	1361	2488	19316
- at home	336	1464	5058	7095	8605	8609	7663	4706	5472	49008
TIVAD* (with and without course)	8	28	70	120	132	131	120	80	106	795

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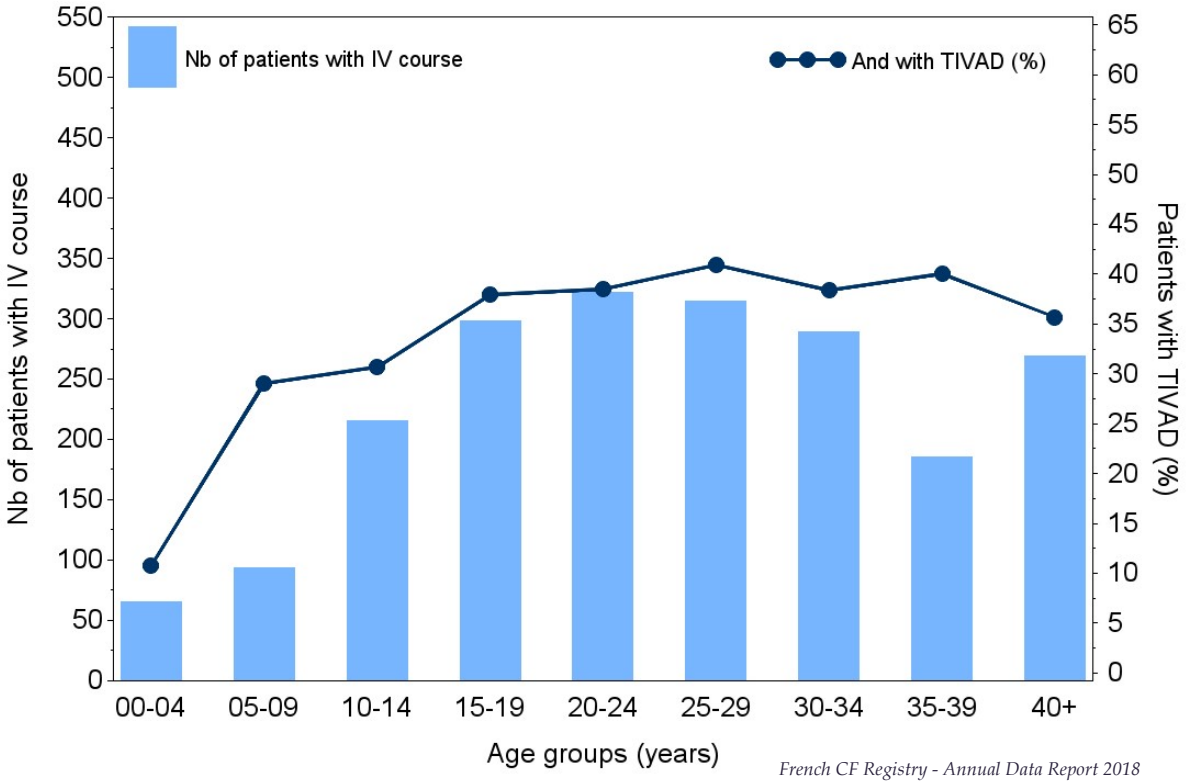
Figure 11.1. Patients with at least one IV antibiotic course and a TIVAD *



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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	1.3	1.9	2.1	2.2	2.5	2.7	2.3	2.3	2.1	2.3
SD	0.9	1.3	1.5	1.8	2.0	2.6	2.0	1.8	1.7	1.9
Median number of courses	1.0	1.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
1st quartile (Q1)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3rd quartile (Q3)	1.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Day of courses										
Mean duration of courses (days)	17.6	26.7	33.4	35.7	39.2	38.6	34.9	35.5	30.6	34.7
SD	15.6	18.3	37.8	36.1	41.9	39.3	37.4	30.1	25.6	35.4
Median duration of courses (days)	14.0	15.0	21.0	28.0	28.0	28.0	26.5	28.0	24.5	27.0
1st quartile (Q1)	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
3rd quartile (Q3)	15.0	42.0	44.0	44.0	45.0	46.0	42.0	42.0	40.0	42.0

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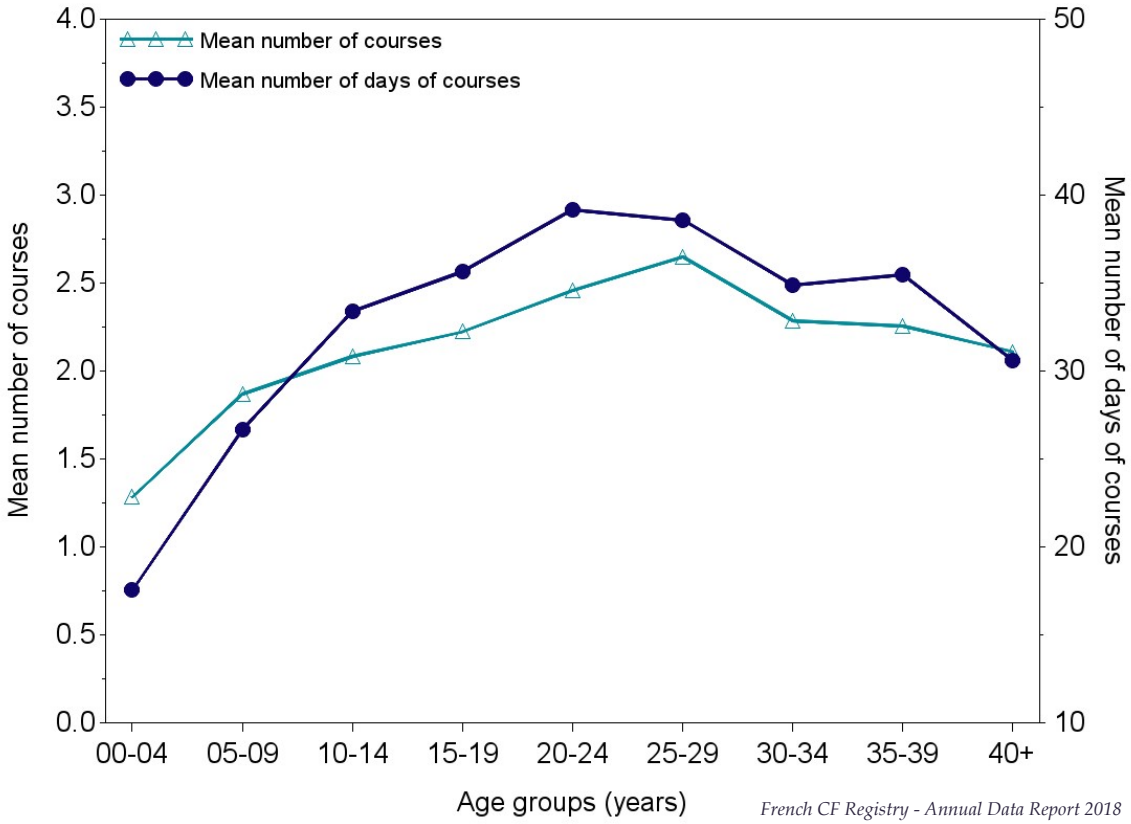
Figure 11.2. Mean number of courses and of days of courses



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11. Therapeutic management

Respiratory /CFTR gene modulators

Table 11.3. Respiratory therapeutics (≥ 3 months)

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Aerosol therapy*	411	625	834	801	701	609	580	392	684	5637	79.7 %
Azithromycin	57	147	251	296	312	330	323	237	423	2376	33.6 %
Oxygen therapy	4	2	16	34	52	63	39	43	95	348	4.9 %
Oral corticosteroids	11	9	20	41	89	150	174	146	257	897	12.7 %
Nasal ventilation	4	15	38	47	40	42	42	21	73	322	4.6 %

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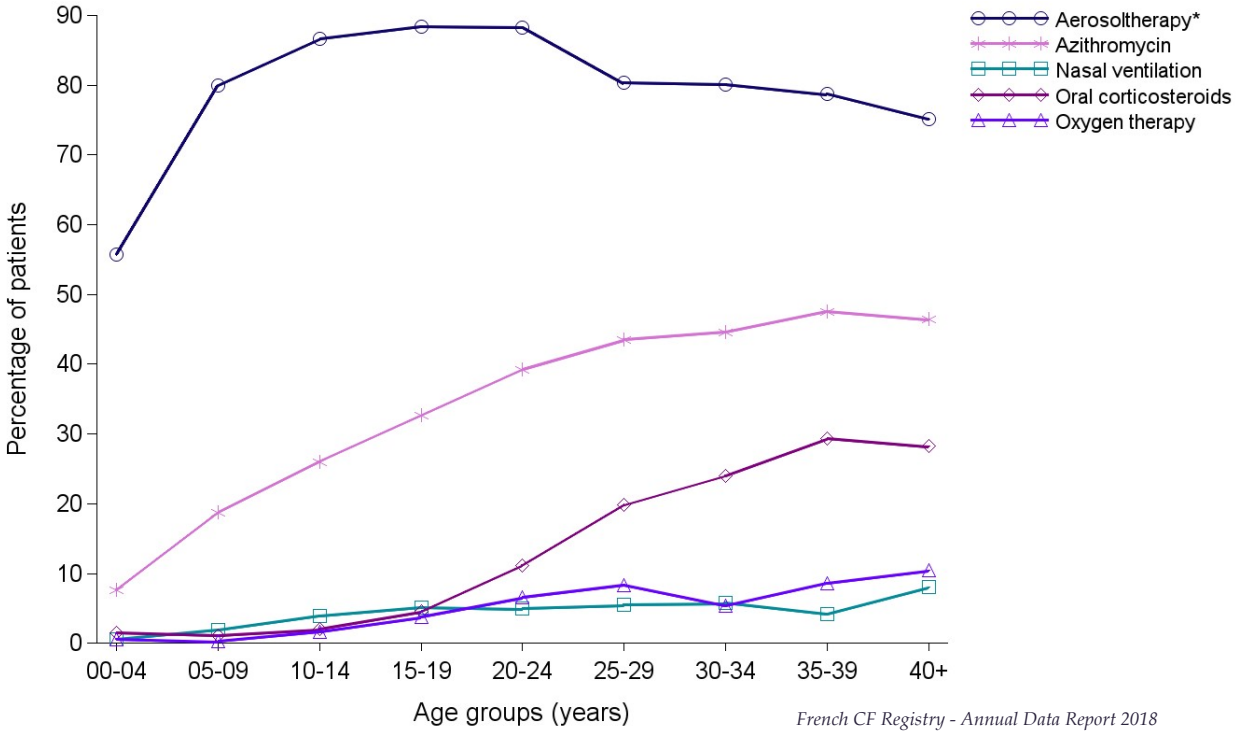
Figure 11.3. Respiratory therapeutics (≥ 3 months)



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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	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Ivacaftor	6	22	25	21	20	19	10	12	23	158	2.2 %
Lumacaftor + Ivacaftor	.	4	188	291	211	176	140	83	71	1164	16.5 %

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11. Therapeutic management

Aerosoltherapy

Table 11.5. Aerosoltherapy treatments (≥ 3 months)

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Patients under aerosol therapy*	**411**	**625**	**834**	**801**	**701**	**609**	**580**	**392**	**684**	**5637**	**79.7 %**
Inhaled antibiotics, including:	122	166	328	382	385	369	336	236	339	2663	37.7 %
- Tobramycin	*51*	*79*	*159*	*208*	*176*	*151*	*124*	*77*	*86*	*1111*	*15.7 %*
- Colistin	*36*	*82*	*176*	*213*	*199*	*193*	*176*	*138*	*195*	*1408*	*19.9 %*
- Aztreonam	*.*	*1*	*17*	*16*	*31*	*35*	*36*	*19*	*36*	*191*	*2.7 %*
Inhaled bronchodilators	270	415	619	603	536	473	444	288	525	4173	59.0 %
Inhaled corticosteroids	140	266	429	422	339	289	267	172	318	2642	37.4 %
Inhaled hypertonic saline	67	95	183	178	65	60	56	46	60	810	11.5 %
RhDNase	104	463	642	564	388	302	229	140	235	3067	43.4 %

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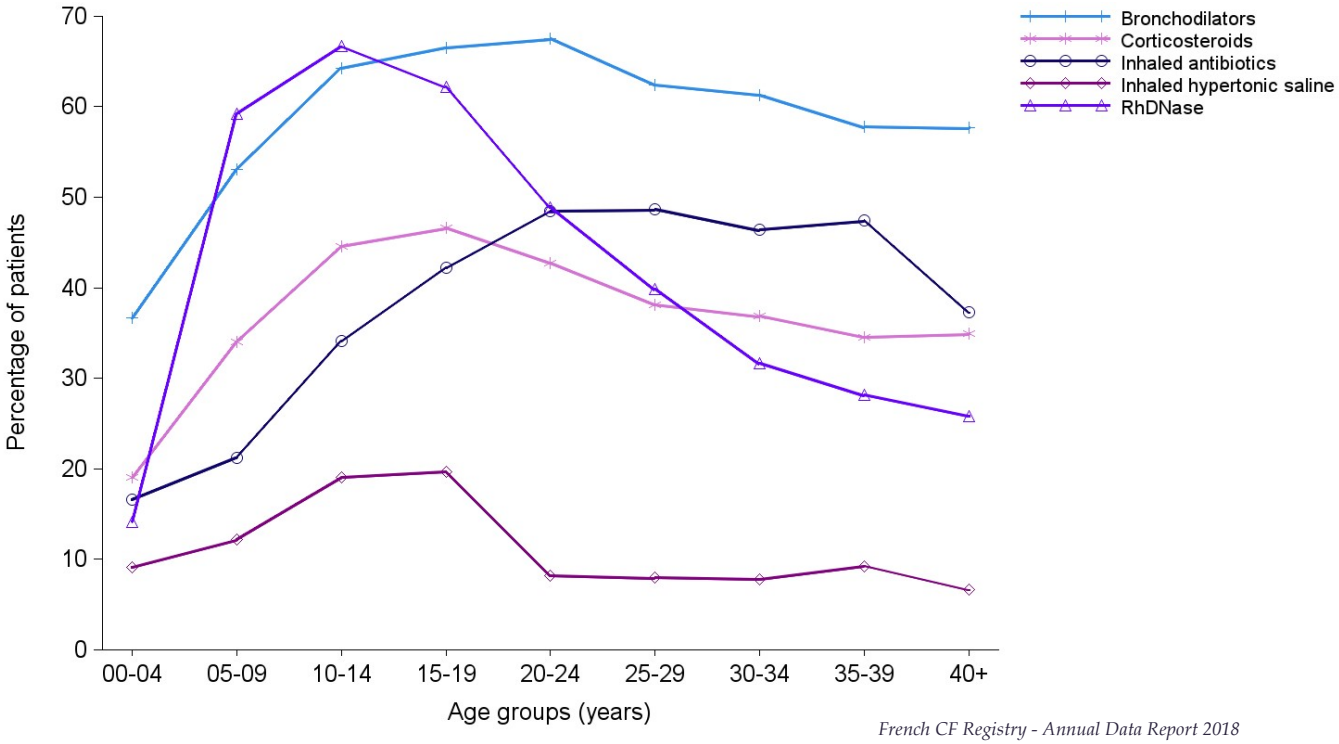
* By nebulization, spray or powder

Figure 11.4. Aerosoltherapy treatments (≥ 3 months)



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11. Therapeutic management

Digestive and nutritional

Table 11.6. Hepatic, digestive and nutritional treatments (≥ 3 months)

	Age groups (years)										
	00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total	%
All patients	*737*	*782*	*963*	*906*	*794*	*758*	*724*	*498*	*910*	*7072*	
Ursodeoxycholic acid	56	116	214	279	236	228	208	115	153	1605	22.7 %
Acid blockers	191	192	310	345	386	399	390	278	518	3009	42.5 %
Pancreatic enzymes	569	601	765	746	685	656	604	416	613	5655	80.0 %
Supplemental tube feeding	52	39	72	82	46	38	15	8	12	364	5.1 %
Oral supplemental feeding	185	278	372	337	319	283	240	157	208	2379	33.6 %
Fat-soluble vitamins	654	698	891	816	715	654	601	421	687	6137	86.8 %

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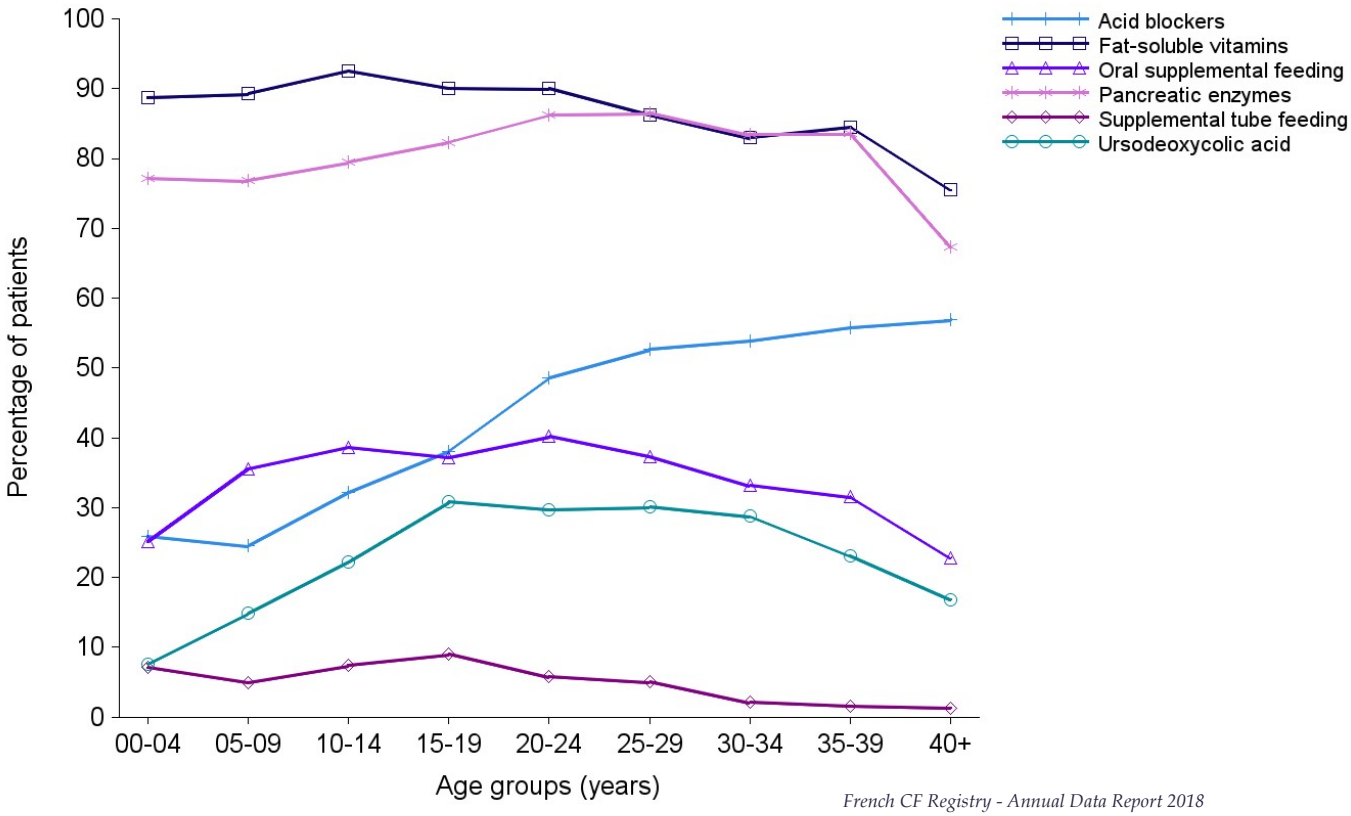
Figure 11.5. Hepatic, digestive and nutritional treatments (≥ 3 months)



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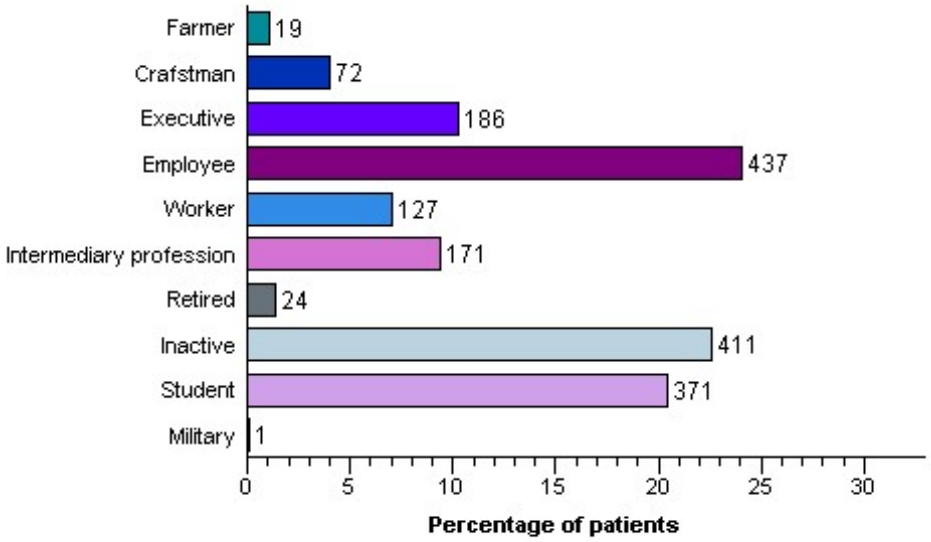
12. Social data

Employment

Figure 12.1. Employment of men ≥ 18 years

N = 1819 (number of men with a known employment situation, corresponding to 85.0 % of adults men).



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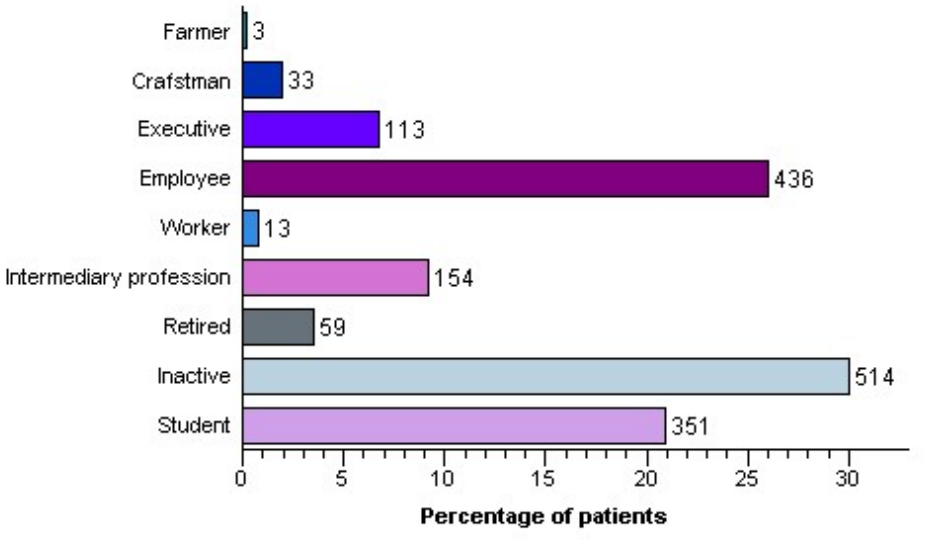
Among men aged 18 to 65, 47.6 % are workers.

Among men aged 18 to 25, 52.6 % are studiants.

Figure 12.2. Employment of women ≥ 18 years

N = 1920 (number of women with a known employment situation, corresponding to 87.3 % of adults women).



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Among women aged 18 to 65, 40.2 % are workers.

Among women aged 18 to 25, 54.6% are studiants.

12. Social data

Marital status

Figure 12.3. Family status of men ≥ 18 years

Number of men with a known family status: 2140 (87.4 % of adult men).

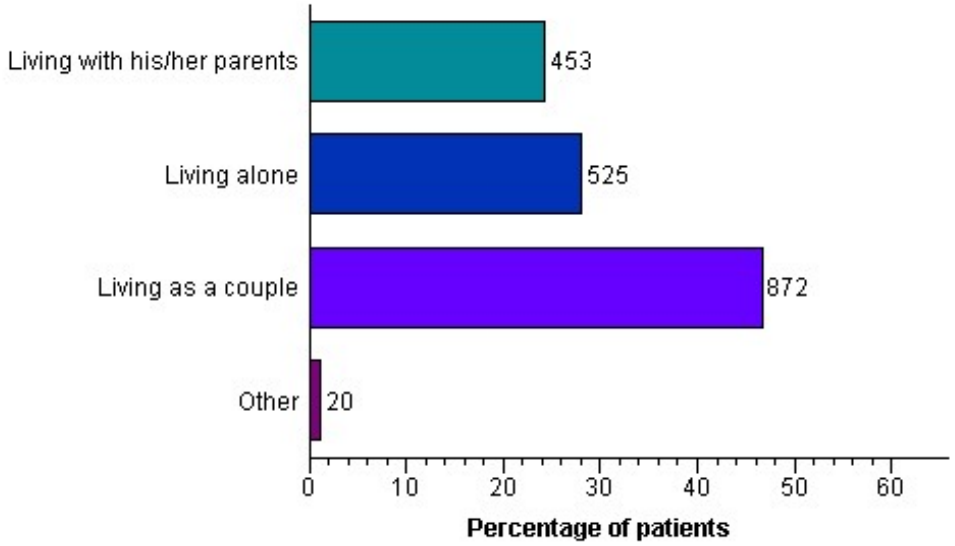

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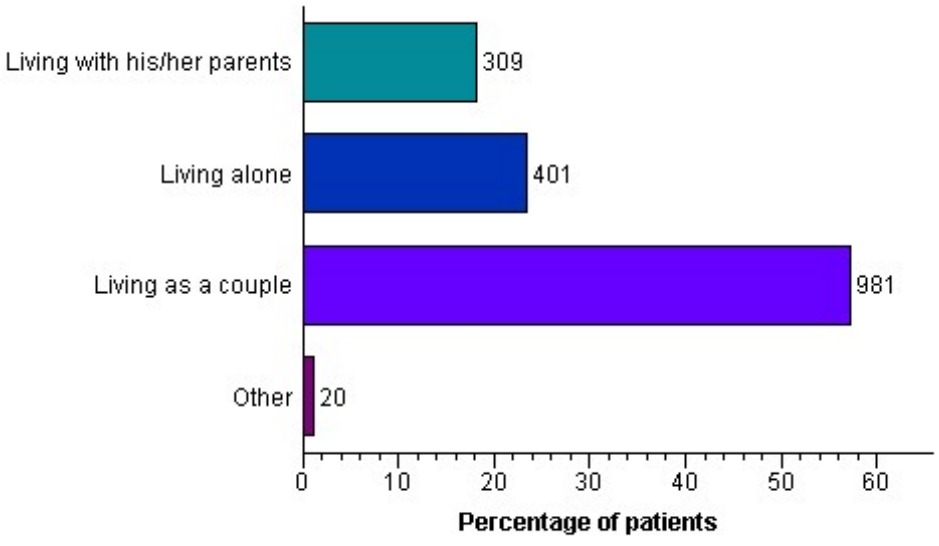
Figure 12.4. Family status of women ≥ 18 years

Number of women with a known family status: 1920 (89.1 % of adult women).



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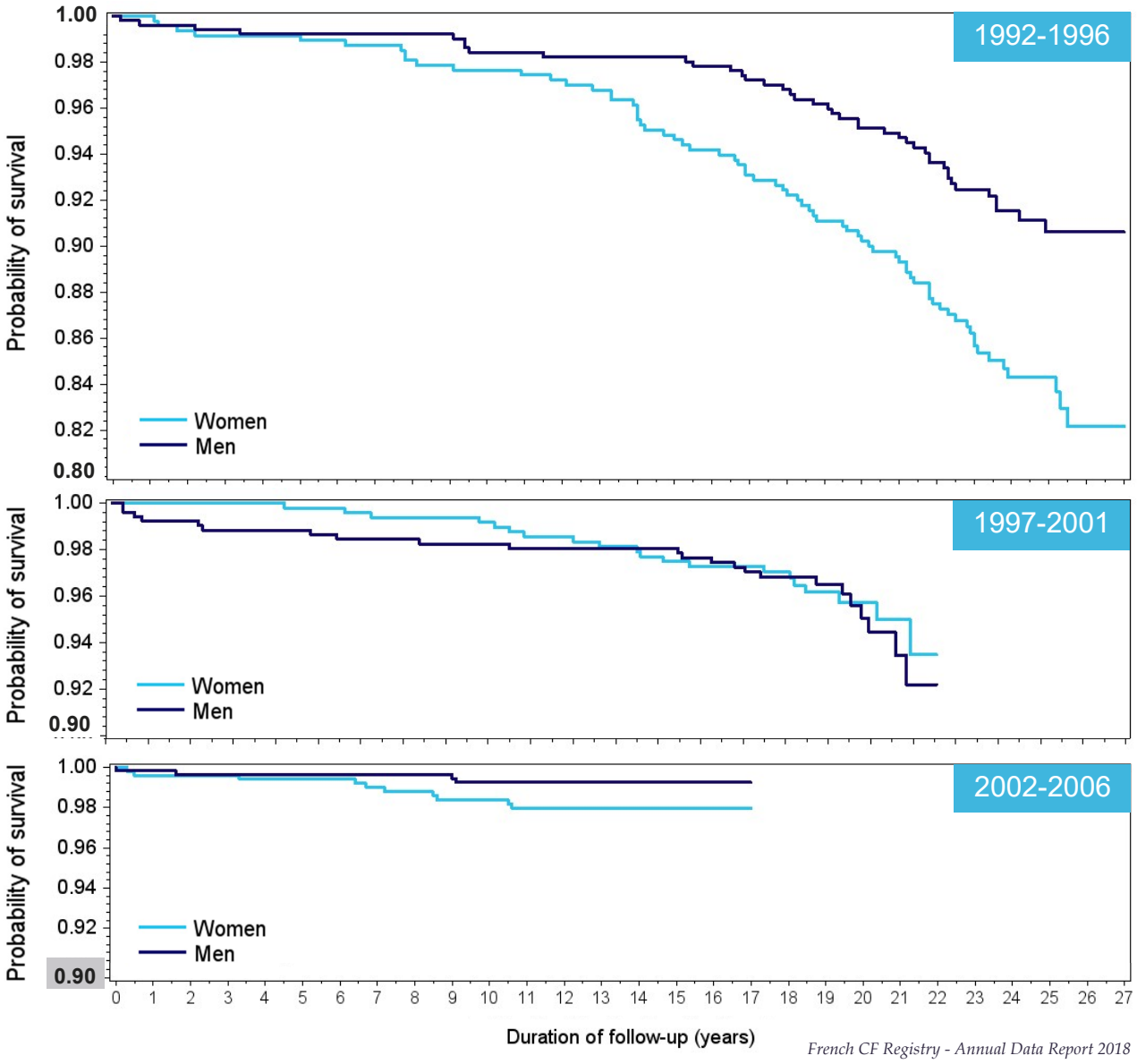
Annex 1

- 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	512	41	472	71
1997-2001	514	23	494	20
2002-2006	547	4	507	11



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 17 years.

Annex 2

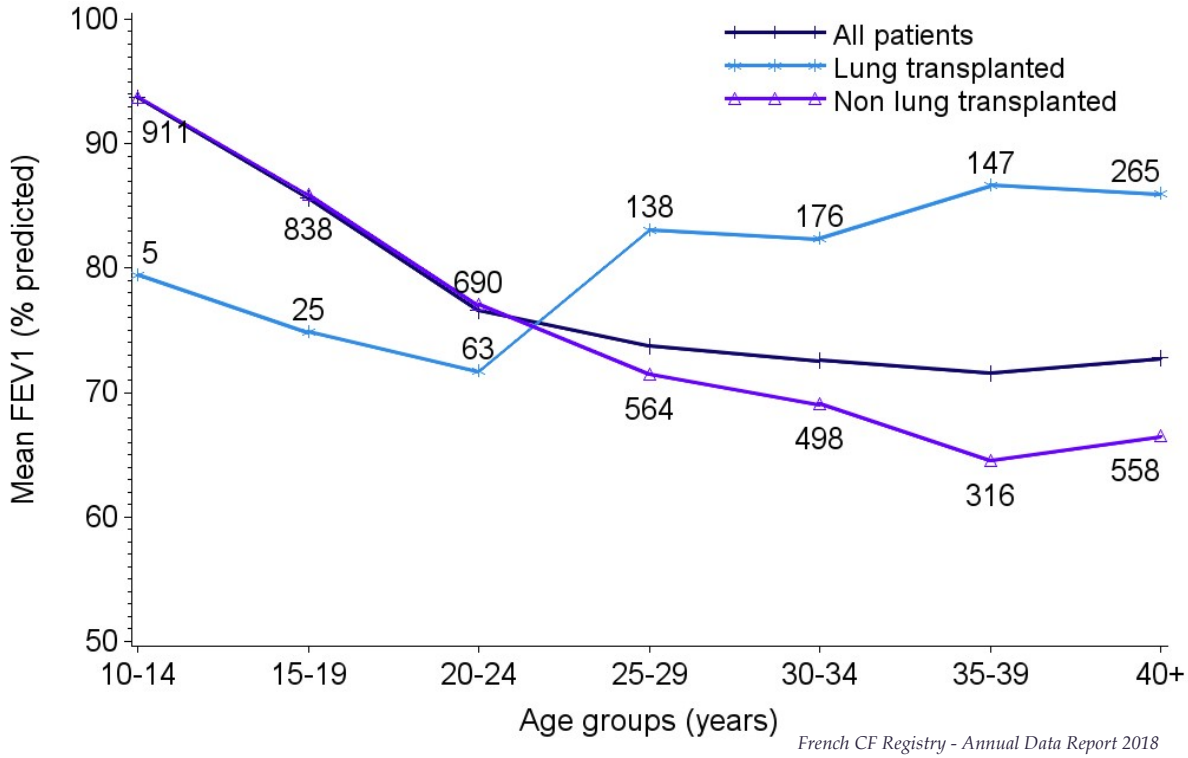
Spirometry and transplantation

This complementary analysis compares by age group the whole CF population to: 1) double lung or heart-lung transplant recipients and, 2) 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.

Figure A2.1. Mean FEV_1 (% predicted) and transplantation



Curve « Lung transplant recipients »:
- The values **above** the curve represent the number of lung transplant recipients with a FEV1 value (eg: 138 patients in the 25-29 age group).
- No pulmonary transplantation has been reported in patients under 10.

Curve « Non lung transplant recipients »:
- The values **below** the curve represent the number of non lung transplant recipients with a FEV1 value (eg: 564 patients in the 25-29 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	
Besançon	68
Bordeaux	166
Grenoble	106
Lille	188
Lyon	270
Marseille	145
Nancy	140
Nantes	109
Paris Necker	202
Paris Robert Debré	165
Paris Trousseau	65
Rennes St Brieuc	141
Saint Denis de la Réunion	61
Strasbourg	111
Toulouse	125
Tours	123
Versailles	64
Adults CF care centres	
Besançon	75
Bordeaux	162
Grenoble	91
Lille	242
Lyon	394
Marseille	255
Nancy	95
Nantes	247
Paris Cochin	490
Rennes	119
Strasbourg	161
Suresnes Foch	530
Toulouse	192
Tours	85
Paediatric and Adults CF care centres	
Amiens	101
Angers-Le Mans	134
Caen	117
Clermont-Ferrand	132
Créteil	122
Dijon	123
Dunkerque	86
Giens	226
Limoges	69
Montpellier	226
Nice	103
Reims	142
Roscoff	166
Rouen	225
Saint Pierre de la Réunion	75
Vannes-Lorient	86

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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 2018 were excluded from those statistics.

Annex 3 (2/2)

Participating centres

Table A3.2. List of the non-CF specific participating centres

Centres	Number of patients*
Paediatric local centres	
Brest	1
Le Havre	20
Montluçon	2
Pointe à Pitre	7
Paediatric and Adults local centres	
Lens	36
Other centres	
Paris HEGP Transplantation	35

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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 2018 were excluded from those statistics.

Annex 4 (1/2)

Table A4.1. Summary of data

	2016	2017	2018
Patients seen during the year and centres participating to the registry			
- Patients registered* (N):	6786	7076	7180
- Patients seen during the year in a centre** (N):	6779	6933	7072
- Centres (N) :			
Paediatric CRCMs:	17	17	17
Adult CRCMs:	14	14	14
Paediatric and Adult CRCMs:	16	16	16
Other centres:	4	4	4
Demographics			
- Male patients (%):	52.3	52.1	52.0
- Age of patients, in years (mean):	21.8	22.3	22.9
- Age of patients, in years (median):	19.9	20.3	20.9
- Age of patients. in years (min-max):	0.1-84.1	0.1-85.1	0.1-86.1
- Patients aged 18 years and over (%):	54.6	55.8	57.4
- Early pregnancies in the year (N):	59	49	55
- Pregnancy rates in women aged 15 to 49 years (for 1000):	32.2	25.9	28.4
- Age at 31st December of the year of early pregancy (mean):	28.2	29.9	30.1
- Deaths (N):	53	56	56
- Crude death rate (for 1 000):	7.8	8.1	7.9
- Age at death, in years (mean):	31.9	35.0	33.7
- Age at death, in years (median):	28.0	33.8	31.3
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	2.1	2.1	2
- New patients diagnosed during the year (N):	189	186	172
- Age at diagnosis of the new patients, in years (median):	1.3	1.7	1.1
- Age at diagnosis of the new patients, in years (min-max):	0-72	0-72	0-81
- Full genotypes identified (%):	97.9	97.8	97.7
F508del / F508del:	41.6	41.4	41
F508del / Other:	41.6	41.5	41.4
Other / Other:	14.7	14.9	15.3
F508del / Missing:	0.5	0.5	0.6
Other / Missing:	0.7	0.7	0.7
Missing / Missing:	0.9	0.9	1
Anthropometry			
- Patients aged 17 years and less, Height z-score (mean):	0.01	0.05	0.02
Weight z-score (mean):	-0.19	-0.18	-0.19
- Patients aged 18 years and over, Height z-score (mean):	-0.49	-0.5	-0.51
Weight z-score (mean):	-0.18	-0.13	-0.12

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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

	2016	2017	2018
Spirometry			
- Patients aged 17 years and less, FEV_1 (% predicted) - Knudson (mean):	92.1	92.9	93.3
- Patients aged 18 years and over, FEV_1 (% predicted) - Knudson (mean):	72.2	73.1	74.5
Microbiology			
- Patients with at least one sputum during the year (%):	87.3	87.6	85.9
H. influenzae:	17.3	16.6	17.6
MSSA:	56.8	57.6	57.7
MRSA:	7.2	6.3	6.1
P. aeruginosa:	38.3	37	37.1
S. maltophilia:	10.6	10.7	10.3
B. cepacia:	1.7	2.3	2.1
Aspergillus:	24.5	29.5	27.7
Achromobacter xylosoxidans:	6.3	6.7	6.7
Complications and transplantations			
- Aspergillus (%) :	9.9	9.6	8.6
- Abnormal exocrine pancreatic function (%) :	80.5	80.3	79.9
- Treated gastro-oesophageal reflux (%) :	19.7	28.9	27.2
- Osteopenia/osteoporosis (%) :	6.9	14.3	15
- Haemoptysis (%):	5.6	6.5	5.3
- Cirrhosis / portal hypertension (%):	4.1	3.8	3.3
- Insulin-dependent and non insulin-dependant diabetes (%):	19.4	19.2	19.7
- Transplanted patients (N):	811	867	886
Including patients transplanted during the year:	103	99	76
- Patients on waiting list (N):	158	152	124
Including patients listed during the year:	96	100	74
Deaths on waiting list:	7	3	2
Therapeutic management			
- IV courses (%):	30.5	29.4	29
- Oxygenotherapy (%):	4.9	4.6	4.9
- Nasal ventilation (%):	4.4	3.9	4.6
- Azithromycin (%):	43.1	33.9	33.6
- Pancreatic enzymes (%):	81.2	80.6	80

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Annex 5

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

	Transplanted patients	Non transplanted patients	2018 data
- Patients seen during the year in a centre* (N):	883	6189	7072
Demographics			
- Age of patients, in years (mean):	35.8	21.1	22.9
- Age of patients, in years (median):	34.8	18.6	20.9
- Patients aged 18 years and over (%):	97.8	51.6	57.4
- Early pregnancies during the year (N):	9	46	55
- Deaths (N):	35	21	56
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	5.4	1.8	2
- Full genotypes identified (%):	97.3	97.8	97.7
F508del / F508del:	50.8	39.6	41
F508del / Other:	36.1	42.1	41.4
Other / Other:	10.3	16	15.3
F508del / Missing:	0.6	0.6	0.6
Other / Missing:	0.6	0.8	0.7
Missing / Missing:	1.6	0.9	1
Anthropometry and spirometry			
- Patients aged 17 years and less, Height z-score (mean):	-1.09	0.03	0.02
Weight z-score (mean):	-1.41	-0.19	-0.19
BMI z-score (mean):	-0.54	-0.11	-0.12
- Patients aged 18 years and over, Height z-score (mean):	-0.72	-0.45	-0.51
Weight z-score (mean):	-0.7	0.05	-0.12
BMI (mean):	20.1	21.7	21.4
Spirometry			
- Patients aged 17 years and less, FEV_1 (% predicted) - Knudson (mean):	80.7	93.4	93.3
- Patients aged 18 years and over, FEV_1 (% predicted) - Knudson (mean):	83.1	72.1	74.5
Complications			
- Treated aspergillosis (%)	5.5	9	8.6
- Abnormal exocrine pancreatic function (%) :	95.9	77.6	79.9
- Treated gastro-oesophageal reflux disease (%) :	62.5	22.2	27.2
- Osteopenia/osteoporosis (%) :	48.2	10.3	15
- Haemoptysis (%):	2.4	5.7	5.3
- Cirrhosis / portal hypertension (%):	2.7	3.4	3.3
- Insulin-dependent and non insulin-dependant diabetes (%):	62.2	13.6	19.7
Therapeutic management			
- Pancreatic enzymes (%) :	94.3	77.9	80
- Oral steroids (%) :	75.9	3.7	12.7

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** The difference between the number of transplanted patients page 35 (886) and the number of patients shown in this table (883) are the patients who died and were not seen in 2018.*

Annex 6

Table A6.1. Summary of data - classical vs atypical CF

Atypical CF includes CFSPID/CRMS and mono-symptomatic CFTR-RD.

	CF	Atypical CF	All
- Patients seen during the year in a centre* (N):	6117	435	7072
Demographics			
- Age of patients, in years (mean):	21.9	23.9	22.9
- Age of patients, in years (median):	19.6	16	20.9
- Patients aged 18 years and over (%):	54.9	46.7	57.4
- Early pregnancies during the year (N):	48	3	55
- Deaths (N):	50	1	56
Diagnosis and genetics			
- Age at diagnosis, in months (median) :	1.7	29.1	2
- Full genotypes identified (%):	98.5	88.3	97.7
F508del / F508del:	44.3	1.1	41
F508del / Other:	40.2	59.3	41.4
Other / Other:	13.9	27.8	15.3
F508del / Missing:	0.4	1.8	0.6
Other / Missing:	0.5	4.1	0.7
Missing / Missing:	0.6	5.7	1
Anthropometry and spirometry			
- Patients aged 17 years and less, Height z-score (mean):	-0.02	0.51	0.02
Weight z-score (mean):	-0.25	0.51	-0.19
BMI z-score (mean):	-0.15	0.28	-0.12
- Patients aged 18 years and over, Height z-score (mean):	-0.56	0.08	-0.51
Weight z-score (mean):	-0.2	0.84	-0.12
BMI (mean):	21.1	23.7	21.4
Spirometry			
- Patients aged 17 years and less, FEV_1 (% predicted) - Knudson (mean):	92.7	102.1	93.3
- Patients aged 18 years and over, FEV_1 (% predicted) - Knudson (mean):	74.4	85.5	74.5
Complications			
- Treated aspergillosis (%)	8.6	3.4	8.6
- Abnormal exocrine pancreatic function (%) :	85.4	11.7	79.9
- Treated gastro-oesophageal reflux disease (%) :	28.6	12.6	27.2
- Osteopenia/osteoporosis (%) :	13.6	4.6	15
- Haemoptysis (%):	4.9	2.1	5.3
- Cirrhosis / portal hypertension (%):	3.5	0.2	3.3
- Insulin-dependent and non insulin-dependant diabetes (%):	20.8	2.1	19.7
Therapeutic management			
- Pancreatic enzymes (%) :	85.4	13.1	80
- Oral steroids (%) :	13.5	1.4	12.7

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** Diagnosis type is missing for 520 patients.*

FRENCH CYSTIC FIBROSIS REGISTRY

Coordinated by the patient organization Vaincre la Mucoviscidose, the French Cystic Fibrosis Registry collects annual clinical data from the CF care centers. This epidemiological database allows evaluation of the CF patients' characteristics, health status and care monitoring. It is also used for research and feasibility studies.

In partnership with the French Cystic Fibrosis-CFTR Network.

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