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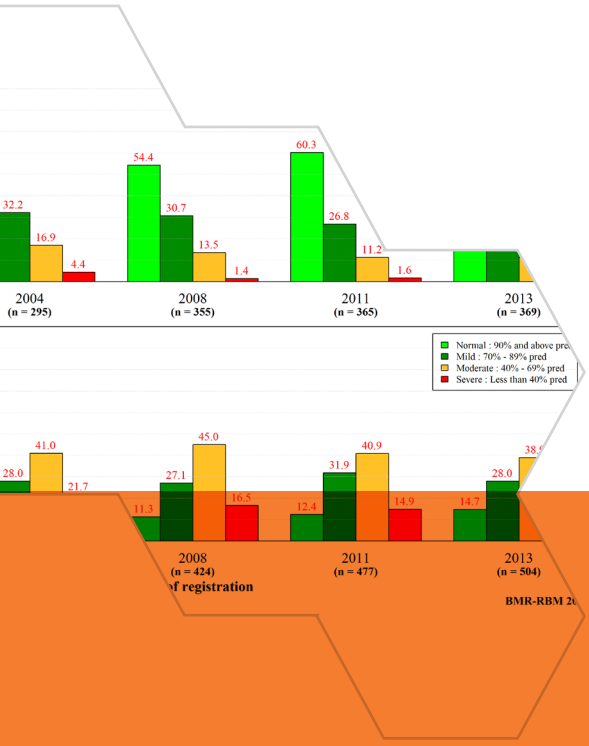

BELGISCH MUCOVISCIDOSE REGISTER
REGISTRE BELGE DE LA MUCOVISCIDOSE
THE BELGIAN CYSTIC FIBROSIS REGISTRY
(BMR-RBM-BCFR)

ANNUAL REPORT
BELGIAN CYSTIC FIBROSIS REGISTRY
2013

Annual report
Belgian Cystic Fibrosis Registry
2013

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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The registry team

SUMMARY

This report presents the data collected in 2013. It is our hope that the analysis of the registry data will provide readers with information on various aspects of CF and continue to provide an important tool for monitoring the patient's quality of care and trends.

Since its establishment in 1998, the Belgium CF registry (BMR-RBM) has grown steadily and had 1186 patients registered in 2013. This number excludes 7 whose diagnosis for CF was revoked and 7 whose diagnosis was not confirmed. There were 28 newly diagnosed patients in 2013, among them two adults, with a median age at diagnosis of 8.2 months and age range 0.0 – 25.7 years. Most of the new patients were genotyped.

Among the patients in follow-up in 2013, 52.0% were male and 57.0% adults with a median age of 20.7 years. This can be compared to the start of the registry 15 years ago when 39.0% were adults with a median age of 14.9 years. In 2013, 45.4% of the patients are homozygous for the F508del mutation while 40.4% are F508del heterozygous. The main reasons for diagnosis of CF remained acute or recurrent respiratory problems (43.6%) and failure to thrive (24.9%). About 17.0% were diagnosed via neonatal screening even though there is no national neonatal screening program in Belgium as yet. Within the year, 5 deaths were reported (2 of them in transplanted patients) with age at death range of 17.1 – 30.1 years while 5 patients benefitted from a lung transplant.

Among the adults, the proportion of patients with BMI < 18.0 kg/m^2 continues to decline from about 36.3% in 1998 to 17.4% in 2010 and 14.3% in 2013; this decline was noted even amongst the F508del homozygous patients. Amongst the patients up to 20 years, the proportion with BMI below the tenth percentile has also been declining over the years. The above suggests better nutritional management in the patients. The patient population continues to record an improvement in lung function expressed as the mean percentage of predicted FEV_1. Among the F508del homozygous patients, 38.0% of the children and 5.1% of the adults had $FEV_1 \geq 90.0\%$ of predicted in 1998 compared to 52.9% and 7.0% in 2010 and 57.4% and 8.7% respectively among the children and adults in 2013.

The overall annual prevalence of *Pseudomonas aeruginosa* reported in 2013 was 42.2% and was stable compared with a prevalence of 41.8% in 2011. The prevalence of the *Burkholderia cepacia* complex on the other hand had remained lower than 3.0% over the years till 2010. In 2011 the prevalence increased to 3.6%, (not statistically significant) while in 2012 and 2013 it was 4.0% and 4.5% respectively with an upward trend and both statistically significant over the 2010 prevalence of 2.4%. There has also been a steady increase in the prevalence of an emerging infection *Achromobacter xylosoxidans* from 5.9% in 2009 to 10.5% in 2013.

Thanks to improved treatment, the life expectancy and the quality of life of patients with CF has increased. The percentage of patients with CF aged 18 years and above increases every year. But this progress is also accompanied by different complications in adults. CF related diabetes has a prevalence of 26.6% in non-transplanted adults. Other complications are early osteoporosis, CF related arthritis/arthropathy…This evolution requires specific care for adult patients.

CHAPTER 1: BACKGROUND

This section briefly describes CF care in Belgium, the history, role and objectives of the Belgian Cystic Fibrosis registry (BMR-RBM) and the important contributions of the CF patients' association (BVSM-ABLM), the National Institute for Health and Disability Insurance (INAMI - RIZIV) and the CF reference centers in the provision of care and management of CF.

WHAT IS CYSTIC FIBROSIS?

Cystic Fibrosis (CF) is a progressive hereditary disease with autosomal recessive transmission: only subjects who have inherited two disease causing mutations – one from each parent - are affected. Parents who are both carriers for a CFTR mutation associated with classical CF have a 1 in 4 chance of having a child with CF, in each pregnancy. It is commonly found in populations of white Caucasian descent, such as those of Europe, North America and Australasia. Prevalence is however different from country to country and is 1/2850 live births in Belgium[1]. The earliest clear medical descriptions of CF date from the 1930s [2, 3]. CF obviously existed prior to this dates even though it remained largely unrecognized and so went undiagnosed. In these early times, it was even thought of to be a result of witchcraft (http://www.cfmedicine.com/history/earlyyears.htm).

The disease is caused by the alteration (mutation) of the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene which is located on the long arm of chromosome 7. More than 1800 (http://www.genet.sickkids.on.ca/SearchPage.html) mutations have been identified in the CFTR gene since its discovery in 1989[4], but not all are associated with classical CF . The CFTR gene codes for the CFTR protein. This is an ion channel involved in the regulation of chloride ion transport across the cell membrane. It is mainly found in the cell membranes of the respiratory and digestive tract, the sweat glands and the reproductive tract. The dysfunction of the CFTR protein leads to the production of sweat with a high salt content and mucus secretions with an abnormal viscosity causing dysfunction of many organs such as the lungs, pancreas and liver.

In the respiratory tract, thick mucus production results in persistent cough caused by chronic infection and inflammation leading to severe bronchial obstruction and finally lung destruction. In the pancreas, the sticky exocrine pancreatic secretions lead to obstruction and blocking of the ducts with secondary damage to the secretory gland tissue. Diminished secretion of pancreatic enzymes leads to fat and protein malabsorption causing steatorrhoea (fatty stools) and failure to thrive. Fat malabsorption also causes deficiency of fat soluble vitamins (A, D, E and K).

Most of the children with CF have a history of recurrent chest infections, steatorrhoea and failure to thrive. New-borns with CF can be affected by meconium ileus: intestinal obstruction with vomiting, abdominal distension and delay in passing the first meconium stools. The spectrum of presenting features is very wide and can vary with the age at time of clinical presentation. The diagnosis is usually made in early childhood but in some patients with late or milder symptoms it can occur later into adulthood.

CF can be identified in the first weeks of life in infants by assessing their blood immunoreactive trypsin (IRT) combined with the most frequent CFTR mutations. In Belgium, there is no neonatal CF screening program yet.

The sweat test remains the gold standard for the diagnosis of CF. In the majority of patients with typical features, the sweat test is diagnostic. It will reveal an excessive quantity of chloride (salt) (> 60 mEq/L). In atypical forms, the sweat test chloride levels can fall into the intermediate range (30-60 mEq/L).

It is advised to perform genotyping in all patients with CF, to identify the CF causing mutations. The F508del is the most common mutation not just in the Belgian CF population but also worldwide.

Today there is no causal cure for CF, treatment is symptomatic and is essentially based on respiratory (e.g. physiotherapy, inhalation therapy, antibiotics), digestive and nutritional management (e.g. pancreatic enzymes and hypercalorie diet). Due to medical progress and intensification of the care for patients with CF, the quality of life and the life expectancy have increased.

Several promising treatments aiming to correct the basic defect are currently being evaluated. The first therapy has been approved for use in a subset of patients carrying the G551D mutation[5] and is being evaluated for patients carrying other gating mutations.

CF PATIENT CARE IN BELGIUM

Since 1999, 7 CF reference centres have been accredited by the National Institute for Health and Disability Insurance (INAMI - RIZIV) and receive financial support. An annual care and revalidation agreement (CF convention) for patients with CF is signed between each of the 7 CF reference centres and the RIZIV-INAMI[6,7]. Each centre has specific expertise in CF care and ensures multidisciplinary follow-up of the patients in order to provide optimal medical, paramedical, psychological and social care to the patient and their relatives. Most of the persons with CF in Belgium are followed in one of the national CF reference centres and are registered in the national CF Registry (BMR-RBM).

THE BELGIAN CYSTIC FIBROSIS REGISTRY (BMR-RBM)

The intent of a registry is to include, in a single database, the entire population of people with a given condition (or meeting a certain criteria), say chronic illness, within a defined geographical area.

The BMR-RBM was started in 1999 as a scientific project initiated by the Medical Committee of the Belgian Cystic Fibrosis Association (BCFA) and the 7 CF-reference centres in Belgium collecting data of 1998. It was coordinated by the Vrije Universiteit Brussel (VUB). The main sponsor was the CF-Patient organisation; the cosponsor was the Fund Alfonse and Jean Forton of the King Baudouin Foundation. The VUB sponsored the overheads. After 5 years the scientific project came to an end and new sponsors were contacted.

In 2006, the RIZIV-INAMI became the principal sponsor and the Registry was transferred to the Operationale Directorate of Public Health and Surveillance of the Scientific Institute of Public Health (WIV - ISP). Since then, the WIV - ISP ensures the collection and the management of the data under the supervision of the board of the BMR-RBM and the guidance of a scientific steering group. The board consists of a physician from each CF centre and the scientific collaborators of the WIV - ISP. The scientific steering group holds all stakeholders (representatives of the INAMI-RIZIV, patient association, CF Centers and scientific collaborators of the Scientific Institute).

The Belgian CF Registry lies since 2006 within the framework of the CF convention described above. Participation in collection of data for the CF Registry is one of the obligatory tasks of the CF reference centres.

OBJECTIVES OF THE CYSTIC FIBROSIS PATIENT REGISTRY

The aims of the CF patient registry are to study epidemiological aspects of the disease among people with CF in Belgium and to provide an evaluation tool for the assessment of the management and quality of care for patients with CF. It also provides a database for scientific research to CF researchers both at the Scientific Institute and the CF reference centres. The registry also participates in activities organized by and contributes to the European Cystic Fibrosis Society Patient Registry (ECFSPR)[8] and other international projects.

CHAPTER 2: POPULATION AND METHODOLOGY

In this section, we describe the target population and methodology used. We briefly describe the data collection procedures and its evolution over the years and give the general structure of the database by listing some of its components. We look at the reporting procedures and use a flow chart to summarize the entire process.

STUDY POPULATION

The target population for the registry is people with cystic fibrosis who are living in Belgium. In 2013, there were 1186 patients included in the registry and 1282 patients who were registered as members of the patient's association (BCFA), 727 Flemish and 555 French speaking. About 56.0% of these were adults ≥ 18 years. For the moment, the registry is estimated to have a coverage of more than 90% of all people with CF (PWCF) living in Belgium.

Prior to the registration, the physicians (at the accredited CF reference centre) provide each patient and their parents (or legal representative) information about the objectives of the Registry. The patients are only included in the Registry after signing an informed consent. They are identified by their national registry number at the centre level. This number is then encrypted into a unique code by a trusted third party (eHealth) before the data are transmitted to the registry. The patients' names are never transferred to the Registry.

DATA COLLECTION

The clinical and demographic data is collected for all patients once each year by the treating physician from medical records and consists of more than 200 recorded items.

These data are divided into two sections:

1. The core data which contains demographic data, age of CF diagnosis and initial symptoms, genotype (mutations), sweat test results and nasal transepithelial potential difference results including information on neonatal screening. These data are collected when the patient enters the Registry and is updated if necessary during follow-up years.

2. Yearly follow-up sheets collect clinical data (height, weight), lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC)), complications that occurred or still active during the registration year, microbiology results, treatments and medications taken as well as social data.

SOFTWARE

Until 2010, the data was collected via an Access based computer application on CD-Rom. A new web-based application which works with a trusted third party (eHealth) was developed and has been used for data collection since year 2011. The procedures for data collection, including the digital questionnaire and some definitions, are provided in the appendix.

FEEDBACK

Each of the seven reference centres (ten clinics) gets a copy of the national annual report. Since 2006, they receive a centre report made using data from patients within the individual centre. Starting 2008, a feedback report has been provided with analyses that compare the results of each centre with data from the other centres so that the quality of care provided can be improved for points that score weaker in a centre, e.g. BMI. This method to optimize the care to the patients is called benchmarking. These analyses are corrected for some known factors such as patient age and gender with further corrections planned as more confounding data are collected by the registry, including socioeconomic data.

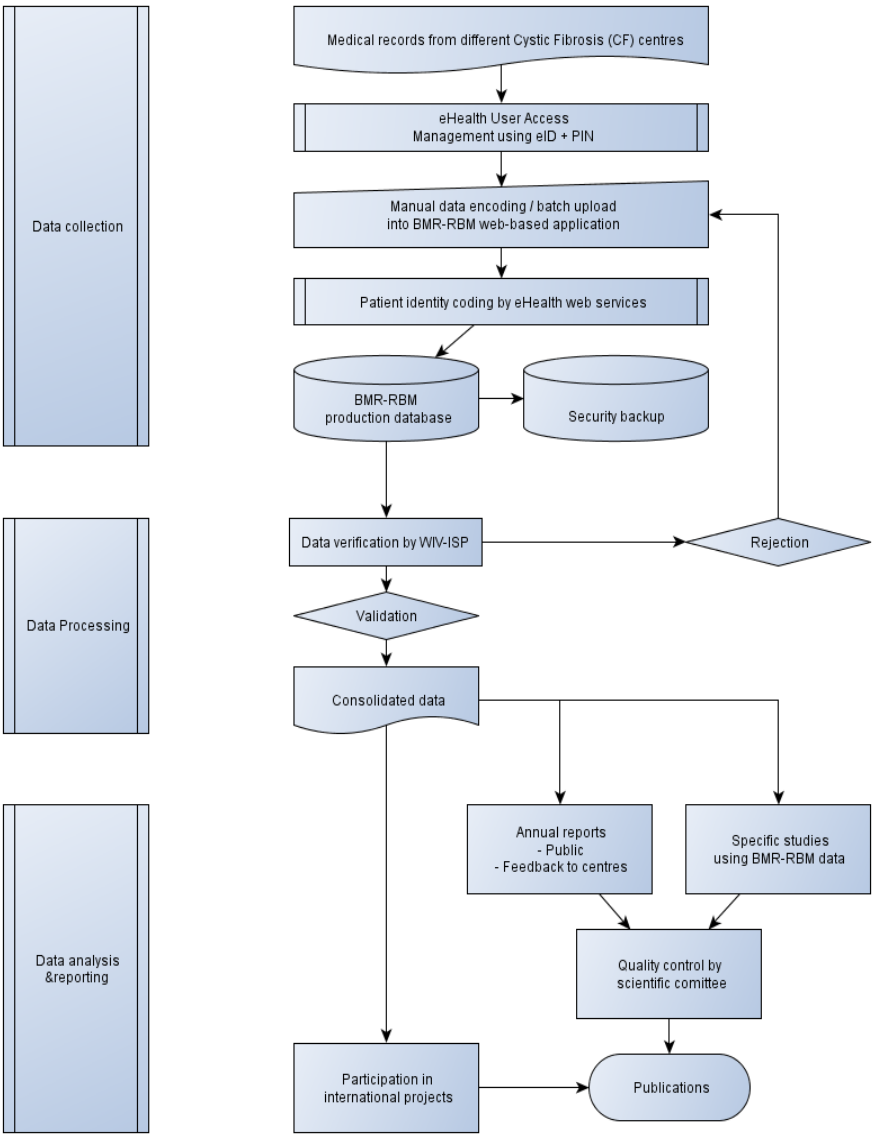
Physicians from the centres and researchers can submit research questions to the BMR-RBM, and currently a number of research questions are being analysed. Several abstracts have been presented at national or international conferences[9 - 13] and different articles are in preparation.

A subset of variables with similar definitions among several European countries is sent each year to the European CF Patient Registry (ECFSPR). Their annual reports are available on their website[8].

DATA FLOW

Following the development and use of a new web-based program from registry year 2011, the schema below shows various stages from data entry and processing to reporting and publication.

Figure 1 | Data flow chart



DEMOGRAPHIC SUMMARY OF DATA REPORTS 2010 - 2013

Table 1 | A comparison of demographic data for years 2010 - 2013

	2010	2011	2012	2013
Number of CF patients[1]	1138	1171	1184	1186
Number of CF patients with complete records	1132	1161	1154	1153
Number of CF patients without observation[4]	6	10	30	33
Number of CF patients with a transplant	128	134	141	142
Number of patients without a confirmed diagnosis[2]	-	20	11	7
Number of CF patients who were not seen	-	9	16	17
New CF diagnoses[5]	26	36	27	28
Median patient age in years (range)[3]	18.9 (0.2 - 69.4)	19.7 (0.0 - 70.4)	20.3 (0.1 - 71.5)	20.7 (0.1 - 76.6)
Median patient age male (range)[3]	18.5 (0.2 - 63.0)	19.6 (0.2 - 64.2)	20.2 (0.1 - 65.2)	20.5 (0.1 - 66.2)
Median patient age female (range)[3]	19.3 (0.2 - 69.4)	19.8 (0.0 - 70.4)	20.4 (0.1 - 71.5)	20.7 (0.2 - 76.6)
Males (%)	51.5	51.8	51.4	52.0
Adults ≥ 18 years (%)	52.9	54.7	56.4	57.0
Median age at diagnosis (months)[6]	6.6	6.5	6.1	5.3
Age range at diagnosis (years)	0.0 - 65.0	0.0 - 65.0	-0.4 - 65.0	-0.4 - 74.2
Median age at diagnosis, male (months)	6.3	6.5	6.2	5.3
Age range at diagnosis, male (years)	0.0 - 55.7	0.0 - 49.2	-0.4 - 46.9	-0.4 - 46.9
Median age at diagnosis, female (months)	7.0	6.7	6.0	5.6
Age range at diagnosis, female (years)	0.0 - 65.0	0.0 - 65.0	-0.2 - 65.0	-0.2 - 74.2
Median age at diagnosis new cases in years (range)	0.9 (0.0 - 32.8)	0.2 (0.0 - 49.2)	0.2 (-0.1 - 35.9)	0.7 (0.0 - 25.7)
Number of transplants performed	16	16	8	6
Total number of deaths reported	7	8	10	5
Median age at death in years (range)	32.5 (22.7 - 59.5)	27.7 (9.3 - 45.8)	30.2 (9.3 - 52.0)	24.9 (17.1 - 30.1)
Number of deaths among transplant patients	5	2	5	2
Overall mean FEV_1 % Predicted[17,20]	76.3 (25.1)	77.8 (25.6)	77.6 (26.3)	76.0 (25.7)
Mean FEV_1 % predicted (male)	79.5 (24.9)	80.9 (26.3)	80.5 (26.5)	78.4 (25.2)
Mean FEV_1 % predicted (female)	72.6 (24.7)	74.5 (24.5)	74.4 (25.8)	73.3 (26.0)

1. Patients with revoked diagnosis excluded (n = 7 in 2013)
2. not included in the total number of CF patients starting 2013
3. Patient's age at the last consultation
4. Patients without at least four filled-in clinical items, postulated alive or registered as deceased, and are not used in the analysis of clinical data
5. The new CF diagnoses are patients with the earliest diagnosis date from amongst the clinical diagnosis date, TEPD date, genotype date or the sweat test date done within the registry data year.
6. Prenatal diagnosis is considered without setting to zero the age at diagnosis allowing negative values since 2013. This explains the difference observed in the 2013 value when compared to the previous years.

CHAPTER 3: DEMOGRAPHIC DATA

In this section, the age at the end of the year by gender is presented in five-year categories. Information on the district of residence is provided, including maps of residence districts with estimated prevalence of CF based on the Belgian population in January 2013.

AGE ON DECEMBER 31 2013

Table 2 | Age on December 31 2013 by gender

Age years (on 31 Dec 2013)	Males			Females			All Patients		
	n	cum n	cum %	n	cum n	cum %	n	cum n	cum %
0 -< 5	59	59	9.6	54	54	9.5	113	113	9.5
5 -< 10	47	106	17.2	79	133	23.4	126	239	20.2
10 -< 15	100	206	33.4	62	195	34.3	162	401	33.8
15 -< 20	84	290	47.0	75	270	47.5	159	560	47.2
20 -< 25	76	366	59.3	66	336	59.1	142	702	59.2
25 -< 30	63	429	69.5	69	405	71.2	132	834	70.3
30 -< 35	65	494	80.1	58	463	81.4	123	957	80.7
35 -< 40	50	544	88.2	38	501	88.0	88	1045	88.1
40 -< 45	35	579	93.8	23	524	92.1	58	1103	93.0
45 -< 50	20	599	97.1	19	543	95.4	39	1142	96.3
≥ 50	18	617	100.0	26	569	100.0	44	1186	100.0
Total	**617**			**569**			**1186**		

The overall median age on 31, December 2013 was 20.7 years; 20.5 for male and 20.7 for female patients respectively.

The figures below compare the age distribution by gender for 2000 and 2013 data with an increase in the number of patients above age 40 years : 11.6% (n=138) in 2013 versus 1.2% (n=9) in 2000.

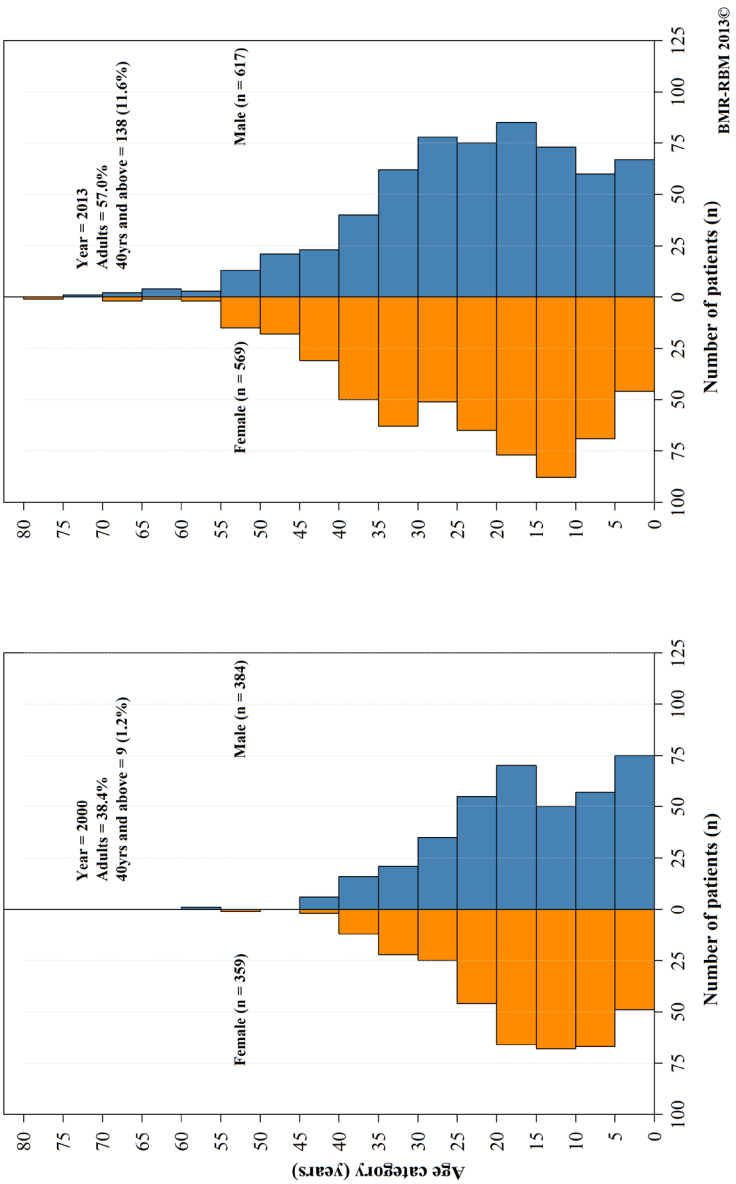
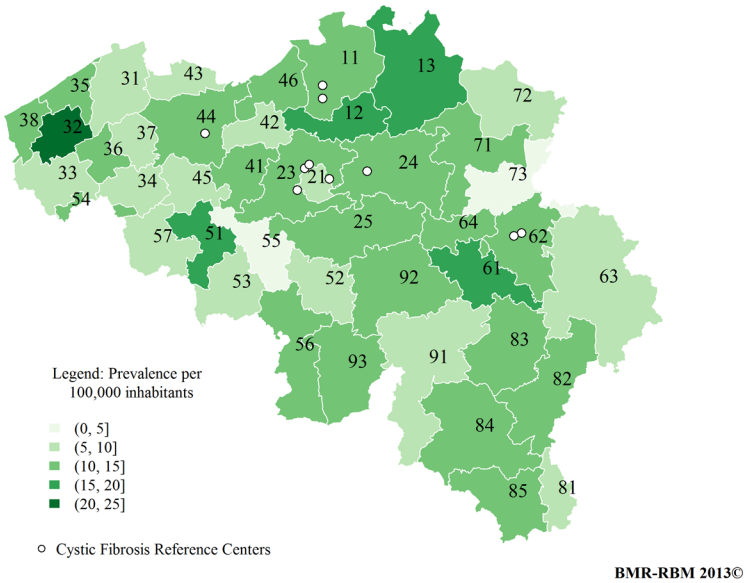


Figure 2 | Age distribution by gender in 2000 (left figure) and 2013 (right figure)

PREVALENCE OF CYSTIC FIBROSIS PER DISTRICT OF RESIDENCE

The map below illustrates the prevalence of Cystic Fibrosis in each district of residence in Belgium based on the population as at the beginning of 2013. A list with the district names and exact number of people with cystic fibrosis residing in each district is provided on page 25.

Figure 3 | Captured prevalence per 100,000 inhabitants based on district of residence in January 2013

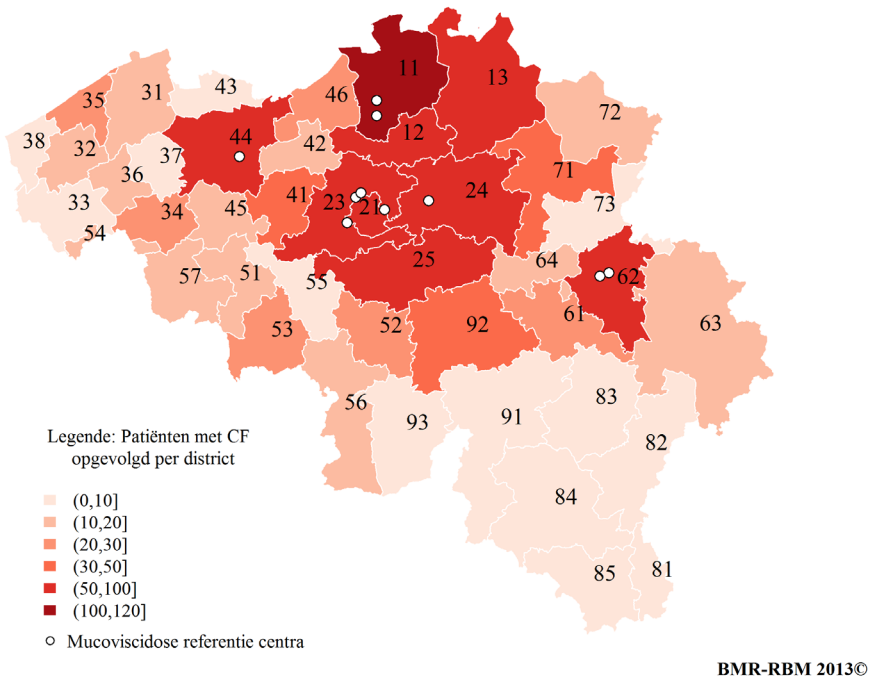


The figure 3 indicates that the highest prevalence of 21.8 in 100,000 is in Diksmuide District, code 32, with 11 patients in a population of 50,501 at the beginning of the year. District 55, Zinnik had the lowest prevalence of 4.8 in 100,000 given that there were 9 patients in a population of 185,987 during the reference period.

PWCF UNDER FOLLOW-UP PER DISTRICT OF RESIDENCE

The figure below illustrates the number of Cystic Fibrosis patients resident in each district in Belgium at the beginning of 2013. A list with the district names and exact number of people with cystic fibrosis residing in each district is provided on page 25.

Figure 4 | Number of PWCF per district of residence in January 2013



In the figure above, we see more patients concentrated in the central and northern sides of the country. Due to its populous nature though, Antwerp district with 106 patients in a population of slightly over a million had a prevalence of 10.4 in 100,000 inhabitants.

DISTRICT OF RESIDENCE

The table shows the number of patients in the registry according to their district of residence. Most of the patients reside in Belgium. There are however some patients who reside in neighbouring countries and/or whose data was not reported.

Table 3 | District of residence

	District / Arrondissement	n	%		District / Arrondissement	n	%
11	Antwerpen	106	8.9	61	Huy	21	1.8
12	Mechelen	57	4.8	62	Liège	76	6.4
13	Turnhout	77	6.5	63	Verviers	17	1.4
21	Brussel Hoofdstedelijk Gewest Région Bruxelles Capitale	83	7.0	64	Waremme	11	0.9
23	Halle-Vilvoorde	73	6.2	71	Hasselt	46	3.9
24	Leuven	51	4.3	72	Maaseik	15	1.3
25	Nivelles	52	4.4	73	Tongeren	10	0.8
31	Brugge	18	1.5	81	Arlon	4	0.3
32	Diksmuide	11	0.9	82	Bastogne	6	0.5
33	Ieper	10	0.8	83	Marche-en-Famenne	7	0.6
34	Kortrijk	28	2.4	84	Neufchâteau	9	0.8
35	Oostende	21	1.8	85	Virton	6	0.5
36	Roeselare	17	1.4	91	Dinant	9	0.8
37	Tielt	8	0.7	92	Namur	39	3.3
38	Veurne	9	0.8	93	Philippeville	7	0.6
41	Aalst	31	2.6				
42	Dendermonde	17	1.4				
43	Eeklo	8	0.7				
44	Gent	66	5.6				
45	Oudenaarde	12	1.0		**subtotal**	**1180**	
46	Sint-Niklaas	26	2.2		**Foreign country**	**-**	
51	Ath	17	1.4		**missing**	**6**	**0.5**
52	Charleroi	27	2.3		**total**	**1186**	
53	Mons	22	1.9				
54	Mouscron	11	0.9				
55	Soignies	9	0.8				
56	Thuin	19	1.6				
57	Tournai	11	0.9				

CHAPTER 4: DIAGNOSIS

In this section, we present the symptoms and clinical reasons suggesting a CF diagnosis. We also present a table of the procedure used for CF diagnosis which classifies the people with CF into two groups depending on whether or not they meet the conditions set for inclusion into the European Cystic Fibrosis Society Patient Registry (ECFSPR). Also presented is the age at diagnosis and the mutations found after genotyping.

SYMPTOMS AND CLINICAL REASONS SUGGESTING CF

In a patient with suggestive symptoms, a family history of cystic fibrosis or a positive neonatal screening test, the diagnosis of CF is confirmed by an abnormal sweat test (chloride > 60 mEq/L) and/or the identification of two mutations in the CFTR gene. Although no national neonatal screening program was implemented in Belgium, some children were screened for CF. Most patients present with a combination of respiratory and/or gastrointestinal symptoms. Chronic cough, recurrent chest infections, chronic sinusitis are the most common presenting respiratory signs. Common gastrointestinal symptoms include meconium ileus (obstruction of the bowel with sticky secretions in the new-born infant), chronic diarrhoea and failure to thrive due to malabsorption. Less frequently, salt loss, jaundice or a rectal prolapse are the first diagnostic signs. In some cases, the diagnosis of cystic fibrosis is delayed until adulthood. Most of these patients are expected to have had a milder clinical course, or to present with atypical symptoms, such as infertility.

The diagnostic signs or clinical presentation are illustrated in table 4. In the Belgian CF registry, it is possible to report more than one diagnosis sign or symptom for the same patient. Over the years, the commonest clinical presentation of CF remains acute or recurrent respiratory problems. Other common features on presentation were failure to thrive, chronic diarrhoea/ steatorrhoea and meconium ileus. About 17.0% of the patients were diagnosed via neonatal screening test.

Table 4 | Symptoms and clinical reasons for CF diagnosis

	Data 1998 – 2013		Newly diagnosed 2012		2013	
	n	%	n	%	n	%
Acute or Recurrent Respiratory Problems	493	43.6	11	40.7	12	46.2
Failure to thrive	282	24.9	7	25.9	7	26.9
Chronic diarrhoea/streatorrhea/ malabsorption	231	20.4	4	14.8	5	19.2
Neonatal screening test	191	16.9	4	14.8	6	23.1
Meconium ileus	161	14.2	4	14.8	3	11.5
Family history	115	10.2	4	14.8	3	11.5
Nasal polyposis / chronic sinusitis	50	4.4	1	3.7	3	11.5
Rectal prolapse	30	2.7	0	0.0	0	0.0
Intestinal obstruction (other than meconium ileus)	25	2.2	0	0.0	0	0.0
Prenatal diagnosis	34	3.0	2	7.4	1	3.8
Dehydration / electrolyte imbalance	19	1.7	1	3.7	1	3.8
Neonatal jaundice	2	0.2	0	0.0	1	3.8
Infertility	11	1.0	0	0.0	0	0.0
Diagnosis other	87	7.7	0	0.0	1	3.8
*No diagnosis reasons given	54		0		2	

* The overall percentages are based on 1132, 54 patients did not have information on any of the above reasons given in the 2013 data and were excluded from the calculations. There were 28 newly diagnosed in 2013, percentages are based on 26 patients.

Note: Reasons for diagnosis are not mutually exclusive.

DOCUMENTATION OF CF DIAGNOSIS

Table 5 | Documentation of CF diagnosis including sweat tests, clinical symptoms, genotyping and family history

Procedure	Data 1998 – 2013		Newly diagnosed Patients 2013	
	n	%	n	%
Patients meeting inclusion criteria for the European Cystic Fibrosis Society Patient Registry				
Clinical symptoms and/or family history, sweat test and genotyping	687	57.9	19	67.9
Clinical symptoms and/or family history and sweat test	36	3.0	.	.
Clinical symptoms and/or family history and genotyping	199	16.8	.	.
Neonatal screening test, sweat test and genotyping	100	8.4	2	7.1
Clinical symptoms and/or family history, neonatal screening test, sweat test and genotyping	60	5.1	2	7.1
Sweat test and genotyping	16	1.3	2	7.1
Clinical symptoms and/or family history, neonatal screening test and genotyping	13	1.1	2	7.1
Subtotal	**1111**	**93.7**	**27**	**96.4**
Patients not meeting inclusion criteria for the European Cystic Fibrosis Society Patient Registry				
Clinical symptoms and/or family history only	19	1.6	1	3.6
Genotyping only	36	3.0	.	.
Neonatal screening test and genotyping	16	1.3	.	.
Clinical symptoms and/or family history and neonatal screening test	2	0.2	.	.
Missing	2	0.2	.	.
Subtotal	**75**	**6.3**	**1**	**3.6**
Total	**1186**	**100.0**	**28**	**100.0**

Important Information: The data in the table above refers to documentation of CF diagnosis. The clinical diagnosis was considered if at least one of a set of symptoms was identified (see page 24; excluding neonatal screening); the sweat chloride had to be greater than 60 mmol/L while genotyping was considered confirmatory if two CF mutations were reported.

According to the European Cystic Fibrosis Society Patients Registry (ECFSPR), for a patient to be included, he/she must meet at least one of the following three criteria listed on the next page. We have used those criteria to explore the documentation of the diagnosis of the patients in our registry. These data are presented in the table above.

Inclusion criteria for patients into the European Cystic Fibrosis Society Patient Registry (ECFSPR)

For a patient to be included in the ECFSPR, at least one of the following three criterions must be met:

1). two sweat tests returning results of sweat chloride > 60 mmol/L

2). one sweat test with chloride > 60 mmol/L and DNA Analysis/Genotyping done where two disease causing CF mutations are identified

3). if sweat chloride value is ≤ 60 mmol/L then at least two of the conditions below should be fulfilled: -

i. A DNA Analysis/Genotyping where two disease causing CF mutations are identified

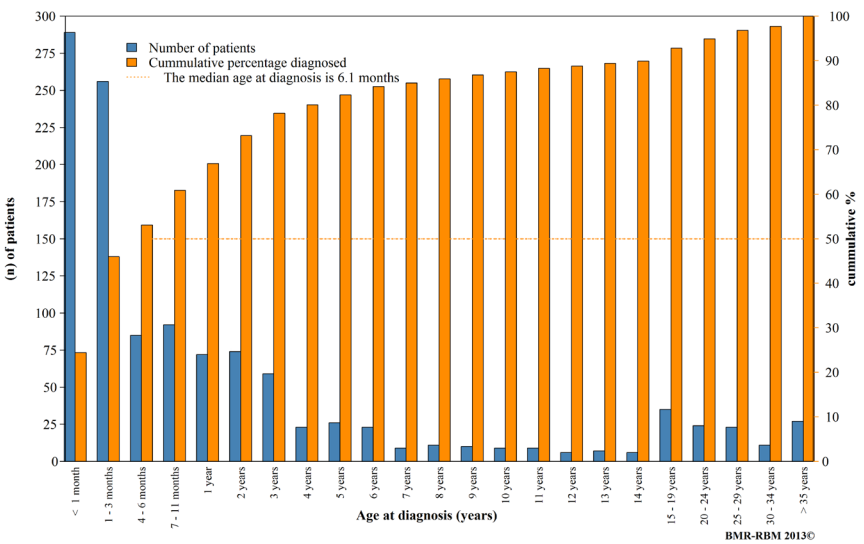
ii. A Trans epithelial (Nasal) Potential Difference value – Consistent with a diagnosis of CF

iii. Clinical Presentation – Where typical features of CF are identified

AGE AT DIAGNOSIS

The figure gives the cumulative percentage of age at diagnosis for data 2013. The median age at diagnosis was 5.3 months; 5.3 months for male and 5.6 months for female patients respectively. At the age of 18 years 92.5% of the patients were diagnosed. The median age at diagnosis was 3.0 months for the F508del homozygous patients, 9.0 months for the F508del heterozygous while for patients with other mutations it was 11.3 months.

Figure 5 | Age at Diagnosis



The median age at diagnosis for the 28 newly diagnosed patients in 2013 was 8.2 months; 13.9 months for male and 2.9 months for female patients respectively.

GENOTYPE

In 2013, 1183 (99.7%) of the patients had undergone a genetic analysis while for three (0.3%) patients, this information was unknown or missing. Almost half (45.4%) were homozygote for F508del and 86% of the patients had this mutation on at least one of their alleles (table 6).

Table 6 | General mutation pairs

Mutation pair	n	%	cumulative %
F508del --- F508del	538	45.4	45.4
F508del ---OTHER	446	37.6	83.0
F508del ---NI	33	2.8	85.8
OTHER---OTHER	143	12.1	97.8
OTHER---NI	8	0.7	98.5
NI---NI	15	1.3	99.7
subtotal	**1183**		
missing	**3**	**0.3**	
total	**1186**		

NI = Not Identified

Table 7 | Number and proportion of patients and alleles with at least one of the listed mutations

Mutation	Patients		Alleles	
	n	%	n	%
F508del	1017	85.8	1555	65.6
N1303K	65	5.5	71	3.0
G542X	60	5.1	67	2.8
3272-26A->G	39	3.3	39	1.6
1717-1G->A	37	3.1	37	1.6
S1251N	30	2.5	30	1.3
A455E	27	2.3	27	1.1
2789+5G->A	24	2.0	24	1.0
L927P	21	1.8	22	0.9
R117H	22	1.9	22	0.9
3849+10kbC->T	18	1.5	18	0.8
R553X	17	1.4	17	0.7
2183AA->G	16	1.3	16	0.7
R1162X	13	1.1	16	0.7
W1282X	16	1.3	16	0.7
[delta]I507	10	0.8	10	0.4
3659delC	9	0.8	9	0.4
306insA	8	0.7	8	0.3
D1152H	7	0.6	7	0.3
E60X	7	0.6	7	0.3
W401X	7	0.6	7	0.3
394delTT	6	0.5	7	0.3
L227R	4	0.3	7	0.3

Mutation	Patients		Allèles	
	n	ù	n	%
IVS8-T5	6	0.5	6	0.3
R334W	6	0.5	6	0.3
Y1092X	6	0.5	6	0.3
G178R	5	0.4	5	0.2
G85E	5	0.4	5	0.2
G970R	5	0.4	5	0.2
L165S	5	0.4	5	0.2
R347H	5	0.4	5	0.2
Q493X	5	0.4	5	0.2
Del exon 2- 3	4	0.3	5	0.2
G551D	4	0.3	5	0.2
3905insT	4	0.3	4	0.2
4218insT	4	0.3	4	0.2
621+1G->T	4	0.3	4	0.2
S1255P	4	0.3	4	0.2
3120+1G->A	3	0.3	4	0.2
711+1G->T	3	0.3	4	0.2
L997F	3	0.3	4	0.2
D579G	.	.	4	0.2
Others	**164**	**13.8**	**166**	**7.0**
Not identified	**52**	**4.4**	**66**	**2.8**
subtotal			**2361**	
missing	**8**	**0.7**	**11**	**0.5**
Total			**2372**	

The mutations detected in less than four patients were summarized into the "others" category for this purpose.

CHAPTER 5: ANTHROPOMETRY (HEIGHT, WEIGHT AND BMI)

Persons with CF are known to be prone to nutritional deficiencies. Because of thick mucus, the pancreas is unable to produce and/or carry digestive enzymes to the gut. This leads to poor absorption of proteins, fats and fat soluble vitamins resulting in poor weight gain and growth. Nutritional care is of great importance for patients with CF. Maintaining or achieving a better nutritional status has a positive impact on lung function. For this reason, close follow-up of height, weight and BMI is standard practice in all CF care centers.

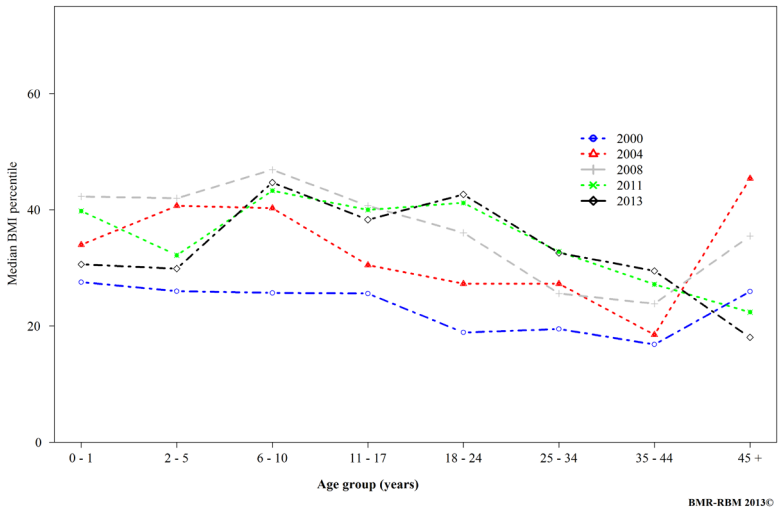
We present classifications of the patients into BMI, height and weight percentiles, compared to their healthy peers. The analysis of the height, weight and BMI z-scores is based on CDC[14] and Cachera[15] reference equations. An evolution of BMI and height data from selected years is also presented by age category.

In this section, data from 136 patients with a transplant (64 male, 72 female) were excluded from the analysis.

BMI PERCENTILES USING CACHERA REFERENCE VALUES

Cachera equations cover BMI z-scores for ages 0.0 - 58.0 years for male (56.0 female) patients. In 2013 data from 1001 patients was analysed. The figure 6 shows a general trend to better median BMI over the years with lines moving upwards until 2008. After this, there has been a further improvement of the median BMI in the adults, and a stabilization in age categories 6-17 years. No further improvement was found from 2008 onwards in the patients younger than 5 years.

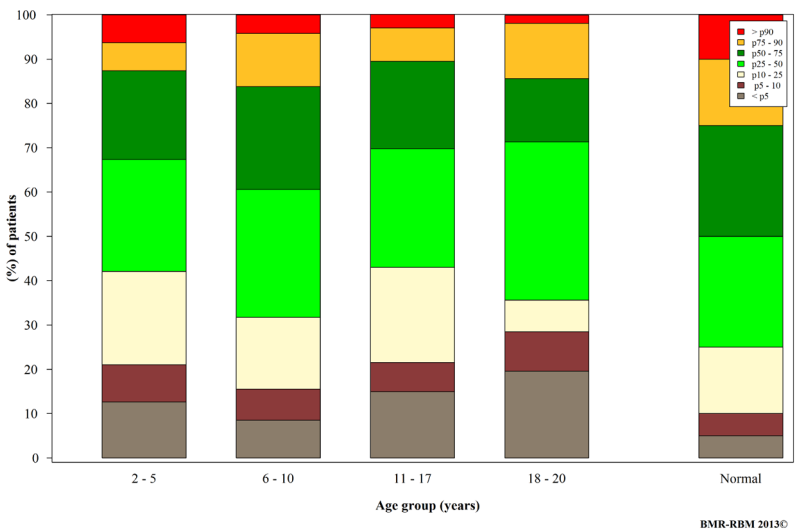
Figure 6 | Median BMI percentile by age group and year



BMI PERCENTILES USING THE CDC GROWTH CHARTS

CDC growth charts cover BMI for ages 2.0 – 20.1 years. The trend depicted is quite similar to the Cachera references above. In 2013 data from 521 patients was analysed. The figure below displays the proportion in each percentile category.

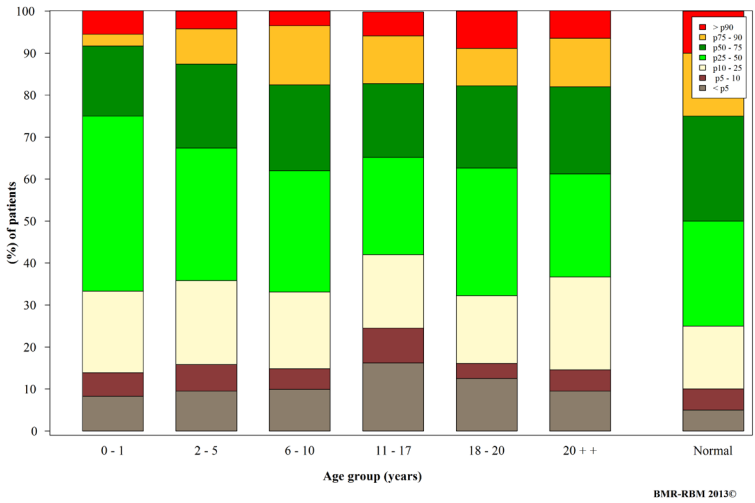
Figure 7 | CDC BMI percentiles by age



HEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover height from 0.0 – 20.1 years. The values for patients older than 20.1 years are based on the extrapolated reference at age 20.0 years. In 2013 data from 1010 patients was analysed. The figure below indicates the proportion in each percentile category.

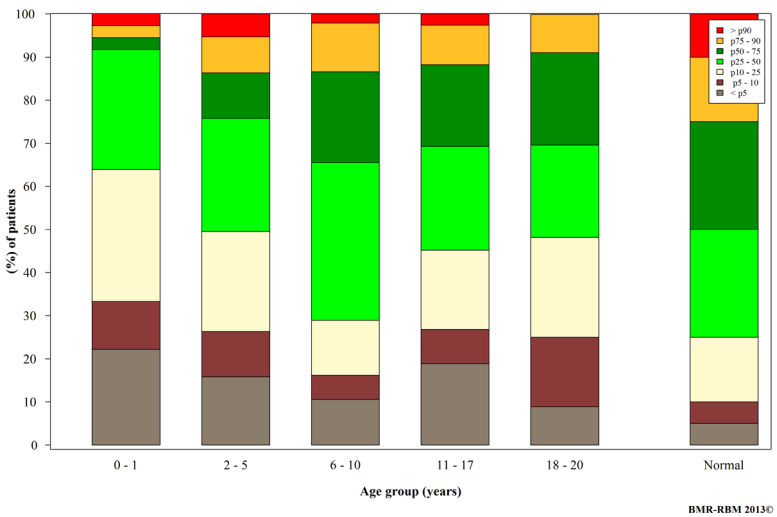
Figure 8 | CDC height percentiles by age



WEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover weight from 0.0 – 20.1 years. In 2013 data from 557 patients was analysed. The figure below indicates the proportion in each percentile category. A higher proportion with weight for age below the 5th percentile is seen in patients up to one year. This proportion declines in the years thereafter and increases again in pre-teenage children over the age 11 years. This pattern has been observed in the registry over the years.

Figure 9 | CDC Weight percentiles by age



CHAPTER 6: SPIROMETRY (LUNG FUNCTION)

Because most patients with CF develop progressive pulmonary disease, measures of pulmonary involvement, in particular FEV_1, are used to follow up the lung disease.

The forced expiratory volume in 1 second (FEV_1) is the amount of air that a person is able to expire forcefully in one second, following full inspiration. It is expressed as a percentage of the predicted value for a reference population with same age, gender and height.

The percentage of predicted FEV_1 is a clinical parameter to monitor lung function impairment. The FEV_1 partly determines the prognosis[16]. However, considerable heterogeneity exists in prognosis and severity, even among patients of the same genotype[17].

FEV_1% predicted values are divided in four classes for the CF population corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) impairment.

Since lung function measurements below the age of 6 years are not reliable, data from those patients (69 male, 62 female) was excluded from the lung function analysis. Those with a transplant (64 male, 72 female) were also excluded. The values obtained at the last consultation of the year, pre or post bronchodilator, were analysed. An evolution of lung function from selected years by age category is also presented.

PERCENTAGE OF PREDICTED FEV_1

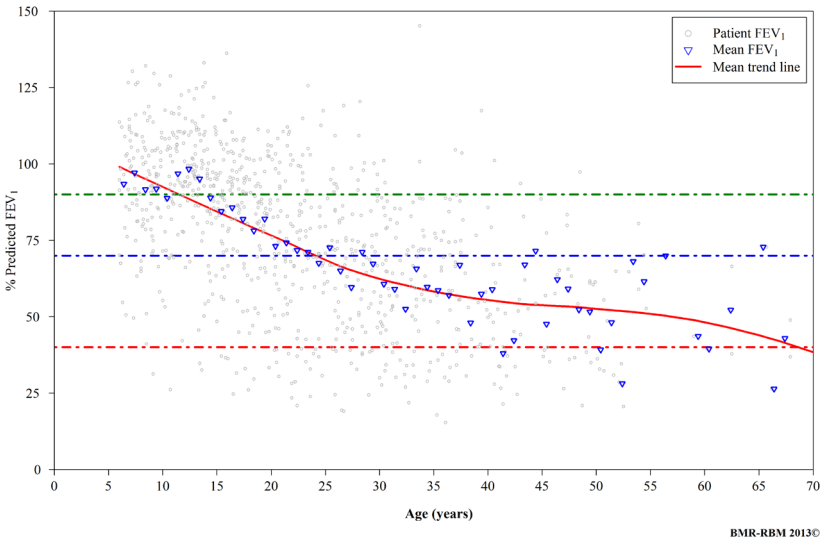
Wang's equations[18] were used for male, 6 – 17 years and female patients 6 – 15 years, while Hankinson's[19] were used for predictions for the male 18 years and above and female patients from 16 years onwards.

In 2013 data from 873 patients was analysed. The overall mean % predicted FEV_1 is 76.0 (SD = 25.7). The mean % predicted FEV_1 was 78.4 % (SD = 25.2) and 73.3 % (SD=26.0) respectively for 458 male and 415 female patients. The mean % predicted FEV_1 was 91.0 % (SD = 20.4) and 65.0 % (SD=23.5) respectively for 369 children and 504 adult patients.

Amongst the 391 F508del homozygous, the means were 73.9% (SD = 25.6) and 71.9% (SD = 25.7) respectively for the 205 male and 186 female patients. The means were 89.3% (SD = 22.1) and 61.3% (SD = 21.4) respectively for the 162 children and 229 adults F508del homozygous.

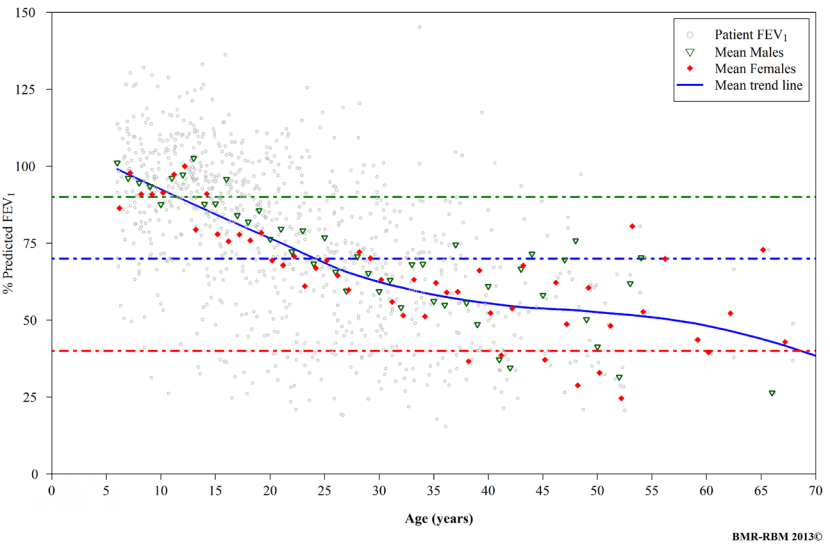
The figure below shows a scatter plot of the FEV_1 (% of predicted) with the means calculated at yearly intervals. It shows on average declining values with age, with a steeper slope up to about 35 years of age when it levels off.

Figure 10 | Mean percentage of predicted FEV_1 by age



In the figure below, the scatter plot is plotted with means according to age and gender.

Figure 11 | Mean percentage of predicted FEV_1 by age and gender



FEV_1 CATEGORIES BY AGE GROUP

FEV_1% predicted values were divided in four classes for the CF population corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) lung function impairment. The table below shows the classification for children and adults based on the data collected in 2013.

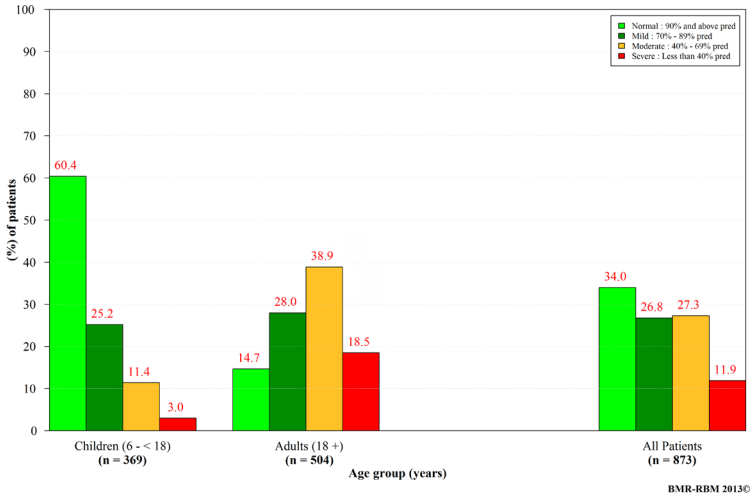
Table 8 | Proportions in each FEV_1 severity category for children and adults

Group	Children (6-17 years)		Adults (≥ 18 years)		Total	
	n	%	n	%	n	%
Normal : ≥ 90% predicted	223	60.4	74	14.7	297	34.0
Mild : 70% - 89% predicted	93	25.2	141	28.0	234	26.8
Moderate : 40% - 69% predicted	42	11.4	196	38.9	238	27.3
Severe : < 40% predicted	11	3.0	93	18.5	104	11.9
subtotal	**369**		**504**		**873**	
transplants	**4**		**132**		**136**	
< 6 years	**131**		**.**		**131**	
missing	**1**	**.**	**12**	**.**	**13**	
total	**505**		**648**		**1153**	

The FEV_1 was higher than 70.0% of predicted in 60.8% of the patients :- in 85.6% of the children (6 – 17 years) and 42.7% of the adults (18 years and above).

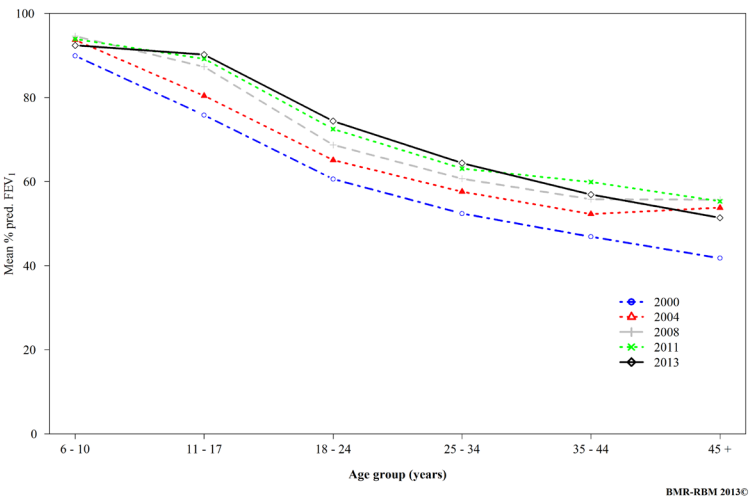
The figure 12 represents the lung function severity groups for children and adults in 2013. Using the Wang – Hankinson equations, 11.9% of the patients had FEV_1 below 40%, 34.0% had FEV_1 of at least 90% in 2013. This is comparable to 2012 where 34.0% of the patients had also FEV_1 of at least 90%.; 59.7% of the children and 14.5% of the adults.

Figure 12 | Percentage of predicted FEV_1 groups by age group



In the figure below, the mean % of predicted FEV_1 calculated cross-sectional shows improving lung function over time in all age categories.

Figure 13 | Mean percentage of predicted FEV_1 by age group for selected years



In the figure 14, a comparison of the proportion in each severity group over selected years is given. There has been a general increase in the number of children with normal lung function and a reduction in the proportion of adults with severe lung function impairment over the years.

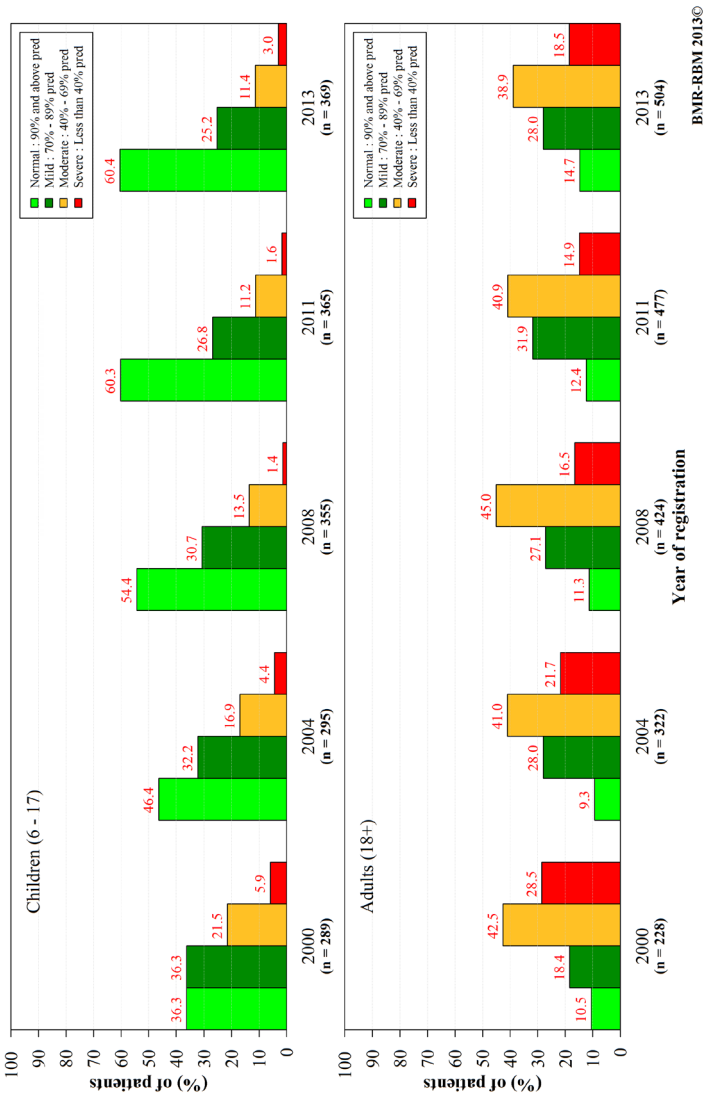


Figure 14 | Percentage of predicted FEV_1 groups by age group for selected years

CHAPTER 7: MICROBIOLOGY

Decreased mucus clearance and impaired bacterial killing lead to inflammation and infection and are responsible for progressive lung damage.

Bacterial colonisation occurs very early in the natural history of the disease. In children common bacteria such as *Staphylococcus aureus* and *Haemophilus influenzae* infect the lungs[22]. Infection by *Pseudomonas aeruginosa* and sometimes *Burkholderia cepacia* complex and other gram negative pathogens occur at a latter age. The airways of patients with CF may also be chronically colonized by fungi like *Aspergillus fumigatus*[23].

One of the main goals of CF care is to prevent or postpone by all possible means infections with the above named pathogens and to reduce the risk of chronic infection which increases respiratory morbidity and treatment burden.

In this section, we present the annual prevalence of recorded pathogens including the prevalence of chronic infections. Data from transplant patients was excluded from the respiratory microbiology analysis.

The analysis presented is based on the pathogens found at least once during the whole year (annual prevalence). The prevalence is also compared over a selected period in children and adults or by age category.

ANNUAL PREVALENCE OF ISOLATED PATHOGENS

During the year 2013, 1009 (99.2%) of the 1017 non-transplant patients had at least one culture done. The largest proportion (78.7%) had at least four exploitable months during the year. Sputum samples were done in 794, throat swabs in 367 while 32 patients had a bronchoalveolar lavage.

The prevalence shown in table 9 refers to pathogens ever found during the year.

Table 9 | Isolated pathogens and microbes 2010 - 2013

	2010		2011		2012		2013	
	n	%	n	%	n	%	n	%
Methicillin Resistant Staphylococcus aureus (MRSA)	86	8.7	97	9.5	87	8.8	66	6.5
Methicillin Sensitive Staphylococcus aureus (MSSA)	564	56.8	598	58.7	612	61.8	630	62.4
Pseudomonas aeruginosa	385	38.8	426	41.8	420	42.4	426	42.2
Aspergillus	283	28.5	329	32.3	346	34.9	331	32.8
Haemophilus influenzae	269	27.1	276	27.1	294	29.7	288	28.5
Stenotrophomonas maltophilia	90	9.1	91	8.9	118	11.9	119	11.8
Achromobacter xylosoxidans	74	7.5	91	8.9	106	10.7	106	10.5
Burkholderia cepacia complex	24	2.4	37	3.6	40	4.0	45	4.5
Scedosporium spp.	6	0.6	8	0.8	9	0.9	4	0.4
Non – tuberculous mycobacterium (NTM)	6	0.6	8	0.8	11	1.1	8	0.8
Other pathogen	200	20.1	160	15.7	147	14.8	168	16.7

Percentages are based on 993, 1019, 991 and 1009 patients with a culture respectively for the years 2010 through 2013

While 5.0% of the children (n = 25) and 8.1% of the adults (n = 41) had MRSA, 28.3% (n = 142) and 55.9% (n = 284) respectively had a *Pseudomonas aeruginosa* infection. *Burkholderia cepacia* complex infection was found in 12 (2.4%) children and 33 (6.5%) adults. The prevalence of *Achromobacter xylosoxidans* in 2013 (10.5%) is significantly higher (P = 0.0169) than the value in 2010 (7.5%).

ANNUAL PREVALENCE OF CHRONIC INFECTIONS

Table 10 | Chronic infections and colonisation 2010 - 2013

	2010		2011		2012		2013	
	n	%	n	%	n	%	n	%
Chronic *Pseudomonas aeruginosa*	294	29.6	287	28.2	276	27.9	296	29.3
Chronic *Burkholderia cepacia complex*	15	1.5	23	2.3	27	2.7	29	2.9
Chronic *Stenotrophomonas maltophilia*	23	2.3	30	2.9	27	2.7	37	3.7
Chronic *Achromobacter xylosoxidans*	29	2.9	39	3.8	54	5.4	64	6.3
Chronic MRSA	46	4.6	45	4.4	51	5.1	45	4.5

Percentages are based on 993, 1019, 991 and 1009 patients with a culture respectively for the years 2010 through 2013

About 11.4% of the children (n = 57) and 47.0% of the adults (n = 239) had chronic *Pseudomonas aeruginosa* infection.

The figures below show the annual prevalence of infections over selected periods. Prevalence up to 2006 was based on a positive culture at the last consultation of the year. Since 2007, prevalence is based on any positive culture for a given pathogen among those collected during the year. In the interpretation of the graphs below, this should be taken into account.

Figure 15 | Prevalence of *Burkholderia cepacia* complex infections by year and age

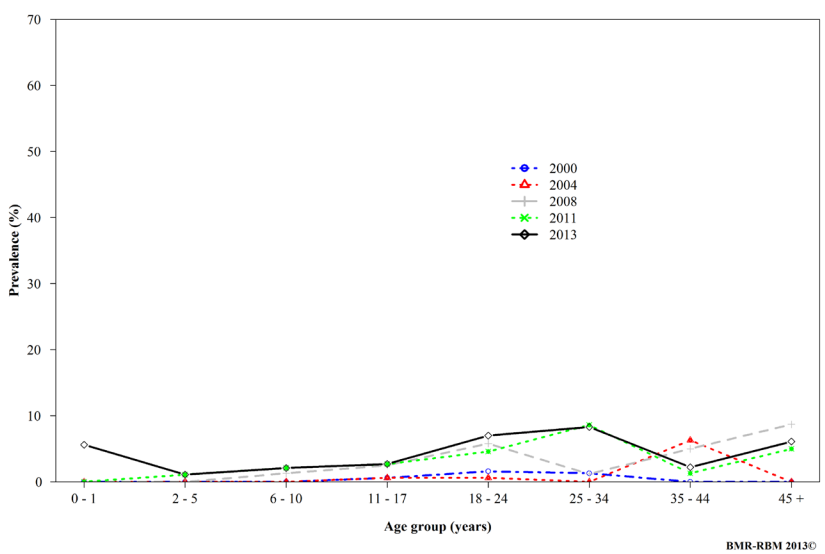


Figure 16 | Prevalence of *Pseudomonas aeruginosa* infections by year and age

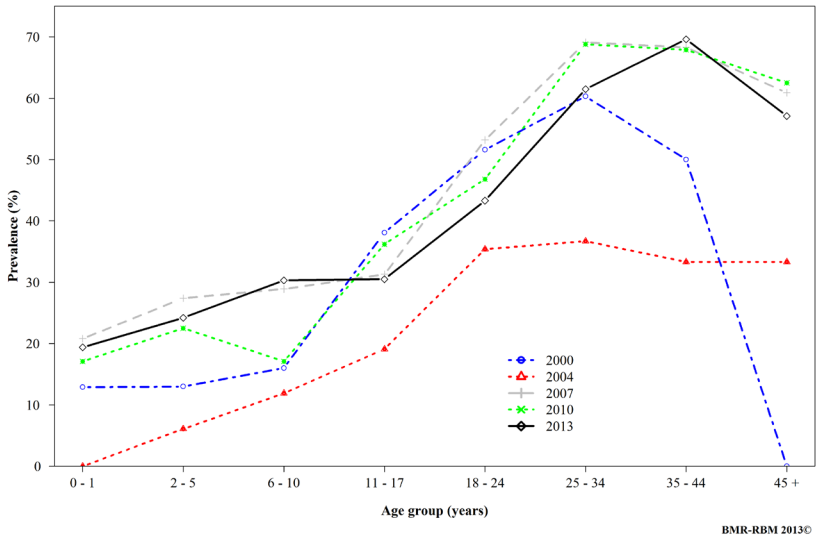
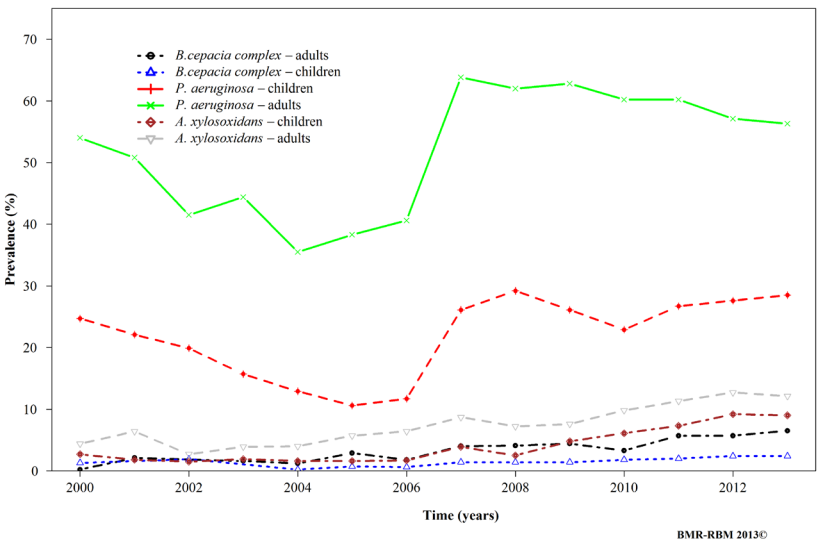


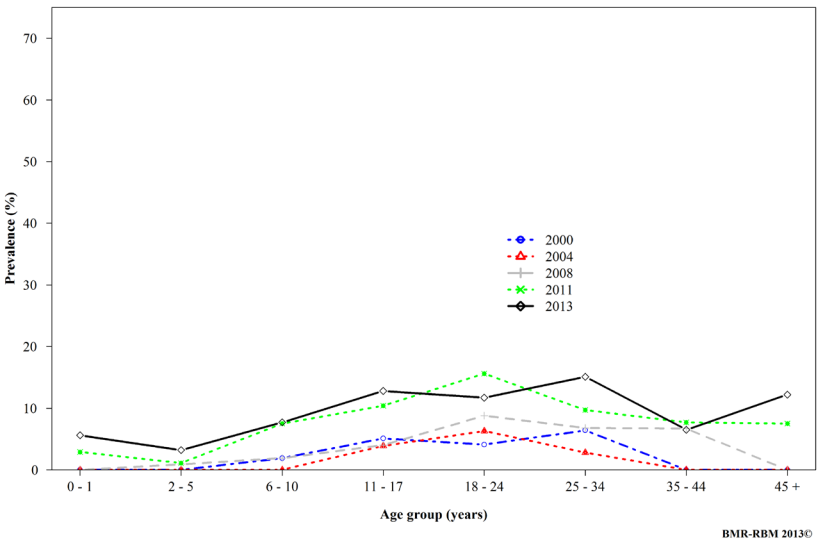
Figure 17 | Prevalence of *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans* and *Burkholderia cepacia* complex by age group and year



The change in the prevalence over the period 2006 – 2007 is due to the change in the reporting system from a positive test at the last culture of the year (until 2006) to any positive ever found among the cultures done during year (since 2007).

There has been an increase in the importance of some pathogens such as *Achromobacter xylosoxidans*, figures 17 - 18, which have shown an increase in the prevalence over the years.

Figure 18 | Prevalence of *Achromobacter xylosoxidans* by age group and year



CHAPTER 8: COMPLICATIONS

Cystic Fibrosis affects the respiratory[24], digestive[25,26], and reproductive[27,28], systems with variable degrees of severity. The defective chloride channel in CF causes a range of disturbances within the human body. Chloride channels are needed to regulate fluid exchanges at the surface of the epithelial cells. In CF, the transport through the cell wall of chloride, other ions and water are disturbed. Complications in CF are mainly found in organs where mucus linings are needed (airways, intestines) and glands which need fluid to excrete their substances (pancreas, testis...).

In this section we cover the most frequent complications recorded during the year by age category. The overall prevalence is compared to the prevalence reported in previous years.

Data from transplant patients was excluded from the analysis of complications.

RESPIRATORY COMPLICATIONS

Allergic bronchopulmonary aspergillosis (ABPA) : ABPA is an allergic reaction to Aspergillus fumigatus a fungus that colonizes the airway of people with CF. Diagnosis is not always obvious as many symptoms of ABPA (cough, wheezing, shortness of breath, decline in lung function) are common symptoms of CF lung disease. Diagnosis relies on a combination of the clinical picture, blood tests, lung function and imaging.

Nasal polyps : In patient with CF, chronic infections of the upper airways (chronic sinusitis) may cause the formation of nasal polyps which are mucosal overgrowths. They are responsible for nasal obstruction.

Haemoptysis : When the damage within the bronchi reaches a blood vessel the patient with CF is coughing blood. Haemoptysis is mild in most cases, but sometimes the bleeding is so severe that a therapeutic embolization of the bleeding vessel is needed.

A pneumothorax occurs when air reaches the vacuum of the pleural space, mainly caused by destruction of the alveoli causing the leakage of air. This complication is more common in the adults who have more advanced lung disease[29,31] .

Table 11 | Prevalence of respiratory complications

Complication	2010		2011		2012		2013	
	n	%	n	%	n	%	n	%
Allergic Bronchopulmonary aspergillosis (ABPA)	64	6.4	63	6.1	40	3.9	96	9.4
Pneumothorax	1	0.1	2	0.2	3	0.3	2	0.2
Nasal polyps	120	11.9	85	8.3	108	10.6	155	15.2
Sinusitis*	210	20.9	169	16.4	177	17.4		
Massive haemoptysis	18	1.8	10	1.0	6	0.6	11	1.1
Massive haemoptysis requiring embolization	9	0.9	7	0.7	2	0.2	5	0.5

Percentages are based on 1007, 1030, 1018 and 1017 non transplant patients respectively for the years 2010 through 2013
*Not collected since 2013

ABPA is the most frequent major respiratory complication. In 2012 it was reported in 13 (2.6%) children and 27 (5.3%) adults. The prevalence in 2013 was higher with 28 (5.6%) children and 68 (13.2%) adults. This is a significant increase ($P < 0.0001$) in the overall prevalence compared to 2012 and the previous years.

GASTRO-INTESTINAL AND ENDOCRINE COMPLICATIONS

Pancreatic insufficiency : Pancreatic enzymes are needed to digest fat and proteins. Pancreatic insufficiency is the inability of the pancreas to produce and transport enough enzymes in the duodenum to digest fat and proteins resulting in malabsorption with steatorhea (fatty stools), malnutrition and a deficiency in fat-soluble vitamins (ADEK). A small proportion of patients with CF remains pancreatic sufficient (10-15%).

Gastro-oesopahgeal reflux is a condition in which contents of the stomach or small intestine repeatedly move back up into the oesophagus. When repeated it causes oesophagitis and can lead to malnutrition but also respiratory infections and it may worsen the respiratory function.

Distal intestinal Obstruction syndrome (DIOS) : The intestinal cells with defective chloride channels produces thick intestinal mucus which in combination with stools with many undigested food residue can cause intestinal obstruction. DIOS is especially found in the terminal ileum and caecum. It can causes acute abdominal pain and, if left untreated, it can progress to a complete bowel obstruction with vomiting. DIOS usually responds to medical treatment but in a few cases a surgical intervention may be required.

Liver disease : All patients with CF present a defect CFTR protein in their biliary tract. Nevertheless some persons do develop liver disease leading to cirrhosis (replacement of the liver tissue by fibrosis) and others do not; an underlying cause is an alteration of the epithelium tract that gets obstructed by mucus plugs. Sometimes cirrhosis evolves in portal hypertension and in advanced cases a liver transplant can be proposed.

CF related Diabetes : Insulin is produced in the endocrine part of the pancreas. It is a hormone which maintains the balance of sugar in blood. Malfunctioning of the endocrine part of the pancreas by fibrosis leads to an insufficiency of the secretion of insulin leading to diabetes.

Table 12 | Prevalence of gastro-intestinal and endocrine complications

Complication	2010		2011		2012		2013	
	n	%	n	%	n	%	n	%
Pancreatic Insufficiency	847	84.1	855	83.0	830	81.5	838	82.4
Acute pancreatitis	5	0.5	11	1.1	6	0.6	8	0.8
CF related diabetes (CFRD)	122	12.1	143	13.9	128	12.6	159	15.6
Impaired Glucose Tolerance (IGT)	85	8.4	68	6.6	59	5.8	66	6.5
Peptic ulcers*	2	0.2	4	0.4	2	0.2		
Gastro-oesophageal reflux	190	18.9	179	17.4	198	19.4	188	18.5
Cirrhosis with portal hypertension	33	3.3	32	3.1	33	3.2	43	4.2
Gallstones	26	2.6	28	2.7	32	3.1	21	2.1
Intestinal obstruction (surgery)	5	0.5	5	0.5	4	0.4	5	0.5
Intestinal obstruction (no surgery)	75	7.4	55	5.3	74	7.3	52	5.1
Gastroparesis	3	0.3	2	0.2	7	0.7	3	0.3
Clostridium infection (treatment needed)	7	0.7	10	1.0	4	0.4	5	0.5

Percentages are based on 1007, 1030, 1018 and 1017 non transplant patients respectively for the years 2010 through 2013
*Not collected since 2013

The data shows that 424 (84.6%) of the children and 414 (80.2%) of the adults are pancreatic insufficient. CFRD was reported in 22 (4.4%) of the children and 137 (26.6%) of the adults.

MISCELLANEOUS COMPLICATIONS

Reproductive system complications : Most men (95 – 99%) with cystic fibrosis are infertile because of congenital bilateral absence of the vas deferens (which allows the transport of the spermatozoids). However, as the production of spermatozoids is being preserved, techniques of assisted procreation are possible. Although women with cystic fibrosis may be less fertile than other women, it is possible for them to conceive and to have successful pregnancies. Those pregnancies require a higher surveillance.

Osteopenia and osteoporosis: Osteopenia and osteoporosis which are the result of a progressive loss of the bone mass are more frequent and earlier in cystic fibrosis due to various risk factors like malabsorption of vitamins D, use of glucocorticoids, chronic inflammation…

CF related arthritis/arthropathy: Patients with advanced lung disease sometimes develop painful inflammation of joints. The exact cause is not known and regression of joint symptoms is usually seen when respiratory disease is stabilized.

Psychiatric disease: It is difficult to define and quantify, however, the psychological repercussions of this pathology are frequent and often involve a bad compliance with the treatment.

Table 13 | Other complications reported

Complication	2010		2011		2012		2013	
	n	%	n	%	n	%	n	%
CF related Arthritis / arthropathy	52	5.2	98	9.5	72	7.1	102	10.0
Cancer	2	0.2	3	0.3	2	0.2	3	0.3
Surgery	68	6.8	98	9.5	66	6.5	72	7.1
General anaesthesia	66	6.6	86	8.3	73	7.2	102	10.0
Others	138	13.7	126	12.2	143	14.0	161	15.8
Psychiatric disease	18	1.8	23	2.2	24	2.4	36	3.5
Osteopenia/ Osteoporosis*	130	12.9						
Osteopenia			107	10.4	112	11.0	117	11.5
Osteoporosis			24	2.3	24	2.4	23	2.3
Hypertension requiring treatment			16	1.6	14	1.4	31	3.0

Percentages are based on 1007, 1030, 1018 and 1017 non transplant patients respectively for the years 2010 through 2013
*Since 2011, data on the Osteopenia (the lowest z-score on Dual X-ray absorptiometry (DXA) between -1 and -2.5) and Osteoporosis (the lowest z-score on DXA < -2.5) complications are recorded separately.

CHAPTER 9: THERAPY, MEDICATION AND HOSPITALIZATION

Till today no definitive cure for CF exists. The problems of all cystic fibrosis patients are related to defective epithelial function with impaired production of mucus and fluids leading to complications described in the previous section. Treatment of the disease is therefore mostly based on preventing or reducing symptoms in order to avoid complications or to stabilize them. Thanks to those preventive and symptomatic treatments, a steady improvement of the health status is obtained together with a better life expectancy.

In this section, the most common treatments and therapy used in 2013 is presented. An evolution of the proportion of patients hospitalized by age category for selected years is also presented. This analysis excludes data from the transplant patients.

Except for anti-conceptive therapy, the percentages are based on 501 children and 516 adults from a total of 1017 non transplant patients.

VISITS TO CF CARE CENTERS AND HOSPITALIZATION

In 2013, most of the patients 84.7% (n=850) had a minimum of the four recommended visits to a CF reference centre during the year.

The figures below concern the number of days of hospitalization. In 2013, 55.4% of the patients were not hospitalized. Among the children (n=501) and adults (n=516), 62.8% and 48.1% respectively were not hospitalized.

Figure 19 | Number of hospitalization days

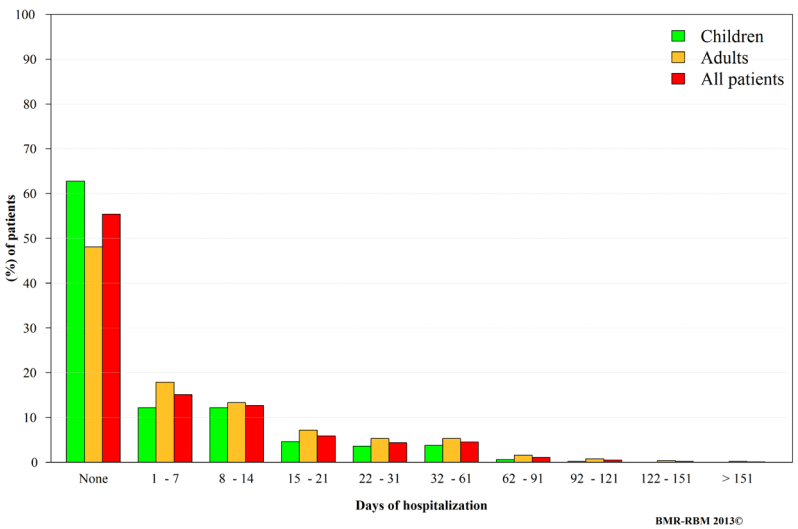
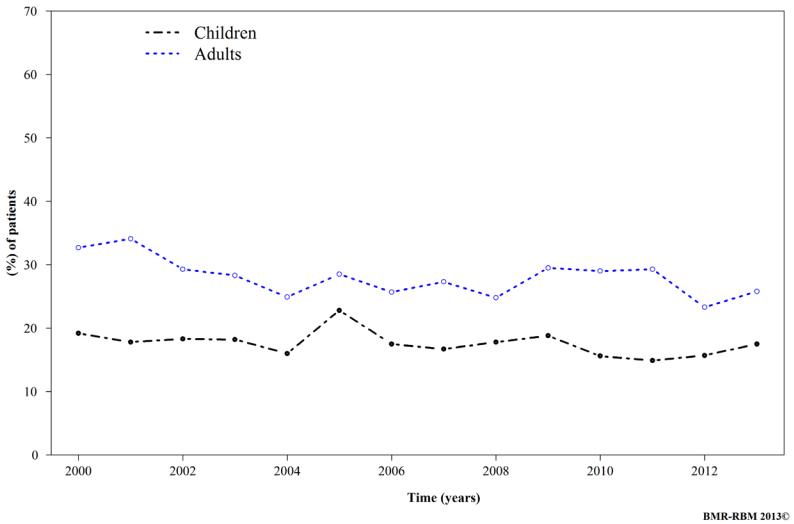


Figure 20 | Proportion of patients hospitalized for more than two weeks by age and year



RESPIRATORY THERAPIES

To Prevent and treat respiratory infections : Because mucus is stuck within the bronchi, evacuating mucus is one the most important interventions. This is the reason why a patient with CF has regular chest physiotherapy sessions. Most of the patients also learn the technique of autogenic drainage where the patients, through breathing techniques, perform drainage to himself.

Different types of inhaled medication are used to treat the symptoms of CF. Maintenance inhaled medications include mucolytics that thin the sticky airway secretions such as RhDNase or hypertonic saline. Bronchodilators are given to open the bronchi. Inhaled antibiotics are used to treat infection, prevent or postpone colonization. In advanced lung disease oxygen is needed[32].

Every year, almost half of the patients with CF are hospitalized, mostly for the treatment of a worsening pulmonary status (pulmonary exacerbations) caused by an infection requiring intravenous antibiotics.

Inflammation caused by repeated infections plays an important role in the progression of lung injury. This explains the interest in the use of anti-inflammatories such as azithromycin, inhaled corticoids or other anti-inflammatory drugs as complementary treatment.

Table 14 | Physiotherapy, inhalation therapy, oral anti-inflammatory and antibiotics

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Regular chest physiotherapy	490	97.8	458	88.8	948	93.2
Antibiotics	446	89.0	449	87.0	895	88.0
Oral only	302	60.3	186	36.0	488	48.0
IV only	7	1.4	12	2.3	19	1.9
Oral and IV	137	27.3	251	48.6	388	38.2
Inhaled antibiotics	252	50.3	342	66.3	594	58.4
Inhalation therapy (excluding antibiotics)	486	97.0	488	94.6	974	95.8
RhDnase	343	68.5	387	75.0	730	71.8
Other mucolytics	118	23.6	94	18.2	212	20.8
Hypertonic saline	280	55.9	300	58.1	580	57.0
Bronchodilators	387	77.2	397	76.9	784	77.1
Corticosteroids	213	42.5	315	61.0	528	51.9
Intranasal steroids	250	49.9	254	49.2	504	49.6
Oral anti-inflammatories	178	35.5	338	65.5	516	50.7
Azithromycin	161	32.1	315	61.0	476	46.8
Systemic corticosteroids	20	4.0	40	7.8	60	5.9
NSAID	6	1.2	48	9.3	54	5.3
Oxygen therapy	4	0.8	18	3.5	22	2.2

GASTRO-INTESTINAL AND NUTRITIONAL THERAPIES

Optimizing the nutritional status: Because the nutritional status of a patient is correlated with the disease severity, every person with CF should take a well-balanced high-calorie and high-fat diet. Most individuals with CF are pancreatic insufficient[25] and must take pancreatic enzymes at every meal to digest food correctly. Also supplements of vitamins ADEK are administered routinely. Some people with CF can only obtain a correct nutritional status by receiving supplemental feedings given overnight by a tube placed into the stomach (enteral feeding) or given intravenously (parenteral feeding).

Table 15 | Digestive and nutritional therapies

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Pancreatic enzymes	432	86.2	419	81.2	851	83.7
Fat soluble vitamins (A,D,E and K)	452	90.2	414	80.2	866	85.2
Proton pump inhibitor and/or H2 receptor blocker	220	43.9	260	50.4	480	47.2
Ursodeoxycholic acid	127	25.3	122	23.6	249	24.5
Enteral feeding	18	3.6	8	1.6	26	2.6
Parenteral feeding	3	0.6	15	2.9	18	1.8
Gastrostomy tube	20	4.0	17	3.3	37	3.6

OTHER TREATMENTS

Monitoring the onset of other complications followed by appropriate therapeutic interventions: Possible complications of the disease need to be regularly monitored. When clinical, biological or imaging finding point towards liver disease, ursodeoxycholic acid is started. This hydrophilic bile acid normally present in human bile stimulates the biliary secretion so that the bile is less thick and would prevent liver damage.

Depending on complications, other medications are prescribed such as insulin therapy when a patient develops CF related diabetes or bisphosphonates for osteoporosis.

The treatment burden for CF patients is high. Most CF patients spend a lot of time every day performing therapies. This imposes also a substantial burden on their family[33].

Table 16 | Other treatments

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Insulin therapy	16	3.2	101	19.6	117	11.5
Oral therapy for diabetes	2	0.4	34	6.6	36	3.5
Bisphosphonates	4	0.8	13	2.5	17	1.7
Anti-conceptive therapy (females aged 12 and over)	10	16.7	98	51.6	108	43.2
Prokinetics	23	4.6	43	8.3	66	6.5
Use of Psychopharmaca	11	2.2	61	11.8	72	7.1
CFTR Modulating Therapy	13	2.6	22	4.3	35	3.4

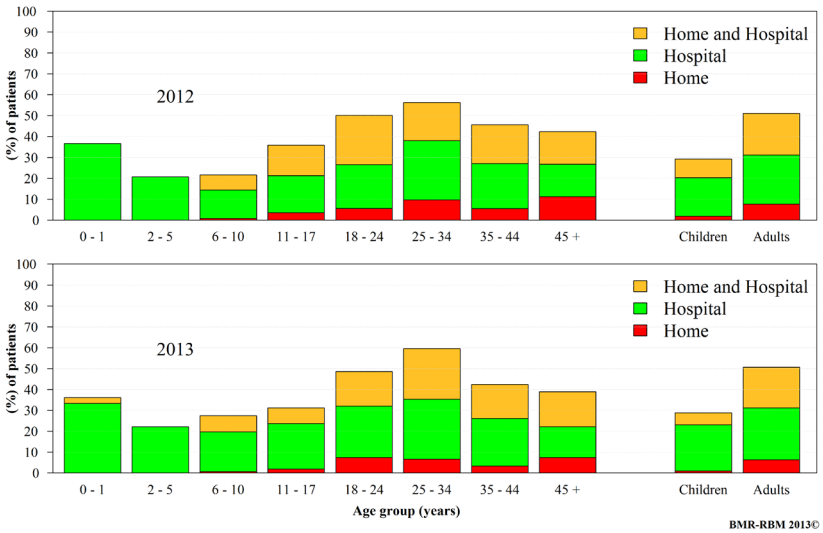
Out of 1017 non transplant patients, 159 had CFRD, among these 105 used insulin therapy only, 20 used only oral therapy for diabetes while nine patients

used both oral therapy for diabetes and insulin therapy. However, 25 patients with CFRD used none of the two treatments.

INTRAVANEOUS ANTIBIOTICS

In the year 2013, 39.8% (n = 405) of the patients received IV antibiotics; 28.7% (n = 144) amongst the children and 50.6% (n = 261) among the adults. The figures below show the proportion that received IV antibiotics at home and/or in hospital in 2012 (top) compared to 2013 (bottom). There are few patients below six years taking IV antibiotics at home. This proportion increases with age.

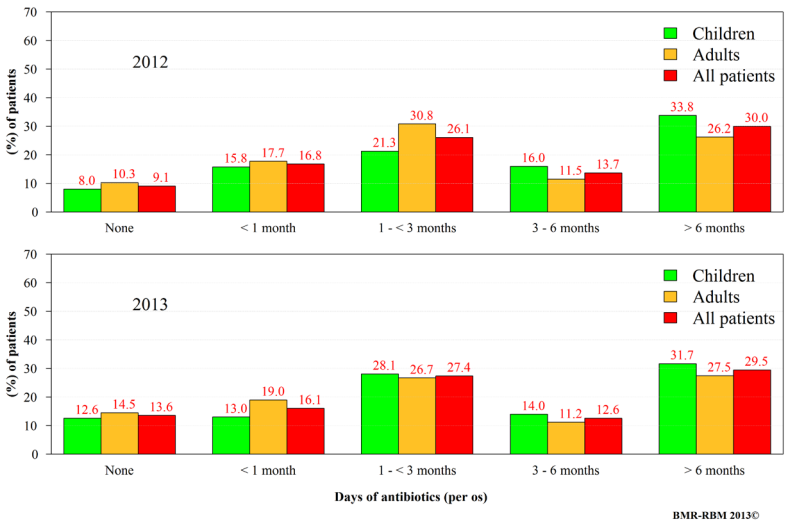
Figure 21 | Proportion that used IV antibiotics treatment by age category



ORAL ANTIBIOTICS

The figures below show the days of oral antibiotics used in 2012 (top) and compared to 2013 (bottom). About 13.6% of the patients did not take any oral antibiotics; 12.6% of the children and 14.5% of the adults. About 30.0% of the patients, more than a quarter of both the children (31.7%) and adults (27.5%), used oral antibiotics for over six months.

Figure 22 | Days of oral antibiotics



CHAPTER 10: TRANSPLANTS AND CYSTIC FIBROSIS

When a patient with CF develops severe and progressive lung disease, lung transplantation may become an option. However, like other major surgeries, lung transplantation involves significant risks. A lung transplant is indicated only for patients who have a severe disease and who have exhausted all other forms of conventional medical treatment. For these patients, lung transplantation may offer prolonged survival and an improved quality of life; in some cases even a 'new' life.

The success rate of lung transplantation for CF patients is steadily improving. At present the actuarial survival rate is > 65 % at 3 years and > 40 % at 10 years after surgery[34]. The longest surviving patients had their transplant operations now more than 20 years ago.

The first (heart)-lung transplant in a Belgian patient with CF was performed in 1988. Since this time more than 200 patients with CF[35] (194 reported in the CF registry) have received a (heart)-lung transplant in Belgium and approximately 10 lung transplants per year are now performed for CF. Some patients with CF will need other types of transplantations such as liver transplantation for end-stage CF-related liver cirrhosis or renal transplantation for end-stage renal disease because of diabetes, antibiotic toxicity or the toxicity of immunosuppressive drugs required after lung transplantation.

This is a short analysis of data concerning the transplant patients. It includes a table with all transplants ever reported in the registry. This table shows the type and year of transplant and also the number of patients presumed still alive by the time of data collection 2013, categorized by the year of first transplant.

TRANSPLANT STATUS

The registry records show that since inception of the registry in 1998, at least 202 patients, 96 male and 106 female, have benefitted from transplantation; either single or multiple. There are 15 patients with a transplant on more than one occasion.

The age at the first transplant was estimated using the last consultation in the year of transplant where available or the last day of the year if the former was missing. The data shows that the mean (SD) and median (IQR) age of the transplant patients in the year of the first transplant was 26.8 (9.0) and 27.0 (11.0) years respectively. The oldest patient at first transplant was 58.0 years. About 12.4% (25 patients) had the first transplant done before age 18 years.

In 2013, there were 142 patients with a recorded transplant. The mean (SD) and median (IQR) age of the transplant patients reported as alive in 2013 was 34.8 (9.9) and 34.0 (14.0) years respectively with a range of 15.0 – 64.0 years at the last consultation in 2013. 68 were male while 74 were female, more than 96.0% of the transplant patients in the 2013 data were adults. Two transplant patients died in 2013.

The data presented in table 17 concerns all recorded transplants in the registry and is compared with data of patients reported alive by the time of data collection for year 2013 (the numbers in the far right column). Slight differences may be noted with previous reports as we seek to consolidate the transplant data. In the table, the numbers of transplants performed do not add up to the number of patients.

TYPE OF TRANSPLANT

The most frequent transplant done is the Lung transplant, either single or with a liver or heart. So far, 176 isolated lung transplants have been carried out.

Table 17 | Type of transplant by year

Year	Type of transplant							Totals	
	Kidney	Liver	Lung	Lung-Heart	Heart	Liver-Kidney	Lung-liver	Transplants performed	Patients Alive
1991	.	.	.	2	.	.	.	2	1
1992	.	.	.	.	.	.	.	.	-
1993	.	.	.	2	.	.	.	2	1
1994	.	.	.	3	.	.	.	3	1
1995	.	1	2	3	.	.	.	6	1
1996	.	.	.	1	.	.	.	1	-
1997	.	.	1	3	.	.	.	4	4
1998	.	.	9	1	.	.	.	10	3
1999	.	.	5	.	.	.	.	5	2
2000	.	.	10	.	.	.	.	10	5
2001	.	4	13	.	.	.	1	18	14
2002	.	2	9	.	.	.	.	11	7
2003	.	1	9	.	.	.	.	10	9
2004	.	.	12	.	.	.	.	12	9
2005	.	2	9	.	.	.	1	12	7
2006	1	1	14	.	1	.	.	17	9
2007	1	1	15	.	.	.	.	17	8
2008	3	.	15	.	.	.	.	18	13
2009	.	1	9	.	.	1	.	11	9
2010	.	1	14	.	.	.	1	16	13
2011	2	.	14	.	.	.	.	16	11
2012	.	.	11	.	.	.	.	11	10
2013	1	.	5	.	.	.	.	6	5
Total	**8**	**14**	**176**	**15**	**1**	**1**	**3**	**218**	***142**

Total number of patients alive in 2013 by transplant year considering the first transplant.

Multiple transplants or grafts are counted as separate transplant occasions in the table above. A total of 218 transplants on 202 patients are so far reported in the registry. There are 15 patients who have had a transplant on more than one occasion.

CHAPTER 11: REPORTED DEATHS

This section has a summary of data on the deaths reported to the registry since inception in 1998. The number of deaths is also classified into age groups with information on the primary cause of death given in the latter part. Note that the stated causes of death are not mutually exclusive.

The data is updated each year from center reports with delays of up to two years noted in the confirmation of the data. From 2013, this background data is automatically updated using the ConsultRN module by linking the registry data collection to the national registry database. The numbers may thus differ slightly from previously reported due to this automatic update.

AGE AT DEATH

The data in the registry data shows that there have been 137 reported deaths, 72 male and 65 female. 17 (12.4%) of the deaths were in children below 18 years while 8 (5.8%) of the deaths were in children younger than ten years. The mean (SD) and median (IQR) age at death for all reported cases are 27.7 (10.7) and 26.7 (12.8) respectively with the youngest at 0.6 years and the oldest case at 59.5 years. The link to the national registry via ConsultRN from 2013 provided an automatic update of this data that resulted in the uncovering of seven previously unreported deaths. The table below shows the year and age at death for confirmed cases.

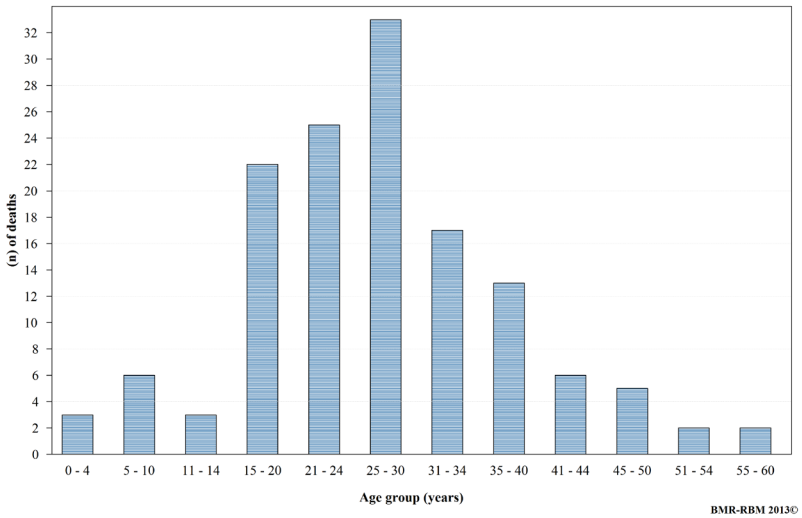
Table 18 | Categorized age at death

Age at death	Years																
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
0 - 4	1	.	.	.	.	.	.	1	1	.	.	.	.	.	.	.	3
05 - 10	.	.	.	2	.	1	.	.	.	1	.	.	.	1	1	.	6
11 - 14	.	.	.	.	.	1	.	.	.	1	.	1	.	.	.	.	3
15 - 20	2	5	1	1	.	3	2	.	2	1	2	1	.	.	1	1	22
21 - 24	.	2	2	3	1	4	2	1	.	.	.	2	3	2	1	2	25
25 - 30	1	4	1	2	3	4	3	1	.	2	3	2	.	3	2	2	33
31 - 34	1	.	3	.	4	1	1	.	.	.	.	2	2	1	2	.	17
35 - 40	.	1	2	2	2	1	.	.	2	1	.	.	.	.	2	.	13
41 - 44	.	.	.	.	.	.	1	.	1	1	.	1	.	1	1	.	6
45 - 50	.	.	.	.	.	1	.	.	.	1	1	1	.	1	.	.	5
51 - 54	.	.	.	.	.	.	.	.	.	.	.	.	1	.	1	.	2
55 - 60	.	.	.	.	1	.	.	.	.	.	.	.	1	.	.	.	2
Total	**5**	**12**	**9**	**10**	**11**	**16**	**9**	**3**	**6**	**8**	**6**	**10**	**7**	**9**	**11**	**5**	**137**
Corrections		**+1**			**+1**	**+3**								**+1**	**+1**		**7**

The table above has data on the year and age at death for confirmed cases, with an update of previously reported cases shown in a row below.

The figure below shows the number of confirmed deceased patients by age category. Most of the deceased patients were in the age category 25 – 30 years.

Figure 23 | Number of reported deaths since 1998 by age category



PRIMARY CAUSE OF DEATH

Table 19 | Primary causes of death for reported cases

Cause of death	n	% *
Respiratory	53	38.7
Transplant	35	25.5
Other	21	15.3
Cardiac	5	3.6
Liver	5	3.6
Cancer	4	2.9
Suicide	3	2.2
Trauma	1	0.7
Unknown + missing	28	20.4

*based on the total reported deaths
Causes of death are not mutually exclusive and these percentages are attributable to the specific cause of death
Other causes of death include and are not limited to: - septic shock, multi-organ failure, terminal renal insufficiency, intoxication , hypoglycaemic coma

The most common primary causes of death are associated with the respiratory system or are as a result of post-transplant complications. Amongst the deaths reported in 2013, one was a patient aged less than 18 years.

CHAPTER 12: EDUCATION AND EMPLOYMENT

People with CF are living longer. According to the registry data the median patient age had increased from 14.9 in 1998 to about 20.7 in 2013 suggesting better life expectancy. Despite their therapy burden, they are now studying, graduating and taking up a career either part-time or even full-time.

This section contains a summary of social and economic data, including education level of the people with CF registered in 2013. It details information on social allowances and employment status. All patients with substantial data, including those with a transplant are included in this analysis.

EDUCATION

Table 20 | Education level

Education level	Children		Adults		Total	
	n	%	n	%	n	%
no school	50	9.9	73	11.5	123	10.8
regular school / education attendance	452	89.9	118	18.6	570	50.1
has finished school/education	1	0.2	438	69.0	439	38.6
unknown	.	.	6	0.9	6	0.5
subtotal	**503**		**635**		**1138**	
missing	**2**		**13**		**15**	
total	**505**		**648**		**1153**	

SOCIAL ALLOWANCES AND EMPLOYMENT

Table 21 | Social allowances or benefits and employment

Description	Children		Adults	
	n	%	n	%
additional child allowance	476	94.3	77	11.9
income support (in adults)	.	.	150	23.1
disability allowance	1	0.2	102	15.7
preferential tariff (in adults)	.	.	387	59.7
pension allowance (in adults)	.	.	11	1.7
Integration support (in adults)			272	42.0
employment*	1	0.2	269	50.8

*data excludes 118 adults still actively in school

Amongst the 269 patients who said they were employed, 154 (57.2%) worked full time, 102 (37.9%) part-time while for 13 patients, this was unknown. Four children and ten adults had no information on social allowances.

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APPENDIX I

SUMMARY OF ITEMS COLLECTED IN THE REGISTRY BMR-RBM

Collect Year :2013	
Demographics	
Patient ID	
Gender	
Birthmonth/Year	/
Age	
Order in the family	
Country of origin father	
Country of origin mother	
Height of father (cm)	
Height of mother (cm)	
District	
Received transplant	
Diagnosis confirmed	
Deceased	❒
Death date	/
Diagnosis	
Date of clinical diagnosis	
Respiratory problems	❒
Nasal polyposis/chronic sinusitis	❒
Chronic dia-steatorrhea/malabsorption	❒
Meconium ileus	❒
Intestinal obstruction (other than meconium ileus)	❒
Rectal prolapse	❒
Dehydration/electrolyte imbalance	❒
Failure to thrive	❒
Prenatal diagnosis	❒
Neonatal screening test	❒
Prolonged icterus	❒
Family history	❒
Infertility	❒
Other	❒
Specify other	
Missing data	❒
NeoNatal Screening	
Sweat test	
Date of sweat test	
Type of sweat test	
Sweat test collected by	
Chloride	
Sodium	
Genotype	
Legacy name	
Chromosome 1	
Chromosome 1 other	
T status 1	
Chromosome 2	
Chromosome 2 other	
T status 2	

cDNA name
Date of genotype
Chromosome 1
Chromosome 1 other (cDNA name)
T status 1
Chromosome 2
Chromosome 2 other (cDNA name)
T status 2
Protein name
Date of genotype
Chromosome 1
Chromosome 1 other (protein name)
T status 1
Chromosome 2
Chromosome 2 other (protein name)
Nasal transep. pot. diff.
Date nasal transep. pot.
Nasal transep. pot. diff.

Observation

Life/Death

Patient alive	❒
Patient status	
Cause of Death	❒ Repiratory ❒ Cardiac ❒ Hepatic ❒ Trauma ❒ Suicide ❒ Associated with cancer Type: ❒ Associated with organ transplant Type: ❒ Other cause ❒ Cause unknown

Last consultation of the year
Date
Anthropometry
Weight (kg)
Height (cm)
Lung function
Executed
FVC (L)
FEV_1 (L)
FEF25-75 (L/s)
Best lung function of the year
Date of best LungFx
FVC (L)
FEV_1 (L)
FEF25-75 (L/s)
Height (cm)

Microbiology

Microbiology: all cultures of the registration year

Microbiololgy executed

Swabs ❒

Sputum ❒

Broncho-alveolar lavage (BAL) ❒

Missing values ❒

Pathogen ever found during the year

Pseudomonas aeruginosa ❒

Burkholderia cepacia complex ❒

Stenotrophomonas maltophilia ❒

Achromobacter xylosoxidans (Alcaligenes) ❒

Methicillin resistant *Staphlylococcus aureus* (MRSA) ❒

Methicillin sensible *Staphlylococcus aureus* (MSSA) ❒

Haemophilus influenzae ❒

Aspergillus ❒

Scedosporium prolificans ❒

Atypical Mycobaterium (NTM) ❒

Other ❒

No pathogens ❒

Missing values ❒

Colonisation

Number of exploitable months

Pseudomonas colonication

B. cepacia compl. colonisation

Stenotrophomonas colonisation

Achromobacter xylosoxidans colonisation

MRSA colonisation

Complications

Respiratory causes

Allergic bronchopulmonary aspergillosis ❒

ABPA Treated

Treatment for ABPA

Pneumothorax ❒

Nasal polyps (having required/requiring therapy) ❒

Massive haemoptysis ❒

Requiring embolization ❒

Digestive causes

CF diabetes

OGTT done this year

Acute pancreatitis ❒

Gastro-oesophageal reflux ❒

Cirrhosis with portal hypertension ❒

Gallstones ❒

Intestinal obstruction: requiring surgery ❒

Intestinal obstruction: not requiring surgery ❒

Gastroparesis ❒

Clostridium ❒

Other complications

CF related arthritis/arthropathy ❒

Osteopenia / Osteoporosis

Date of most recent DEXA

Psychiatric disease ❒

Cancer ❒
Type
Hypertension treated ❒
Chronic renal insufficiency ❒
Other complications ❒
Type
Surgery
Surgery ❒
General anaesthesia ❒
Type

Therapy

Therapy received during the year of registration
Number of consultations
Days in hospital
Respiratory system
Systemic antibiotics
Days per os
Days iv at home
Days iv in hospital
Inhaled antibiotics
Home O2-Therapy
Inhalation therapy (except antibiotics)
Bronchodilators ❒
Mucolytics ❒
Hypertonic saline ❒
Corticosteroids ❒
RhDnase ❒
Intranasal steroids
Antiinflammatories p.o.
Systemic Corticoids ❒
NSAID ❒
Azithromycine ❒
Digestive system
Pancreatic sufficient
Pancreatic enzymes
Fat soluble vitamins (ADEK)
Ursodeoxycholic acid
Tube feeding
Gastrostomy
Parenteral feeding
Miscellaneous
Oral therapy for diabetes
Insulin therapy
Prokinetics
PPI + H2 receptor blocker
Anticonceptive therapy
Psychopharmaca
Bisphosphonates
Regular chest physiotherapy
Randomised drug trial
CFTR modulating therapy

Transplantation

Transplant 1
Transplant status
Type of transplant
Year of transplant
Precise date of entering the Tx waiting list
Precise date of Tx

Transplant 2
Transplant status
Type of transplant
Year of transplant
Precise date of entering the Tx waiting list
Precise date of Tx

Social

Pregnancy/Paternity
Parenthood this year
Birthdays of the biological children of patient
- Child 1
- Child 2
- Child 3
- Child 4
- Child 5
- Child 6

School
School status

Employment data
Patient working
- Percentage

Financial benefits
Additional child allowance
Income support
Disability allowance
Preferential tariff
Pension
Integration support

Family composition
Household composition
Number of siblings including the patient
Number of siblings with CF
Number of siblings decreased from CF
General remark

APPENDIX II

LIST OF ABBREVIATIONS AND DEFINITIONS

ABPA - Allergic bronchopulmonary aspergillosis

BCFR - The Belgian Cystic Fibrosis registry

BCFA – Belgian Cystic Fibrosis patient's Association

BMI - Body mass index is a measure of relative weight based on an individual's mass and height. It is defined as the individual's body mass divided by the square of their height – with the value universally being given in units of kg/m2.

BMR-RBM - Belgisch Mucoviscidose Register - Registre Belge de la Mucoviscidose

Bronchoalveolar lavage - is a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is squirted into a small part of the lung and then collected for examination.

BVSM-ABLM - Belgische Vereniging voor Strijd tegen Mucoviscidose – Association belge de Lutte contre la Mucoviscidose

CDC - The Centers for Disease Control and Prevention is the leading national public health institute of the United States. Its main goal is to protect public health and safety through the control and prevention of disease, injury, and disability.

CDC growth charts - These consist of a series of percentile curves that illustrate the distribution of selected body measurements in children.

CF – Cystic Fibrosis

CFRD - Cystic Fibrosis Related Diabetes refers to a form of diabetes as a direct consequence of having cystic fibrosis.

ConsultRN – a module of the eHealth platform that allows to obtain the demographic data of patients from the national registry database.

Dual energy X-ray absorptiometry - (DXA, previously DEXA) is a means of measuring bone mineral density (BMD).

ECFSPR - European Cystic Fibrosis Society Patient Registry

eHealth – As public institution, the eHealth platform promotes and supports the exchange of electronic information between all stakeholders in health care. eHealth also acts as a Trusted Third party for coding and anonymizing personal health-related data.

FEV_1 - Forced Expiratory Volume is the volume of air that can forcibly be blown out in one second, after full inspiration

FVC - Forced Vital Capacity is the volume of air that can forcibly be blown out after full inspiration, measured in litres.

INAMI - Institut national d'assurance maladie-invalidité

Pseudomonas aeruginosa - is the most important pathogen in the CF airway. *P. aeruginosa* is acquired from environmental reservoirs and can cause both acute and chronic infections, depending on the clinical context.

PWCF - People With Cystic Fibrosis

rhDNase - Recombinant human deoxyribonuclease is an enzyme that breaks down DNA strands in airway secretions, hydrolyzes the DNA present in sputum/mucus of CF patients, reducing viscosity in the lungs and promoting secretion clearance.

RIZIV- Rijksinstituut voor ziekte- en invaliditeitsverzekering

TEPD - Transepithelial potential difference is the voltage across an epithelium, and is the sum of the membrane potentials for the outer and inner cell membranes used in CF diagnosis

VUB - Vrije Universiteit Brussel

WIV - ISP - IPH - Scientific Institute of Public Health

NOTES

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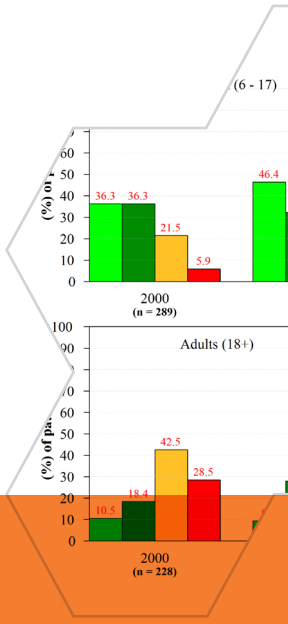

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