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THE BELGIAN CYSTIC FIBROSIS REGISTRY
(BMR-RBM-BCFR)

ANNUAL REPORT BELGIAN CYSTIC FIBROSIS REGISTRY 2015

Annual report
Belgian Cystic Fibrosis Registry
2015

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LIST OF ABBREVIATIONS AND DEFINITIONS

ABPA - Allergic Bronchopulmonary Aspergillosis

BCFA – Belgian Cystic Fibrosis patient's Association

BCFR - The Belgian Cystic Fibrosis Registry

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/m^2.

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.

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 for the extraction of demographic data 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 Turd party for coding and anonymizing personal health-related data.

FEV_1 - Forced Expiratory Volume in one second 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

P.A. (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.

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 clearance of secretions.

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 - Wetenschappelijk Instituut Volksgezondheid / Institut Scientifique de Santé Publique / Scientific Institute of Public Health

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We are pleased to present the annual data report 2015 of the Belgian Cystic Fibrosis (CF) registry.

The last two years have been a transition period, with a lot of challenges to have the registry migrated and integrated in the new Healthdata.be platform and to organize training on the new data collection system. Thank you all for your patience and collaboration. It is foreseen that this system will be in use for a longer period and hence we are confident of less delays due to software development in the near future. We, however, have a back-log and hope to have all the remaining reports completed within this year.

We would like to most sincerely thank all the partners involved in the provision of various services that go toward better care of the people with CF. We single out the nurses and administrative staff who have spent long hours completing the registry entries for their hard work, without which the data collection and reporting would not be possible. We also thank the National Institute for Health and Disability Insurance (RIZIV-INAMI) for their continued financial support and the CF reference centres and their multidisciplinary teams of health care professionals for their continued support to the registry and care to the patients. Finally, we also thank the patients and their parents or care givers for their willingness to participate in the annual data collection processes. This report, and the outcomes of various research questions, enhances the continued monitoring of CF disease by providing a better understanding of disease progression to researchers while stimulating ideas for research into novel treatments and disease management strategies.

The registry team

SUMMARY

This report presents the data collected in 2015. 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 (BCFR) has grown steadily and had 1255 patients registered in 2015. This number excludes one patient whose diagnosis for CF was revoked and twelve without a confirmed diagnosis. There were 25 newly diagnosed patients in 2015, among them three adults, with a median age at diagnosis of 7.0 months with a range from birth to 55.2 years. All the newly diagnosed patients were genotyped; while 20 had sweat chloride values > 60 mmol/L.

Among the patients in follow-up in 2015, 52.1% were male and 59.7% adults with a median age of 22.0 years. This can be compared to the start of the registry 16 years ago when 39.0% were adults with a median age of 14.9 years. 47.0% of the patients are homozygous for the F508del mutation while 38.3% are F508del heterozygous. The main reasons for diagnosis of CF are acute or recurrent respiratory problems (42.7%) and failure to thrive (24.6%). About 17.0% were diagnosed via neonatal screening even though Belgium has no national neonatal screening program so far. Within the year, 15 deaths were reported (8 of them in transplanted patients) with age at death ranging from 22.4 to 60.8 years while 17 patients benefitted from a lung transplant. About 13.0% of the patients in the registry are living with a 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 13.4% in 2015; this decline was noted also 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 55.8% and 11.4% respectively among the children and adults in 2015.

The overall annual prevalence of *Pseudomonas aeruginosa* reported in 2015 was 38.6% and has been declining compared to a prevalence of 42.4% in 2012. This is the first time that the prevalence falls below 40.0%. The prevalence of the *Burkholderia cepacia* complex on the other hand had remained lower than 3.0% over the years till 2010. In 2013 the prevalence increased to 4.5%, (statistically significant compared to 2010) while in 2015 it was 3.5%. There has also been a steady increase in the prevalence of

Achromobacter xylosoxidans from 5.9% in 2009 stabilizing at prevalence levels above 10.0% since 2012.

Thanks to improved disease management practises and novel treatments, the life expectancy and the quality of life of patients with CF has improved significantly when compared to CF cohorts a decade or two ago. The proportion of adult CF patients aged 18 years and above increases each year. But this progress is also accompanied by different challenges, expectations and disease related complications. CF related diabetes had a prevalence of 26.0% in non-transplanted and 58.8% in transplanted adults in 2015. Other complications include early osteoporosis and CF related arthritis/arthropathy. These require specialized care for the adult CF patient.

CHAPTER 1: BACKGROUND

This section briefly describes CF care in Belgium, the history, role and objectives of the Belgian CF Registry (BCFR) and the important contributions of the CF patients' association (BCFA), 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 2000 (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, steatorrhea and failure to thrive. Newborns 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.

Although there is no national neonatal CF screening program in Belgium yet, there are some local initiatives where patients are screened. Infants with CF can be identified in the first weeks of life by assessing their blood immunoreactive trypsin (IRT) combined with the most frequent CFTR mutations. 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 mmol/L). In atypical forms, the sweat test chloride levels can fall into the intermediate range (30-60 mmol/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 most standard treatments are symptomatic and are essentially based on respiratory management (e.g. physiotherapy, mucolytics, antibiotics, antiinflammatories), 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 with most of the patients living to young adulthood.

However, to further improve the life expectancy and quality of life, new and more effective treatments are needed that target molecular defects and act upstream on what the symptomatic treatment do on the cascade of events.

More than 2000 mutations of the *CFTR* gene have been reported. They are grouped in six classes according to their functional defect: Class I: defect of protein synthesis; Class II: default of protein folding with premature degradation which interferes with the protein trafficking to the cell surface; Class III (gating mutations): responsible of deficient channel opening; Class IV: decrease of CFTR conductance channel; Class V: decreased amount of CFTR protein synthesis and Class VI; decreased stability of CFTR protein at the cell membrane. Some CFTR mutations have characteristics of more than one mutation class[21] and for many mutations it is not known to what mutation class they belong.

CFTR modulating therapies are therapies that target the basic defect. They are small-molecule pharmacologic agents that correct the function of

the defective CFTR protein. They do not correct the default in the gene itself. They are specific to certain mutations or class of mutations and thus effective only in patients carrying those specific mutations. There are different types of CFTR modulators: potentiators, correctors and read-through agents.

Currently two of those CFTR modulators are approved in the USA and in Europe for clinical use: ivacaftor (Kalydeco®) for patients carrying a class III (gating) mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) and those carrying the R117H mutation and lumacaftor in association with ivacaftor (Orkambi®) for patients homozygous for the F508del mutation.

Clinically, ivacaftor (a potentiator) has been shown to improve the lung function and the BMI, to reduce the sweat chloride concentrations and improve the quality of life in patients aged 12 years or older with G551D and non-G551D gating mutations[5,6,7,8,13,14]. The efficacy and good tolerance of ivacaftor has also been documented in children aged 6 - 11 years[15,16] and 2 - 5 years[17] with a gating mutation.

In Belgium, ivacaftor is reimbursed (temporarily) for patients older than 6 years carrying one of the nine gating mutations since February 2016 and for children aged 2 - 5 years since October 2016. Patients who received a lung transplant are not eligible for this treatment. The physicians are required to register the data related to the outcome and its evolution on the treated patients to have the temporary reimbursement prolonged.

For patients carrying two copies of the F508del mutation, the combination of ivacaftor and lumacafactor (a corrector) (Orkambi®) has been shown to induce a significant but modest improvement in the FEV_1 % predicted (2.6 - 4.0%)[22]. Orkambi® was approved by the European Medicine Agency (EMA) in September 2015 but in 2017 it was not approved for reimbursement in Belgium.

Other CFTR modulating therapies are currently in development and are being evaluated in several on-going clinical trials. For more information about new therapies we refer to the articles of Fajac I, Quon B and De Boeck K[24,25,26].

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[27,28]. 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 CF REGISTRY (BCFR)

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 BCFR was started in 1999 as a scientific project initiated by the Medical Committee of the Belgian CF Association[1] and the seven CF-reference centres in Belgium collecting data of 1998. It was coordinated by the Vrije Universiteit Brussel (VUB) and co-sponsored by the CF-Patient organisation and the Fund Alfonse and Jean Forton of the King Baudouin Foundation. The VUB covered 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 section 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 BCFR and the guidance of a scientific steering group. The board consists of a physician from each CF centre, a representative of the patients' association and the scientific collaborators of the WIV - ISP. The scientific steering group holds all stakeholders (representatives of the INAMI-RIZIV, patients' association, CF Centers and scientific collaborators of the WIV-ISP).

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 CF 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 a 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)[29] and other international projects.

1 BCFA: Mucovereniging – Association Muco

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 CF who are cared for in Belgium. In 2015, there were 1255 patients included in the registry with about 1350[(2)] patients also registered as members of the patients' association. At the moment, the registry is estimated to have coverage of more than 90% of all people with CF living in Belgium.

Prior to the registration, the physicians (at the accredited CF reference centre) provide each patient and/or 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 pseudonymised 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 and nasal transepithelial potential difference results including information on neonatal screening. These data is 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), forced expiratory flow 25-75% (FEF_{25-75})), complications that occurred or are still active during the registration year, microbiology results, treatments and medications taken as well as social data.

2 Personal communication from the BCFA

SOFTWARE

Until 2010, the data was collected via an Access based computer application on CD-Rom. A web-based application which worked with a trusted third party (eHealth) was then used for data collection 2011 until 2013. A new data collection, validation and analysis tool was developed in collaboration with the Healthdata.be platform and used for the first time for data collection 2014. The digital questionnaire is 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 based on the 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. A new-interactive reporting tool is under development and will be available on the website of Healthstat.be.

Physicians from the centres and researchers can submit research questions to the BCFR and currently a number of research questions are being analysed. While some studies are still on-going, abstracts have been presented at national or international conferences [64,65,66,67,68,69,70,71,72,73] and several articles have been published[74,75,76,77,78].

INTERNATIONAL COLLABORATION

The Belgian CF registry participates to the European CF patient Registry (ECFSPR). A subset of variables with similar definitions among several European countries is sent each year to the ECFSPR. Their annual reports, at-a-glance reports and publications are available on their website[29].

The Belgian CF Registry also contributes data to the CFTR2 project (https://www.cftr2.org). The objective of the CFTR2 project is to define the disease-liability of CFTR variants by means of a multistage process which involves clinical (sweat chloride average), functional (expression in cell-based systems) and epidemiological (mutation analysis in healthy obligate heterozygotes(3)) steps[30,31]. The CFTR2 website provides information for patients, researchers, and the general public about specific variants in what is commonly referred to as the CF gene.

3 An individual in a family who is proven to carry one copy of a recessive allele by having had affected progeny who inherited two copies of the mutant allele, one from each parent

ETHICS AND PRIVACY

The Belgian CF Registry has been approved by the Ethics Committees of all participating CF reference centres and clinics. The BCFR has also received the authorisation of the Privacy Commission for the treatment of coded data[4].

DATA FLOW

The development and use of a new data collection tool on the HealthData.be[5] platform, has improved the data collection and validation procedures. It has also facilitated communication between the researchers and the data providers and enhanced the data verification and error correction. The first data via this system was collected for registry year 2014. The schema in figure 1 shows various stages from data entry and processing to reporting and publication.

- **Data collection (1)**

  A software called HD4DP (HealthData for Data Providers) is installed locally by the data providers in the hospital. This software contains the electronic form to fill in all the requested data. Data that is present in the primary system of the hospital (e.g. in patient electronic files) can also be extracted and uploaded via a .csv file in HD4DP. This means that the system allows for manual data entry in the electronic form or via uploading a .csv file. In the same registration year, both modalities can be used. Several validation rules (ranges, logical checks…) have been implemented in the software at this stage of the process to minimise data entry errors.

- **Data transfer (2)**

  When the registration forms have been completed, they are sent to the researchers in a secure way. The identifiers of the patients (national registry number) and the encrypted medical data are put in a digitally encrypted envelope. The envelope is sent to the "eHealthbox codage" of eHealth. The envelope is then opened. eHealth pseudonymises the identifiers and can not read the encrypted medical data. After pseudonymisation of the identifiers, all the data is put again in an encrypted envelop and sent via the eHealthbox to Healthdata.be at the WIV-ISP. The reopened envelope contains identifiers that are pseudonymised and

4 FR:https://www.privacycommission.be/sites/privacycommission/files/documents/d%C3%A9lib%C3%A9ration_SS_084_2010bis.pdf
NL:https://www.privacycommission.be/sites/privacycommission/files/documents/beraadslaging_AG_084_2010_0.pdf

5 The mission of Healthdata is to facilitate the data exchange between healthcare professionals and researchers to increase public health knowledge and to adjust health care policy in Belgium, with respect for the privacy of the patient, the healthcare professional and the medical confidentiality.

medical data that will be decrypted to make them readable for the researchers. The result is a set of registrations with all necessary medical information but unrecognizable patient data.

- **Data monitoring and validation (3-4)**

  The data arrives to the WIV-ISP in a software called HD4RES (**H**ealth**D**ata for **Res**earchers) for validation by the researchers. The data is loaded into the system and each observation gets a time-stamp of the date and time when it was actually received. During validation, if a registration needs to be sent back to the data provider for verification or correction, the process of decoding and pseudonymisation is done in the opposite direction so that the data provider knows for which patient and which data needs to be checked. The newly corrected data is then sent again to HD4RES as separate record via the described process above and will be assigned a new time stamp when loaded. No data sent by the data provider is changed or replaced including those initially sent with errors. It is stored as it was received.

- **Data storage (5)**

  After validation, all the data, including those that had errors and the new ones received from the data providers after correction, is stored in the data warehouse.

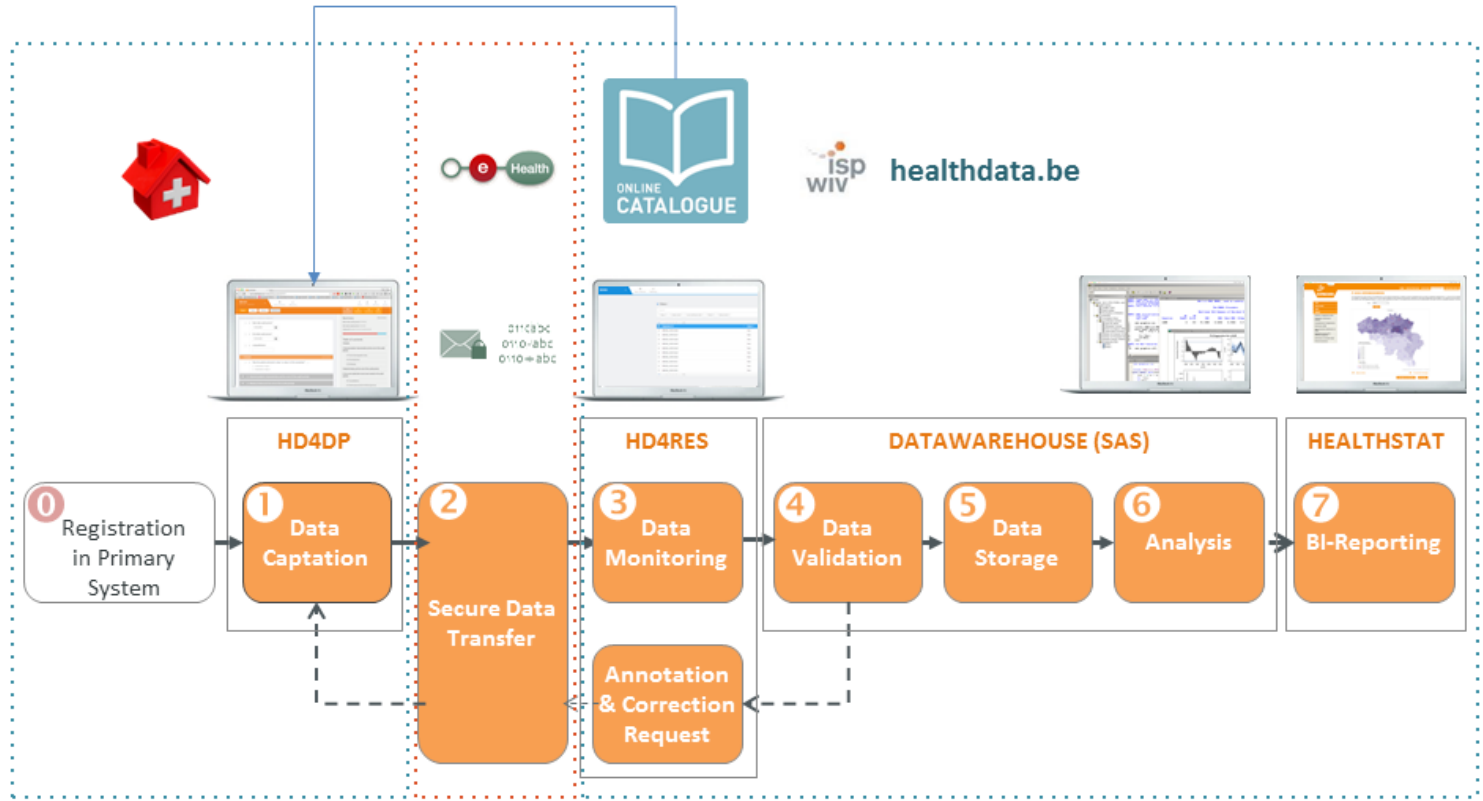
- **Analysis (6)**

  The data used for the analysis is then populated based only on the valid records in the exploration environment. All old records that had been sent back for correction are excluded and only the new ones that replaced them are retained. Specific tables can then be populated for ad-hoc analyses and stored in this environment. An external analysis environment is also available for storage of the data tables sent to third parties such as the European CF Registry or used by other authorized researchers.

- **Reporting (7)**

  A new reporting tool is under development and will be available on Healthstat.be. This environment will be divided in two sections: a public section with information accessible for all users and a secured section accessible only for authorized persons after identification by their electronic identification card (eID). In this section, benchmarking reports will be available.

Figure 1 | Data flow chart



Source: Healthdata.wiv-isp.be

1. 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.
2. 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.
3. Patients without a confirmed diagnosis not included in the total number of CF patients starting 2013.
4. Patients with a revoked diagnosis not included in the total number of CF patients starting 2013.
5. Patient's age at the last consultation.
6. Prenatal diagnosis is considered without setting to zero the age at diagnosis allowing negative values since 2012.

SUMMARY OF DATA REPORTS 2012 - 2015

Table 1 | A comparison of demographic data for years 2012 - 2015

	2012	2013	2014	2015
Number of CF patients	1198	1190	1230	1255
Number of CF patients with complete records	1196	1151	1194	1222
Number of CF patients without observation[1]	2	39	36	33
Number of CF patients with a transplant	143	141	151	165
Number of CF patients who were not seen	17	18	24	27
New CF diagnoses[2]	28	28	36	25
Number of adults among the newly diagnosed patients	4	2	6	3
Number of patients without a confirmed diagnosis[3]	50	12	8	12
Number of patients with a revoked diagnosis[4]	25	9	2	1
Median patient age in years (range)[5]	20.3 (0.0 - 71.5)	20.6 (0.1 - 76.6)	21.3 (0.1 - 76.7)	22.0 (0.2 - 74.4)
Median patient age male (range)[5]	20.2 (0.1 - 65.2)	20.4 (0.1 - 66.2)	21.2 (0.2 - 67.3)	21.9 (0.3 - 68.3)
Median patient age female (range)[3]	20.4 (0.0 - 71.5)	20.8 (0.2 - 76.6)	21.5 (0.1 - 76.7)	22.0 (0.2 - 74.4)
Males (%)	618 (51.6%)	621 (52.2%)	640 (52.0%)	654 (52.1%)
Adults ≥ 18 years (%)	675 (56.3%)	679 (57.1%)	720 (58.5%)	749 (59.7%)
Median age at diagnosis (months)	5.9	5.9	5.7	5.7
Age range at diagnosis (years)	- 0.3 - 65.0	- 0.3 - 74.2	- 0.2 - 74.2	-0.2 - 65.2
Median age at diagnosis, male (months)[6]	5.7	5.9	5.9	5.9
Age range at diagnosis, male (years)	- 0.3 - 46.9	- 0.3 - 46.9	- 0.2 - 59.5	-0.2 - 59.5
Median age at diagnosis, female (months)	6.0	5.9	5.6	5.6
Age range at diagnosis, female (years)	- 0.2 - 65.0	- 0.2 - 74.2	- 0.1 - 74.2	-0.1 - 65.2
Median age at diagnosis new cases in years (range)	0.2 (-0.1 - 35.8)	0.7 (0.0 - 25.7)	0.2 (0.0 - 60.0)	0.6 (0.1 - 55.0)
Number of transplants performed	12	16	9	19
Total number of deaths reported	12	6	10	15
Median age at death in years (range)	32.3 (8.9 - 52.3)	25.5 (17.6 - 30.5)	37.3 (11.5 - 76.9)	37.8 (22.4 - 60.8)
Number of deaths among transplant patients	5	2	4	8

7 Transplant patients are excluded from the spirometry, anthropometry, infections and complications analysis.
8. Only patients who had a culture or sample taken are included in the infections
9. Only patients who had a CT scan done during the year were considered in the case of Bronchiectasis

Table 2 | Spirometry, anthropometry, bacteriology and complications data[7]

	2012	2013	2014	2015
SPIROMETRY: FEV_1 % PREDICTED				
Mean (SD) FEV_1 % predicted[36,37], Last of year	76.3 (25.3)	75.9 (25.7)	76.0 (26.1)	75.3 (25.3)
Male	78.0 (24.6)	78.3 (25.2)	78.4 (25.3)	77.9 (24.4)
Female	74.3 (25.9)	73.2 (26.0)	73.3 (26.7)	72.5 (26.0)
Children	90.2 (20.8)	90.8 (20.6)	92.1 (20.5)	90.9 (18.8)
Adults	65.5 (23.1)	64.9 (23.4)	65.3 (23.9)	65.4 (23.9)
Mean (SD) FEV_1 % predicted[36,37], Best of year	80.5 (24.7)	80.1 (25.0)	80.0 (25.0)	79.7 (25.1)
Male	82.2 (24.1)	82.3 (24.3)	82.5 (24.1)	82.5 (24.3)
Female	78.7 (25.3)	77.6 (25.7)	77.2 (25.6)	76.5 (25.7)
Children	95.2 (19.1)	95.5 (18.8)	96.4 (17.9)	96.0 (18.2)
Adults	69.5 (22.6)	68.9 (23.0)	69.4 (23.1)	69.5 (23.5)
ANTHROPOMETRY: BMI, HEIGHT AND WEIGHT (using CDC references)				
Median (range) BMI Z-score (last of year)	-0.4 (-4.1 - 2.8)	-0.4 (-4.3 - 2.7)	-0.4 (-3.9 - 2.3)	-0.4 (-3.7 - 2.5)
Median (range) Weight Z-score (last of year)	-0.5 (-6.9 - 2.3)	-0.6 (-6.5 - 2.4)	-0.5 (-4.2 - 2.6)	-0.5 (-4.0 - 2.8)
Median (range) Height Z-score (last of year)	-0.4 (-4.1 - 3.2)	-0.4 (-4.8 - 3.2)	-0.4 (-4.1 - 3.2)	-0.3 (-3.9 - 2.6)
INFECTIONS AND BACTERIOLOGY[8]				
Pseudomonas aeruginosa	418 (42.2%)	426 (42.5%)	428 (41.3%)	405 (38.6%)
Burkholderia cepacia complex	40 (4.0%)	45 (4.5%)	38 (3.7%)	37 (3.5%)
MRSA	87 (8.8%)	66 (6.6%)	77 (7.4%)	64 (6.1%)
Haemophilus influenzae	294 (29.7%)	288 (28.7%)	279 (26.9%)	274 (26.1%)
Stenotrophomonas maltophilia	117 (11.8%)	119 (11.9%)	128 (12.3%)	123 (11.7%)
Achromobacter xylosoxidans	106 (10.7%)	107 (10.7%)	104 (10.0%)	109 (10.4%)
Chronic *P. aeruginosa*	274 (27.7%)	295 (29.4%)	289 (27.9%)	290 (27.6%)
Chronic *B. Cepacia* complex	26 (2.6%)	29 (2.9%)	34 (3.3%)	32 (3.0%)
Chronic *S. maltophilia*	27 (2.7%)	37 (3.7%)	40 (3.9%)	46 (4.4%)
Chronic *A. xylosoxidans*	54 (5.5%)	64 (6.4%)	68 (6.6%)	71 (6.8%)
Chronic *MRSA*	50 (5.1%)	45 (4.5%)	43 (4.1%)	38 (3.6%)
COMPLICATIONS				
Allergic Bronchopulmonary Aspergillosis (ABPA)	41 (3.9%)	96 (9.2%)	72 (6.7%)	70 (6.4%)
Haemoptysis requiring embolisation	2 (0.2%)	5 (0.5%)	5 (0.5%)	5 (0.5%)
Pancreatic Insufficiency	830 (79.0%)	838 (80.5%)	867 (80.4%)	880 (80.7%)
CF related diabetes (CFRD)	130 (12.4%)	160 (15.4%)	175 (16.2%)	167 (15.3%)
Bronchiectasis[9]			307 (73.1%)	318 (75.9%)

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 2015.

AGE ON DECEMBER 31 2015

Table 3 | Age on December 31 2015 by gender

Age years (on 31 Dec 2015)	Males			Females			All Patients		
	n	cum n	cum %	n	cum n	cum %	n	cum n	cum %
0 -< 5	53	53	*8.1*	55	55	*9.2*	108	108	*8.6*
5 -< 10	65	118	*18.0*	58	113	*18.8*	123	231	*18.4*
10 -< 15	65	183	*28.0*	84	197	*32.8*	149	380	*30.3*
15 -< 20	116	299	*45.7*	67	264	*43.9*	183	563	*44.9*
20 -< 25	76	375	*57.3*	73	337	*56.1*	149	712	*56.7*
25 -< 30	62	437	*66.8*	68	405	*67.4*	130	842	*67.1*
30 -< 35	63	500	*76.5*	64	469	*78.0*	127	969	*77.2*
35 -< 40	63	563	*86.1*	49	518	*86.2*	112	1081	*86.1*
40 -< 45	40	603	*92.2*	28	546	*90.8*	68	1149	*91.6*
45 -< 50	21	624	*95.4*	22	568	*94.5*	43	1192	*95.0*
≥ 50	30	654	*100.0*	33	601	*100.0*	63	1255	*100.0*
Total	**654**			**601**			**1255**		

The overall median age on 31, December 2015 was 22.0 years; 21.9 for male and 22.0 for female patients respectively

The figures below compare the age distribution by gender for 2000 and 2015 data with an increase in the number of patients above age 40 years: 13.5% in 2015 compared to 1.2% in 2000.

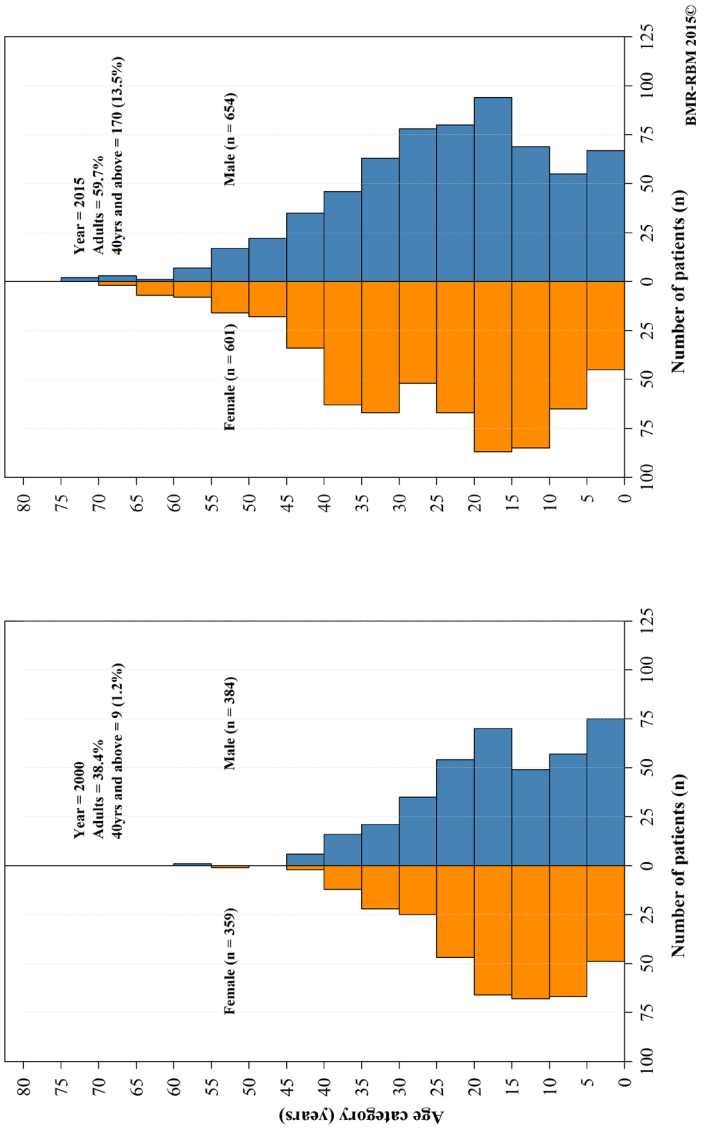
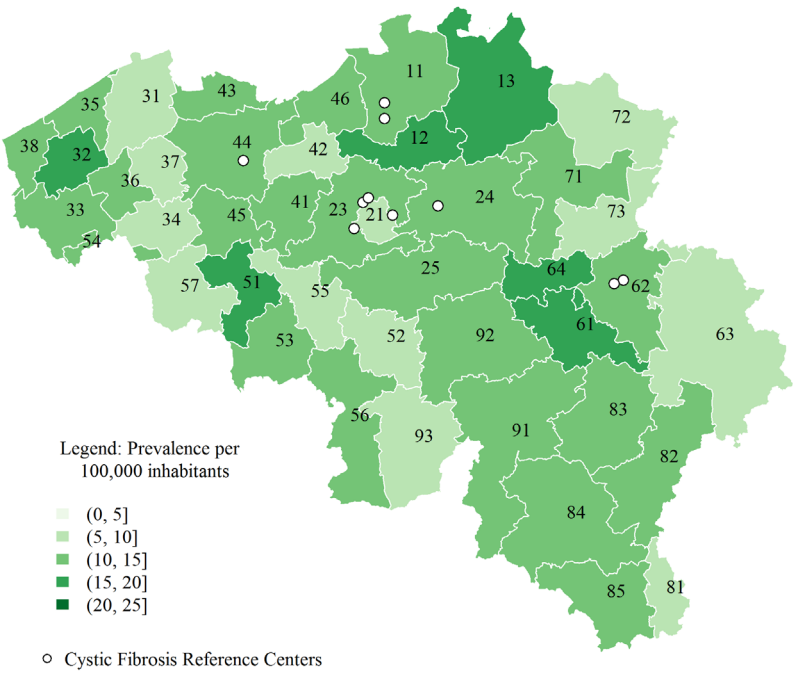


Figure 2 | Age distribution by gender in 2000 (left) and 2015 (right)

PREVALENCE OF CF PER DISTRICT OF RESIDENCE

The map below illustrates the prevalence of CF in each district of residence in Belgium based on the population as at the beginning of 2015. The numbers on the map refer to the district codes. A list with the district names and exact number of people with CF residing in each district is provided on page 33

Figure 3 | Prevalence per 100,000 inhabitants by district of residence in January 2015

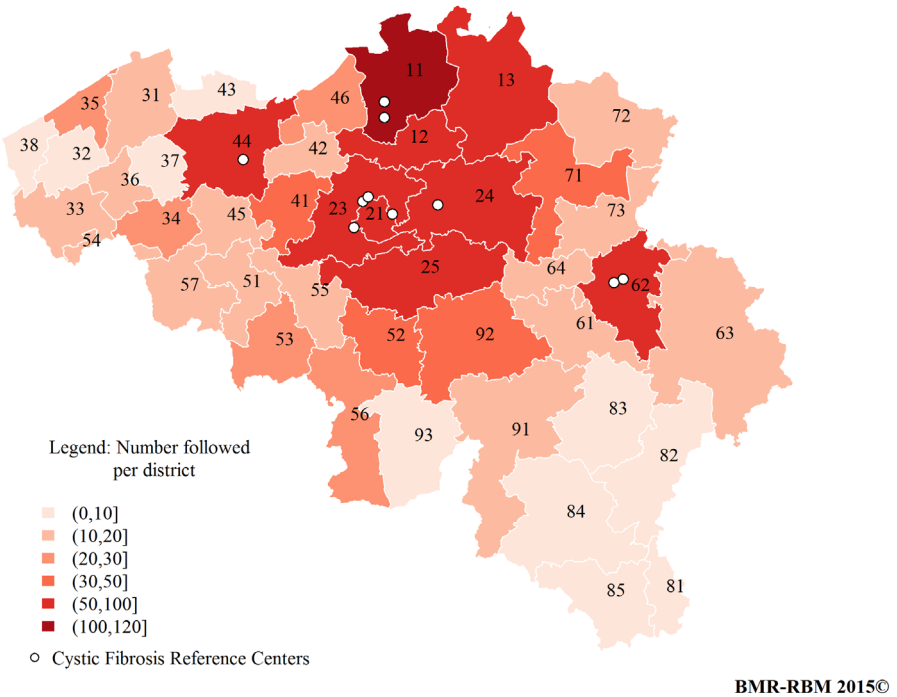


The figure above indicates that the top three districts with the highest prevalence are Dixmude (Diksmuide, code 32), with prevalence 19.6 and population of 50,975, Mechelen (Malines, code 12) with prevalence 18.2 and population 334,966 and Turnhout (code 13) with prevalence 18.1 and population 450,563 at the beginning of the year respectively. The bottom three districts with the lowest prevalence are Verviers (code 63) with prevalence 6.6 and population 285,975, Arlon (Aarlen, code 81) with prevalence 6.6 and population 60,816 and lastly Tongeren (Tongres, code 73) which had the lowest prevalence of 5.5 in 100,000 in a population of 201,814 during the reference period.

PATIENTS WITH CF UNDER FOLLOW-UP PER DISTRICT OF RESIDENCE

The figure below illustrates the number of CF patients resident in each district in Belgium at the beginning of 2015. The numbers on the map refer to the district codes. A list with the district names and exact number of people with CF residing in each district is provided on page 33.

Figure 4 | Number of patients with CF per district of residence in January 2015



In the figure above, we see more patients concentrated in the central and northern sides of the country. Due to their populous nature though, Antwerp (code 11) with 109 patients in a population of about 1.032 million had a prevalence of 10.6 in 100,000 inhabitants and the capital city Brussels (Bruxelles, code 21) coming second with 93 patients in 1.17 million inhabitants and a prevalence of 7.9. The fewest patients lived in Arlon (Aarlen, code 81) with 4 patients in a population of 60,816 inhabitants and prevalence 6.6 followed by Bastogne (Bastenaken, code 82) with 5 patients and population 47,057 with prevalence 10.6.

DISTRICT OF RESIDENCE

The table below 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.

Table 4 | District of residence

	District/Arrondissement	n	%		District/Arrondissement	n	%
11	Antwerpen	109	*8.7*	61	Huy	20	*1.6*
12	Mechelen	61	*4.9*	62	Liège	77	*6.1*
13	Turnhout	82	*6.5*	63	Verviers	19	*1.5*
21	Brussel Hoofdstedelijk Gewest Région Bruxelles Capitale	93	*7.4*	64	Waremme	12	*1.0*
23	Halle-Vilvoorde	80	*6.4*	71	Hasselt	47	*3.7*
24	Leuven	53	*4.2*	72	Maaseik	16	*1.3*
25	Nivelles	55	*4.4*	73	Tongeren	11	*0.9*
31	Brugge	19	*1.5*	81	Arlon	4	*0.3*
32	Diksmuide	10	*0.8*	82	Bastogne	5	*0.4*
33	Ieper	11	*0.9*	83	Marche-en-Famenne	7	*0.6*
34	Kortrijk	27	*2.2*	84	Neufchâteau	9	*0.7*
35	Oostende	21	*1.7*	85	Virton	7	*0.6*
36	Roeselare	17	*1.4*	91	Dinant	12	*1.0*
37	Tielt	9	*0.7*	92	Namur	36	*2.9*
38	Veurne	9	*0.7*	93	Philippeville	6	*0.5*
41	Aalst	34	*2.7*				
42	Dendermonde	16	*1.3*				
43	Eeklo	9	*0.7*				
44	Gent	68	*5.4*				
45	Oudenaarde	15	*1.2*		**Subtotal**	**1242**	
46	Sint-Niklaas	26	*2.1*		**Foreign country**	**13**	***1.0***
51	Ath	15	*1.2*		**Missing**	**-**	**-**
52	Charleroi	32	*2.5*		**Total**	**1255**	
53	Mons	26	*2.1*				
54	Mouscron	11	*0.9*				
55	Soignies	13	*1.0*				
56	Thuin	22	*1.8*				
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 for (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 CF 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. Even though Belgium has no existing national neonatal screening program implemented, 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 newborn infant), chronic diarrhea 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 CF 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 5. The Belgian CF registry collects and reports more than one diagnosis sign or symptom from the same patient. Over the years, the most common clinical presentation of CF remains acute or recurrent respiratory problems. Other common features on presentation were failure to thrive, chronic diarrhea / steatorrhea and meconium ileus. About 17.0% of the patients were diagnosed via neonatal screening test.

Table 5 | Symptoms and clinical reasons for CF diagnosis

			Newly diagnosed			
	Data 1998 – 2015		2014		2015	
	n	%	n	%	n	%
Acute or recurrent respiratory problems	518	*42.7*	12	*33.3*	12	*48.0*
Failure to thrive	298	*24.6*	6	*16.7*	12	*48.0*
Chronic diarrhea/steatorrhea/ malabsorption	238	*19.6*	3	*8.3*	1	*4.0*
Neonatal screening test	205	*16.9*	10	*27.8*	8	*32.0*
Meconium ileus	173	*14.3*	5	*13.9*	1	*4.0*
Family history	127	*10.5*	5	*13.9*	2	*8.0*
Nasal polyposis / chronic sinusitis	58	*4.8*	1	*2.8*	4	*16.0*
Rectal prolapse	32	*2.6*	0	*0.0*	0	*0.0*
Intestinal obstruction (other than meconium ileus)	26	*2.1*	1	*2.8*	1	*4.0*
Prenatal diagnosis	38	*3.1*	2	*5.6*	1	*4.0*
Dehydration / electrolyte imbalance	21	*1.7*	1	*2.8*	1	*4.0*
Neonatal jaundice / Prolonged icterus	2	*0.2*	0	*0.0*	0	*0.0*
Infertility	14	*1.2*	0	*0.0*	1	*4.0*
Diagnosis other	101	*8.3*	6	*16.7*	0	*0.0*
*No diagnosis reasons given	43	*3.5*	0	*0.0*	0	*0.0*

* The overall percentages are based on 1212, 43 patients did not have information on any of the above reasons given in the 2015 data and were excluded from the calculations.
There were 36 newly diagnosed in 2014, percentages are based on 36 patients.
There were 25 newly diagnosed in 2015, percentages are based on 25 patients.
Note: Reasons for diagnosis are not mutually exclusive.

DOCUMENTATION OF CF DIAGNOSIS

Table 6 | Documentation of CF at diagnosis

Procedure	Data 1998 – 2015		Newly diagnosed Patients 2015	
	n	%	n	%
Patients meeting inclusion criteria for the European CF Society Patient Registry				
Clinical symptoms and/or family history, sweat test and genotyping	670	*53.4*	11	*44.0*
Clinical symptoms and/or family history, sweat test, genotyping and abnormal TEPD	60	*4.8*	.	.
Clinical symptoms and/or family history and sweat test	25	*2.0*	.	.
Clinical symptoms and/or family history, sweat test and abnormal TEPD	3	*0.2*	.	.
Clinical symptoms and/or family history and genotyping	198	*15.8*	5	*20.0*
Clinical symptoms and/or family history, genotyping and abnormal TEPD	19	*1.5*	.	.
Neonatal screening test, sweat test and genotyping	110	*8.8*	5	*20.0*
Neonatal screening test, sweat test, genotyping and abnormal TEPD	5	*0.4*	.	.
Clinical symptoms and/or family history, neonatal screening test, sweat test and genotyping	59	*4.7*	3	*12.0*
Sweat test and genotyping	27	*2.2*	1	*4.0*
Sweat test, genotyping and abnormal TEPD	2	*0.2*	.	.
Clinical symptoms and/or family history, neonatal screening test and genotyping	13	*1.0*	.	.
Subtotal	**1191**	***94.9***	**25**	***100.0***
Patients not meeting the European CF Society Patient Registry criteria				
Clinical symptoms and/or family history only	10	*0.8*	.	.
Clinical symptoms and/or family history and abnormal TEPD	5	*0.4*	.	.
Genotyping only	29	*2.3*		
Neonatal screening test and genotyping	17	*1.4*		
Clinical symptoms and/or family history and neonatal screening test	1	*0.1*		
Genotyping and abnormal TEPD	2	*0.2*		
Subtotal	**64**	***5.1***	**.**	**.**
Total	**1255**	***100.0***	**25**	***100.0***

Important Information: The data in the table above refers to documentation of CF at diagnosis. The clinical diagnosis was considered if at least one of a set of symptoms was identified (see page 36; excluding neonatal screening); the sweat chloride if with values greater than 60 mmol/L and genotyping was considered confirmatory if two CF mutations were reported. The results of an abnormal or evocative Transepithelial (Nasal) Potential Difference (TEPD) test are also included in the documentation.

According to the European Cystic Fibrosis Society Patient Registry (ECFSPR), for a patient to be included, he/she must meet at least one of the following three criteria below. 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 on the previous page.

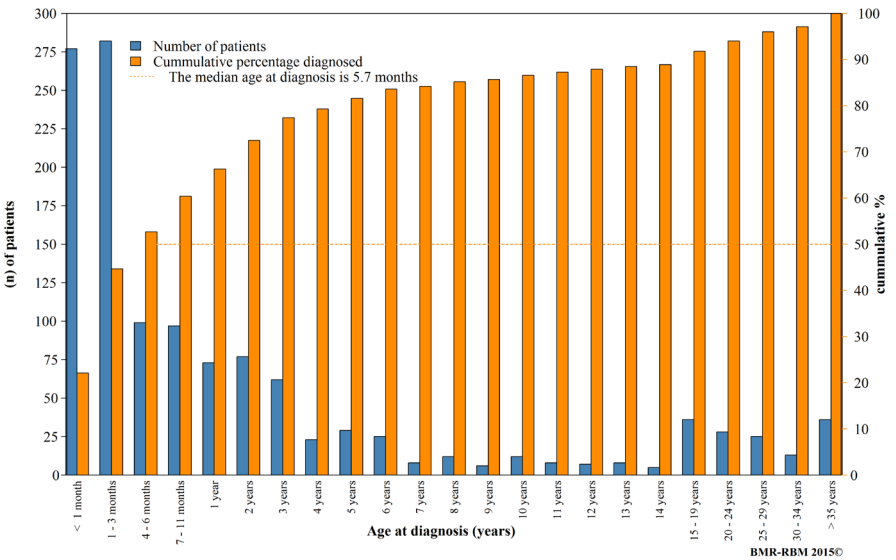
Inclusion criteria for patients into the European CF Society Patient Registry (ECFSPR)
For a patient to be included in the ECFSPR, at least one of the following three criterions must be met:

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 Transepithelial (Nasal) Potential Difference value – Consistent with a diagnosis of CF
   iii. Clinical Presentation at diagnosis – Where typical features of CF are identified

AGE AT DIAGNOSIS

The figure gives the cumulative percentage of age at diagnosis for patients alive in data 2015. The median age at diagnosis was 5.7 months; 5.9 months for male and 5.6 months for female patients respectively. At the age of 18 years 91.5% of the patients were diagnosed. The age range at diagnosis is from two months before birth, due to prenatal diagnosis, to 65.2 years. The median age at diagnosis was 3.1 months for the F508del homozygous patients, 8.5 months for the F508del heterozygous while for patients with other mutations it was 16.8 months.

Figure 5 | Age at Diagnosis



The median age at diagnosis for the 25 newly diagnosed patients in 2015 was 7.0 months; 6.0 months for male and 9.1 months for female patients respectively, with range 0.1 – 55.0 years.

GENOTYPE

All the 1255 patients have undergone a genetic analysis. However, 44 patients (3.5%) had at least one non-identified mutation. Almost half (47.0%) were homozygote for F508del (table 7) and 85.3% of the patients had this mutation on at least one of their alleles (table 8).

Table 7 | General mutation pairs

Mutation pair	n	%	cumulative %
F508del Homozygous	590	*47.0*	*47.0*
F508del Heterozygous	458	*36.5*	*83.5*
F508del---NI	22	*1.8*	*85.3*
OTHER---OTHER	163	*13.0*	*98.2*
OTHER---NI	7	*0.6*	*98.8*
NI---NI	15	*1.2*	*100.0*
Total	**1255**		

NI = Not Identified

Table 8 | Number and proportion of patients by CF allele or mutation

Mutation	Patients		Alleles		Mutation	Patients		Alleles	
	n	%	n	%		n	%	n	%
F508del	1070	*85.3*	1660	*66.1*	G970R	6	*0.5*	6	*0.2*
G542X	65	*5.2*	73	*2.9*	R334W	6	*0.5*	6	*0.2*
N1303K	60	*4.8*	65	*2.6*	5T	5	*0.4*	5	*0.2*
3272-26A->G	43	*3.4*	43	*1.7*	621+1G->T	5	*0.4*	5	*0.2*
1717-1G->A	37	*2.9*	37	*1.5*	G85E	5	*0.4*	5	*0.2*
A455E	30	*2.4*	30	*1.2*	L165S	5	*0.4*	5	*0.2*
S1251N	30	*2.4*	30	*1.2*	Q493X	5	*0.4*	5	*0.2*
2789+5G->A	27	*2.2*	27	*1.1*	3120+1G->A	4	*0.3*	5	*0.2*
R117H	25	*2.0*	27	*1.1*	4218insT	4	*0.3*	4	*0.2*
L927P	23	*1.8*	24	*1.0*	711+1G->T	4	*0.3*	5	*0.2*
3849+10kbC->T	20	*1.6*	20	*0.8*	G551D	4	*0.3*	5	*0.2*
R553X	18	*1.4*	18	*0.7*	L227R	4	*0.3*	7	*0.3*
2183AA->G	17	*1.4*	17	*0.7*	L997F	4	*0.3*	6	*0.2*
W1282X	17	*1.4*	17	*0.7*	Q1313X	4	*0.3*	4	*0.2*
I507del	10	*0.8*	10	*0.4*	R347H	4	*0.3*	4	*0.2*
R1162X	10	*0.8*	14	*0.6*	R347P	4	0.3	4	0.2
306insA	8	*0.6*	8	*0.3*	Y913C	4	*0.3*	4	*0.2*
3659delC	8	*0.6*	8	*0.3*					
D1152H	8	*0.6*	8	*0.3*	Others	194	*15.5*	202	*8.0*
W401X	8	*0.6*	8	*0.3*	Not identified	44	*3.5*	59	*2.4*
G178R	7	*0.6*	7	*0.3*	**Subtotal**			**2510**	
394delTT	6	*0.5*	7	*0.3*	**Missing**	-	-	-	-
E60X	6	*0.5*	6	*0.2*	**Total**			**2510**	

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[32] and Cachera[33] reference equations. An evolution of BMI and height data from selected years is also presented by age category.

In this section, data from **165 patients with a transplant (79 male, 86 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 2015 data from 1048 patients was analysed. The figure below shows a general trend for better median BMI over the years with lines shifting upwards until 2008. There has been stabilization in BMI in the age categories 6-17 years and an improvement in the BMI among the adults.

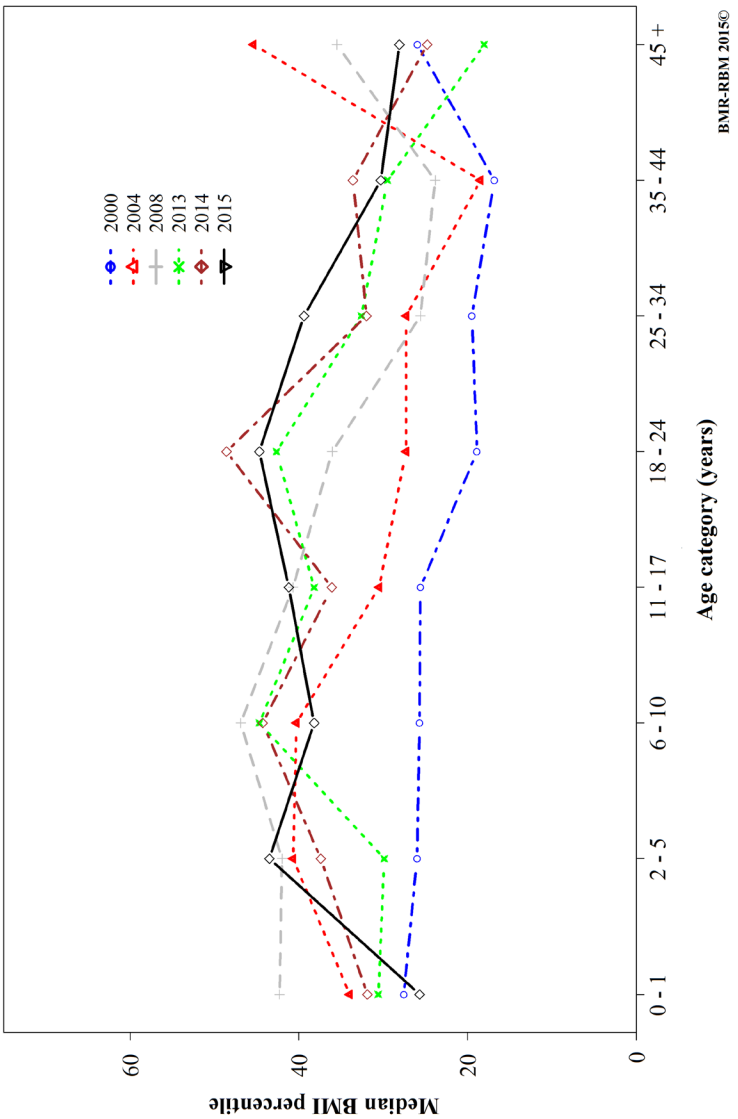
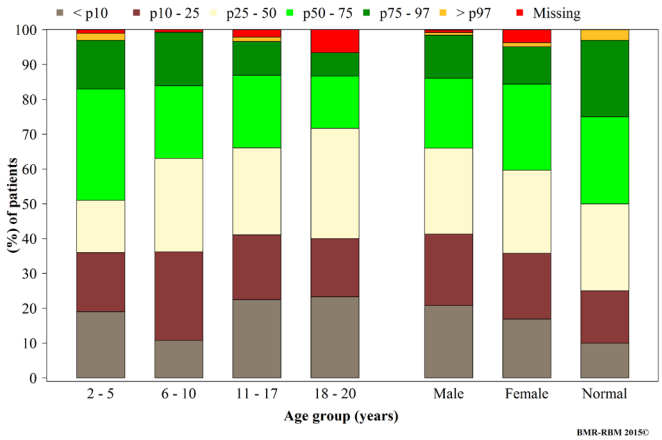


Figure 6 | Median BMI percentile by age group and year

BMI PERCENTILES USING THE CDC GROWTH CHARTS

CDC growth charts cover BMI for ages 2.0 – 20.0 years. The trend depicted is quite similar to the Cachera references above. In 2015 data from 515 patients was analysed. The figure below displays the proportion in each percentile category.

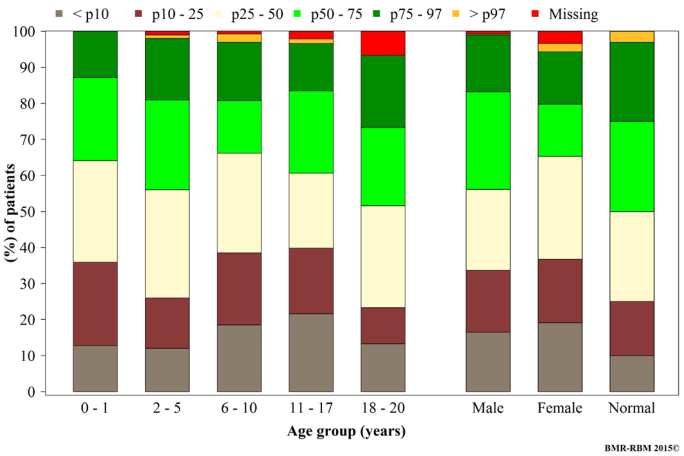
Figure 7 | CDC BMI percentiles by age



HEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover height from 0.0 – 20.0 years. No extrapolation was made to get values for patients older than 20.0 years. In 2015 data from 554 patients was analysed. The figure below indicates the proportion in each percentile category.

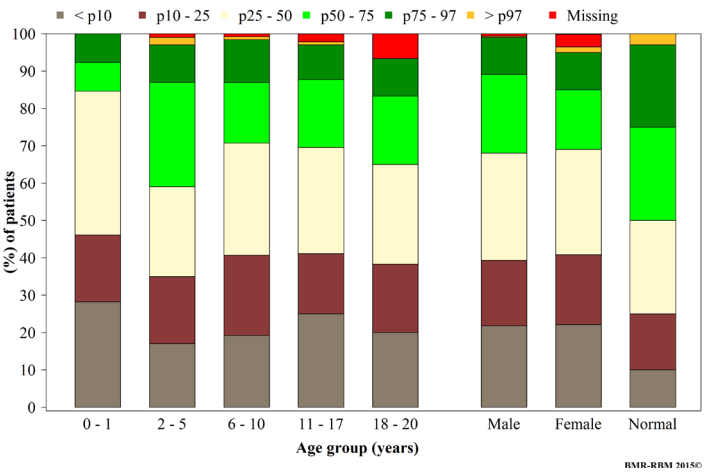
Figure 8 | CDC height percentiles by age



WEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover weight from 0.0 – 20.0 years. In 2015 data from 554 patients was analysed. The figure below indicates the proportion in each percentile category. A higher proportion with weight for age below the 10th percentile is seen in patients up to one year and also among children aged 11 – 17 years.

Figure 9 | CDC Weight percentiles by age



CHAPTER 6: SPIROMETRY (LUNG FUNCTION)

The forced expiratory volume in one 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[34]. 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. However, considerable heterogeneity exists in prognosis and severity, even among patients of the same genotype[35].

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 (**72 male, 67 female**) **was excluded** from the lung function analysis. **Those with a transplant (79 male, 86 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

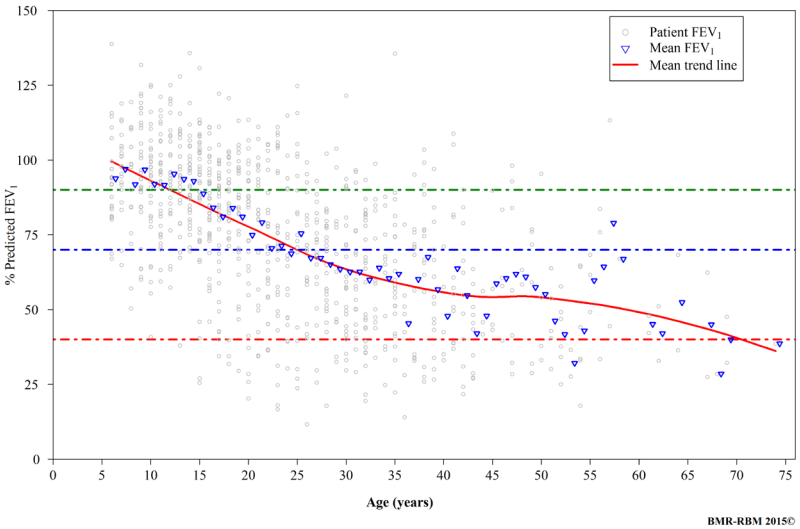
Wang's equations[36] were used for male, 6 – 17 years and female patients 6 – 15 years, while Hankinson's[37] were used for predictions for the male 18 years and above and female patients from 16 years onwards.

In 2015 data from 906 patients was analysed. The overall mean FEV_1 % predicted is 75.3 (SD = 25.3). The mean FEV_1 % predicted was 77.9 % (SD = 24.4) and 72.5 % (SD = 26.0) respectively for 478 male and 428 female patients. The mean FEV_1 % predicted was 90.9 % (SD = 18.8) and 65.4 % (SD = 23.9) respectively for 353 children and 553 adult patients.

Amongst the 402 F508del homozygous, the means were 74.6% (SD = 24.9) and 70.5% (SD = 26.1) respectively for the 212 male and 190 female patients. The means were 89.3% (SD = 21.0) and 62.5% (SD = 22.5) respectively for the 153 children and 249 adults homozygous for the F508del mutation.

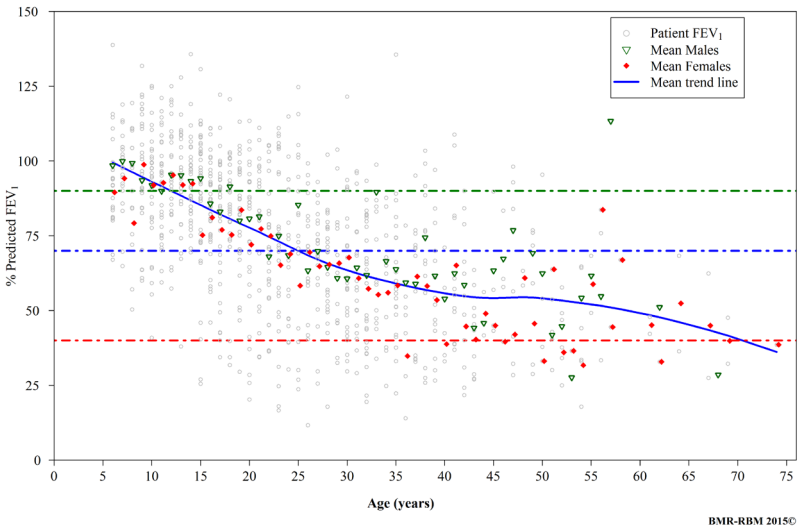
The figure below shows a scatter plot of the FEV_1 % predicted with the means calculated at yearly intervals. It shows on average declining values with age, with a steeper slope up to about 35 years of age when it levels off.

Figure 10 | Mean FEV_1 % predicted by age



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

Figure 11 | Mean FEV_1 % predicted 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 2015.

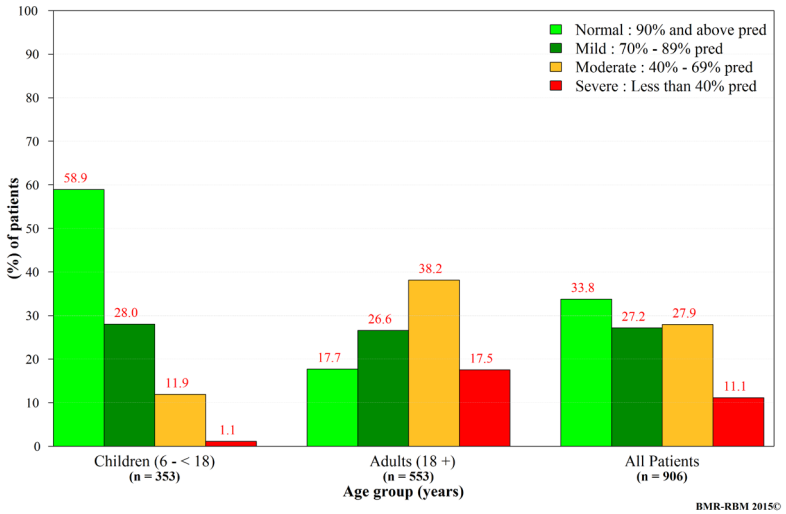
Table 9 | Proportions in each FEV_1 severity category for children and adults

Group	Children (6-17 years)		Adults (≥ 18 years)		Total	
	n	%	n	%	n	%
Normal : ≥ 90% predicted	208	*57.3*	98	*16.7*	306	*32.2*
Mild : 70% - 89% predicted	99	*27.3*	147	*25.0*	246	*25.9*
Moderate : 40% - 69% predicted	42	*11.6*	211	*35.9*	253	*26.6*
Severe : < 40% predicted	4	*1.1*	97	*16.5*	101	*10.6*
Missing	10	*2.8*	35	*6.0*	45	*4.7*
Subtotal	**363**		**588**		**951**	
Transplants	4		161		165	
< 6 years	139		-		139	
Total	**506**		**749**		**1255**	

The FEV_1 was 70.0% of predicted or higher in 58.1% of the patients: - in 84.6% of the children (6 – 17 years) and 41.7% of the adults (18 years and above). About 5.0% had missing FEV_1 data.

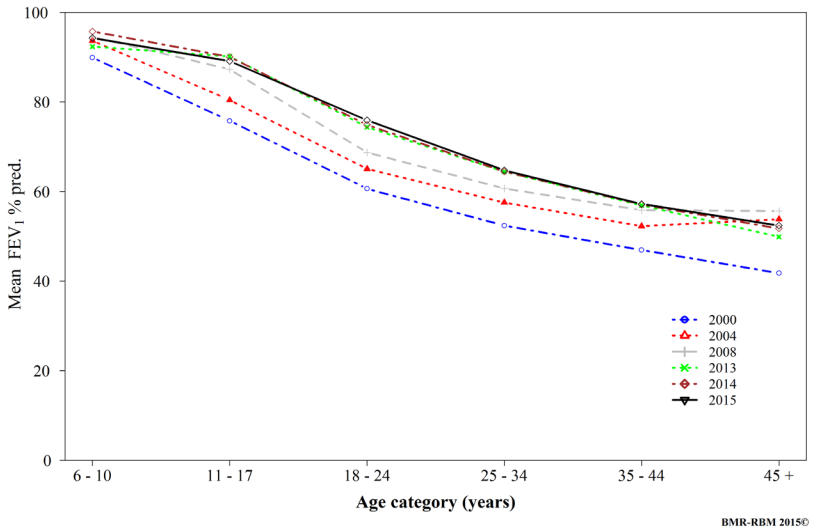
The figure on the next page represents the lung function severity groups for children and adults in 2015 using the Wang – Hankinson equations. When missing data is excluded, 11.1% of the patients had FEV_1 below 40% while 33.8% had FEV_1 of at least 90% in 2015. This is comparable to 2014 where 34.7% of the patients also had FEV_1 of at least 90%; 62.5% of the children and 16.2% of the adults.

Figure 12 | FEV_1 % predicted groups by age group



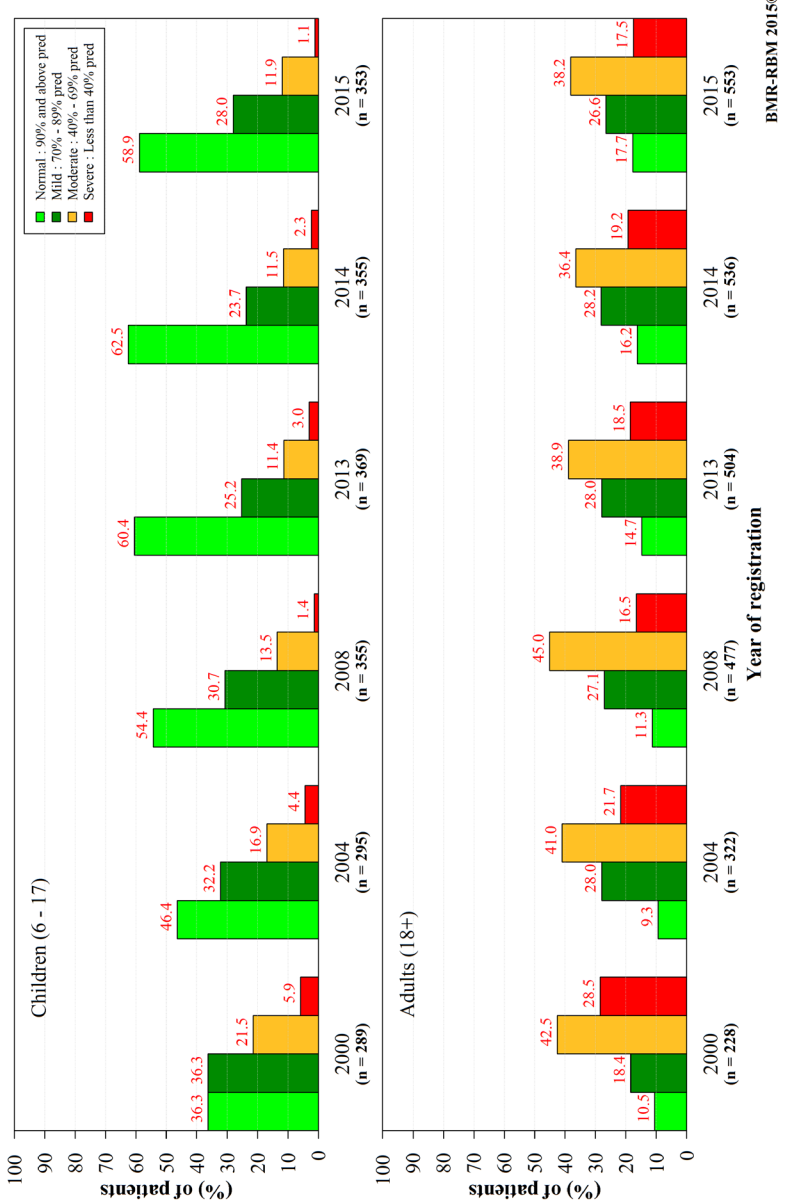
In the figure below, the mean FEV_1 % predicted calculated cross-sectional shows improving lung function over time in all age categories.

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



In the following figure, the proportion in each severity group over selected years is presented. Missing data is excluded. There has been a general increase in the proportion of children with normal lung function with stabilisation over the last 3 years. The proportion of adults with normal lung function has been increasing too. Over the years the proportion of adults with a severe lung function has decreased and then stabilized.

Figure 14 | FEV_1 % predicted groups in children and adults for selected years



CHAPTER 7: MICROBIOLOGY

Decreased mucus clearance and impaired bacterial killing leads 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[40]. Infection by *Pseudomonas aeruginosa* and sometimes *Burkholderia cepacia* complex and other gram-negative pathogens occur at a later age. The airways of patients with CF may also be chronically colonized by fungi like *Aspergillus fumigatus*[41].

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 2015, 497 children and 553 adults i.e. 98.6% of the 1090 non-transplant patients had at least one culture done. The largest proportion (80.7%) had at least four exploitable months during the year. Sputum samples were done in 825, throat swabs in 406 while 46 patients had a broncho-alveolar lavage.

The prevalence shown in the tables below refers to pathogens ever found during the year.

Table 10 | Isolated pathogens 2012 - 2015

	2012		2013		2014		2015	
	n	%	n	%	n	%	n	%
Methicillin Sensitive Staphylococcus aureus (MSSA)	612	*61.8*	630	*62.4*	631	*60.8*	644	*61.3*
Haemophilus influenzae	294	*29.7*	288	*28.5*	279	*26.9*	274	*26.1*
Pseudomonas aeruginosa	420	*42.4*	426	*42.2*	428	*41.3*	405	*38.6*
Methicillin Resistant Staphylococcus aureus (MRSA)	87	*8.8*	66	*6.5*	77	*7.4*	64	*6.1*
Stenotrophomonas maltophilia	118	*11.9*	119	*11.8*	128	*12.3*	123	*11.7*
Achromobacter xylosoxidans	106	*10.7*	106	*10.5*	104	*10.0*	109	*10.4*
Burkholderia cepacia complex	40	*4.0*	45	*4.5*	38	*3.7*	37	*3.5*
Aspergillus	346	*34.9*	331	*32.8*	364	*35.1*	350	*33.3*
Scedosporium spp.	9	*0.9*	4	*0.4*	3	*0.3*	6	*0.6*
Atypical / Non – tuberculous mycobacteria (NTM)	11	*1.1*	8	*0.8*	11	*1.1*	22	*2.1*
Other pathogens	147	*14.8*	168	*16.7*	224	*21.6*	379	*36.1*

Percentages are based on 991, 1009 , 1037 and 1050 patients with a culture respectively for the years 2012 through 2015

While 24.5% of the children (n=122) and 51.2% of the adults (n=283) had a *Pseudomonas aeruginosa*, 5.0% (n=25) and 7.1% (n=39) respectively had a MRSA infection. *Burkholderia cepacia* complex infection was found in 11 (2.2%) children and 26 (4.7%) adults. The prevalence of *Stenotrophomonas maltophilia* has oscillated at about 12.0% since 2012. In 2015 it was about 11.7% in children and 11.8% in the adults. There has been a steadily increase of the prevalence of *Achromobacter xylosoxidans* from 5.9% in 2009 to 10.7% in 2012 and a stabilization since then. The prevalence of Non-tuberculous mycobacteria remains low but doubled in 2015 (2.1%) compared to 2014 (1.1%). The increase in 'Other pathogens' may need a more sensitive classification to detect if a particular new pathogen is responsible.

ANNUAL PREVALENCE OF CHRONIC INFECTIONS

Table 11 | Chronic infections 2012 - 2015

	2012		2013		2014		2015	
	n	%	n	%	n	%	n	%
Chronic *Pseudomonas aeruginosa*	276	*27.9*	296	*29.3*	294	*28.4*	292	*27.8*
Chronic *Burkholderia cepacia* complex	27	*2.7*	29	*2.9*	34	*3.3*	32	*3.0*
Chronic *Stenotrophomonas maltophilia*	27	*2.7*	37	*3.7*	41	*4.0*	47	*4.5*
Chronic *Achromobacter xylosoxidans*	54	*5.4*	64	*6.3*	69	*6.7*	71	*6.8*
Chronic MRSA	51	*5.1*	45	*4.5*	45	*4.3*	38	*3.6*

Percentages are based on 991, 1009 , 1037 and 1050 patients with a culture respectively for the years 2012 through 2015

About 11.9% of the children (n = 59) and 42.1% of the adults (n = 233) had chronic *Pseudomonas aeruginosa* infection.

The figures 15 - 18 show the annual prevalence of infections over selected periods. The prevalence presented is based on any positive culture for a given pathogen among those collected during the year.

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

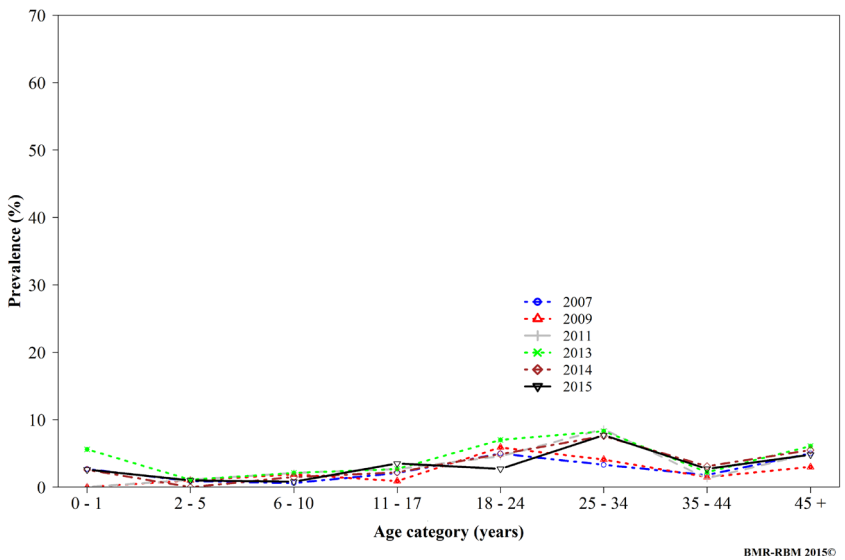


Figure 16 | Prevalence of *Pseudomonas aeruginosa* infections by year and age

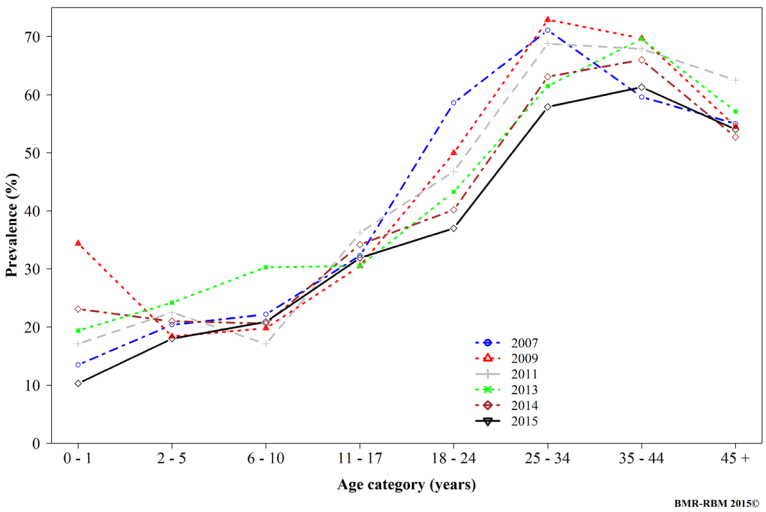
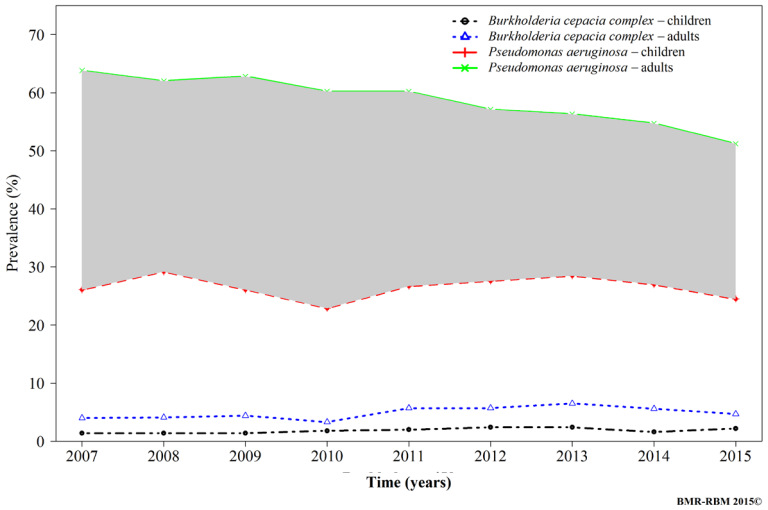


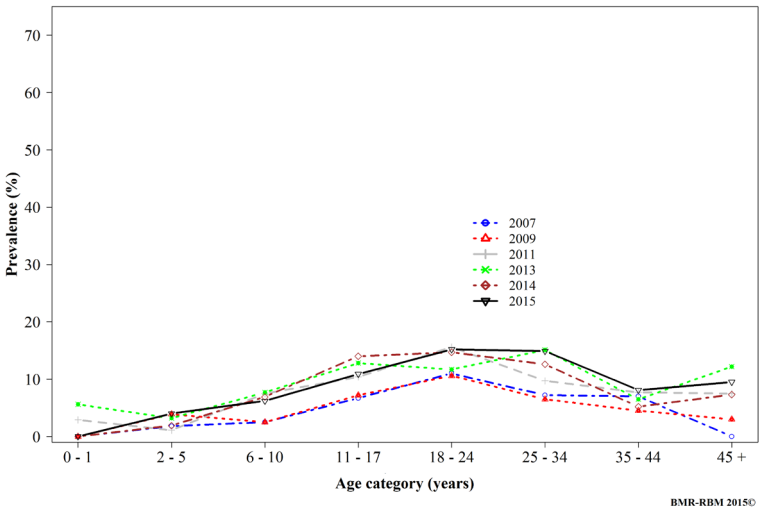
Figure 17 | Prevalence of *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex by age group and year



Note: The shaded area is the difference in *Pseudomonas aeruginosa* prevalence between children and adults. While the prevalence in children seems to be stable, the gap between prevalence in adults and children seems to be reducing.

There has been an increase in the importance of the pathogen *Achromobacter xylosoxidans*, figure 18, whose prevalence has been rising across most age categories over the years.

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



The prevalence of various pathogens may differ according to the age of the patients. In the following figures, the annual prevalence of various pathogens and that of chronic infections is presented by age category. This analysis is only for those patients who had at least one culture analysed or sample taken during the year. The transplant patients are excluded. The values may, however, be affected by small cell counts in some of the age categories.

Figure 19 | Annual prevalence of selected microbes by age group

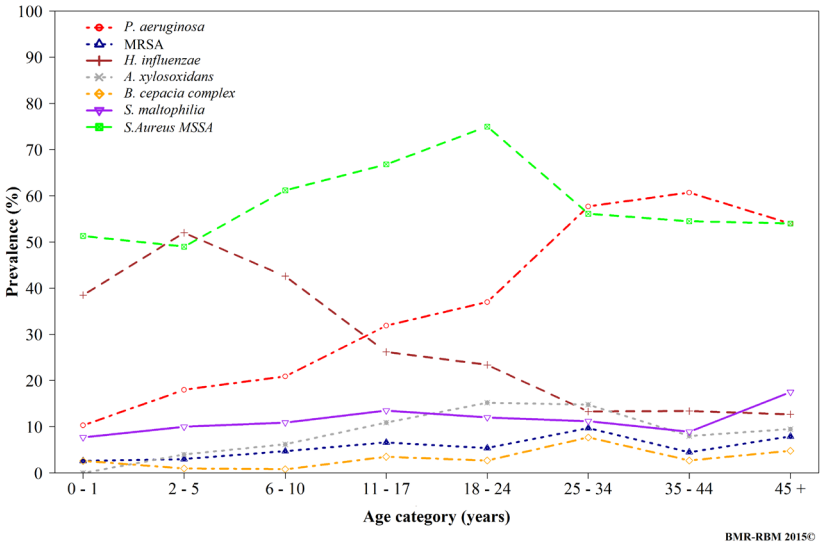
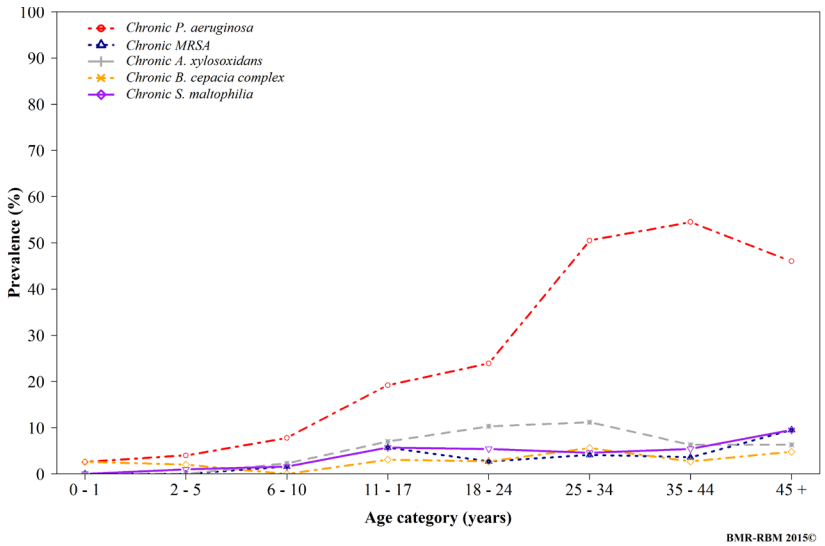


Figure 20 | Prevalence of chronic infections by age group



CHAPTER 8: COMPLICATIONS

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. Cystic Fibrosis affects the respiratory[42], digestive[43,44] and reproductive[45,46] systems with variable degrees of severity. 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, testicles…).

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 165 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 can colonize the airways of people with CF. Diagnosis is not always obvious as many symptoms of ABPA (cough, wheezing, shortness of breath and 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 patients 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 up blood. Haemoptysis is mild in most cases, but sometimes the bleeding is so massive (> 250 cc/24h) that a therapeutic embolization of the bleeding vessel can be indicated.

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[47,49]

Table 12 | Prevalence of respiratory complications

Complication	2012		2013		2014		2015	
	n	%	n	%	n	%	n	%
Allergic bronchopulmonary aspergillosis (ABPA)	40	*3.9*	52	*5.1*	72	*6.7*	70	*6.4*
Pneumothorax	3	*0.3*	2	*0.2*	3	*0.3*	1	*0.1*
Nasal polyps	108	*10.6*	155	*15.2*	205	*19.0*	152	*13.9*
Massive haemoptysis	6	*0.6*	11	*1.1*	15	*1.4*	10	*0.9*
Massive haemoptysis requiring embolization	2	*0.2*	5	*0.5*	5	*0.5*	5	*0.5*
Bronchiectasis*					307	73.1	318	75.9

Percentages are based on 1018, 1017, 1079 and 1090 non-transplant patients respectively for the years 2012 through 2015

*Only patients who had a CT scan considered

In this analysis, complications data from 502 children and 588 adults was used. ABPA is one of the most frequent major respiratory complications. In 2015 ABPA was reported in 20 (4.0%) children and 50 (8.5%) adults. Bronchiectasis was reported in 90 (53.9%) children and 228 (90.5%) of the adults who had a CT scan during the year.

GASTRO-INTESTINAL AND ENDOCRINE COMPLICATIONS

Exocrine 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 to 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 remain pancreatic sufficient (10-15%).

Gastro-oesophageal 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 produce thick intestinal mucus which in combination with stools and undigested food residues can cause intestinal obstruction. DIOS is especially found in the terminal ileum and caecum. It can cause 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 defective CFTR protein in their biliary tract. Some patients develop liver disease leading to cirrhosis (replacement of the liver tissue by fibrosis) and others do not. Cirrhosis may be complicated by portal hypertension and in rare cases a liver transplant is required.

CF-related diabetes (CFRD) : Insulin is produced in the endocrine part of the pancreas. It is a hormone which maintains the balance of sugar in blood. The malfunctioning of the endocrine part of the pancreas by fibrosis leads to an insufficiency of the secretion of insulin leading to diabetes.

Table 13 | Prevalence of gastro-intestinal and endocrine complications

Complication	2012		2013		2014		2015	
	n	%	n	%	n	%	n	%
Exocrine pancreatic insufficiency	830	*81.5*	838	*82.4*	867	*80.4*	880	*80.7*
Acute pancreatitis	6	*0.6*	8	*0.8*	14	*1.3*	10	*0.9*
CF related diabetes (CFRD)	128	*12.6*	159	*15.6*	176	*16.3*	167	*15.3*
Impaired Glucose Tolerance (IGT)	59	*5.8*	66	*6.5*	77	*7.1*	90	*8.3*
Gastro-oesophageal reflux	198	*19.4*	188	*18.5*	265	*24.6*	271	*24.9*
Cirrhosis with portal hypertension	33	*3.2*	43	*4.2*	43	*4.0*	50	*4.6*
Gallstones	32	*3.1*	21	*2.1*	36	*3.3*	14	*1.3*
Intestinal obstruction (surgery)	4	*0.4*	5	*0.5*	2	*0.2*	1	*0.1*
Intestinal obstruction (no surgery)	74	*7.3*	52	*5.1*	37	*3.4*	55	*5.0*
Gastroparesis	7	*0.7*	3	*0.3*	2	*0.2*	1	*0.1*
Clostridium infection (treatment needed)	4	*0.4*	5	*0.5*	15	*1.4*	12	*1.1*

Percentages are based on 1018, 1017, 1079 and 1090 non-transplant patients respectively for the years 2012 through 2015

In non-transplant patients, the data shows that 421 (83.9%) children and 459 (78.1%) adults are pancreatic insufficient. CFRD was reported in 14 (2.8%) children and 153 (26.0%) adults.

MISCELLANEOUS COMPLICATIONS

Reproductive system complications : Most men (95 – 99%) with CF 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 CF 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 CF 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 the extend of psychological repercussions in CF. In this report, the analysis is based on patients who visited or were treated by a specialist (psychiatrist or neurologist)

Table 14 | Other complications reported

Complication	2012		2013		2014		2015	
	n	%	n	%	n	%	n	%
CF-related arthritis / arthropathy	72	*7.1*	102	*10.0*	23	*2.1*	20	*1.8*
Cancer	2	*0.2*	3	*0.3*	4	*0.4*	2	*0.2*
Surgery	66	*6.5*	72	*7.1*	97	*9.0*	92	*8.4*
General anaesthesia	73	*7.2*	102	*10.0*	109	*10.1*	77	*7.1*
Psychiatric disease	24	*2.4*	36	*3.5*	41	*3.8*	33	*3.0*
Osteopenia	112	*11.0*	117	*11.5*	113	*10.5*	111	*10.2*
Osteoporosis	24	*2.4*	23	*2.3*	21	*1.9*	27	*2.5*
Hypertension requiring treatment	14	*1.4*	31	*3.0*	14	*1.3*	22	*2.0*
Others	143	*14.0*	161	*15.8*	170	*15.8*	126	*11.6*

Percentages are based on 1018, 1017, 1079 and 1090 non-transplant patients respectively for the years 2012 through 2015

*Since 2011, data on Osteopenia (the lowest z-score on Dual X-ray absorptiometry (DXA) between -1.0 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 patients with CF 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 2015 are 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 502 children and 588 adults from a total of 1090 non transplant patients.

VISITS TO CF CARE CENTERS AND HOSPITALIZATION

In 2015, most of the patients (83.1%, n=906) had a minimum of the four recommended visits to a CF reference centre during the year.

The figure below concerns the number of days of hospitalization. In 2015, 56.1% of the patients were not hospitalized: 62.4% of the children (n = 313) and 50.7% of the adults (n = 298). A small proportion (11 patients, 1.0%), was hospitalized for over two months. The median number of hospitalization days was about two weeks.

Figure 21 | Number of hospitalization days

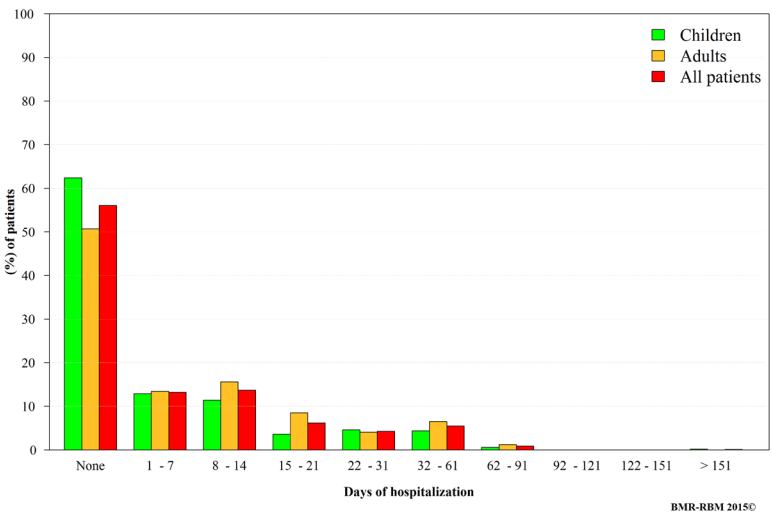
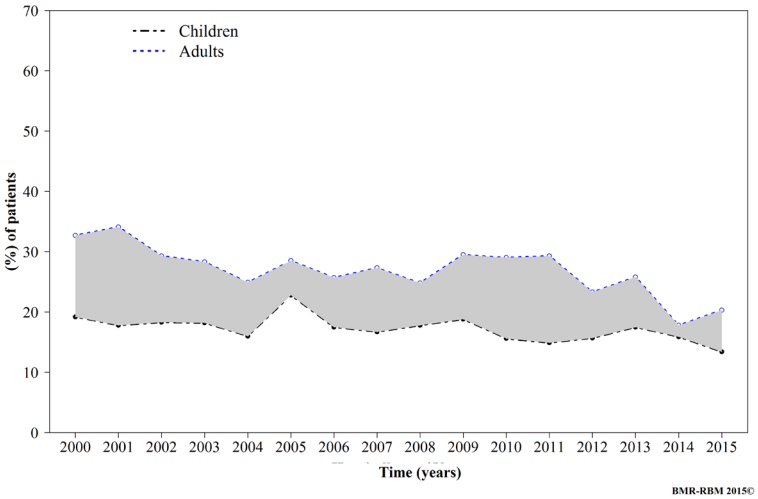


Figure 22 | Proportion of patients hospitalized for more than two weeks by age and year



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 by themselves.

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 dilate the bronchi. Inhaled antibiotics are used to treat infection, prevent or postpone colonization. In advanced lung disease oxygen is needed[50].

Every year, about 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 15 | Physiotherapy, inhalation therapy, oral anti-inflammatories and antibiotics

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Regular chest physiotherapy	499	*98.8*	561	*95.9*	1060	*97.2*
Antibiotics	445	*88.1*	508	*86.8*	953	*87.4*
Oral only	282	*55.8*	186	*31.8*	468	*42.9*
IV only	6	*1.2*	14	*2.4*	20	*1.8*
Oral and IV	136	*26.9*	268	*45.8*	404	*37.1*
Inhaled antibiotics	237	*46.9*	360	*61.5*	597	*54.8*
Inhalation therapy (excluding antibiotics)	484	*95.8*	538	*92.0*	1022	*93.8*
RhDnase	388	*76.8*	462	*79.0*	850	*78.0*
Other mucolytics	98	*19.4*	122	*20.9*	220	*20.2*
Hypertonic saline	295	*58.4*	363	*62.1*	658	*60.4*
Bronchodilators	401	*79.4*	435	*74.4*	836	*76.7*
Corticosteroids	217	*43.0*	373	*63.8*	590	*54.1*
Intranasal steroids	253	*50.1*	285	*48.7*	538	*49.4*
Oral anti-inflammatories	175	*34.7*	367	*62.7*	542	*49.7*
Azithromycin	167	*33.1*	347	*59.3*	514	*47.2*
Systemic corticosteroids	9	*1.8*	36	*6.2*	45	*4.1*
NSAID	8	*1.6*	47	*8.0*	55	*5.0*
Oxygen therapy	5	*1.0*	22	*3.8*	27	*2.5*

GASTRO-INTESTINAL AND NUTRITIONAL THERAPIES

Optimizing the nutritional status: The nutritional status of a patient is correlated with the disease severity. Therefore every person with CF should take a well-balanced high-calorie and high-fat diet. Most individuals with CF are pancreatic insufficient[43] 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 achieve a correct nutritional status by receiving supplemental feedings given by a tube placed into the stomach (enteral feeding) or given intravenously (parenteral feeding).

Medications that inhibit the gastric acid secretion (proton pump inhibitors or H2 blockers) are given to treat symptoms of gastro-oesophageal reflux or to improve the efficacy of pancreatic enzymes in a higher pH environment. Prokinetics are medications that increase the tone of the lower oesophagus sphincter and enhance the gastrointestinal motility resulting in an acceleration of gastric emptying.

Table 16 | Digestive and nutritional therapies

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Pancreatic enzymes	425	*84.2*	455	*77.8*	880	*80.7*
Fat soluble vitamins (A,D,E and K)	435	*86.1*	450	*76.9*	885	*81.2*
Proton pump inhibitor and/or H2 receptor blocker	226	*44.8*	308	*52.6*	534	*49.0*
Prokinetics	15	*3.0*	24	*4.1*	39	*3.6*
Ursodeoxycholic acid	127	*25.1*	132	*22.6*	259	*23.8*
Enteral feeding	20	*4.0*	3	*0.5*	23	*2.1*
Parenteral feeding	8	*1.6*	13	*2.2*	21	*1.9*
Gastrostomy tube	31	*6.1*	12	*2.1*	43	*3.9*

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 could 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[51].

Table 17 | Other treatments

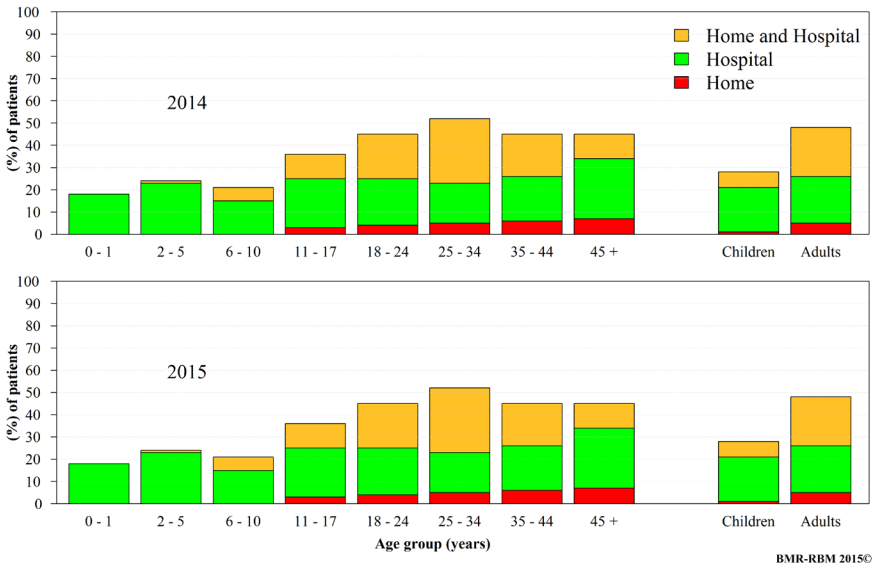
Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Insulin therapy	13	*2.6*	121	*20.7*	134	*12.3*
Oral therapy for diabetes	3	*0.6*	30	*5.1*	33	*3.0*
Bisphosphonates	.	.	20	*3.4*	20	*1.8*
Anti-conceptive therapy (females aged 12 and over)	7	*12.7*	104	*58.4*	111	*47.6*
Use of Psychopharmaca	7	*1.4*	55	*9.4*	62	*5.7*
CFTR Modulating Therapy	22	*4.4*	47	*8.0*	69	*6.3*

Note: Out of 1090 non transplant patients, 167 had CFRD. Among these, 122 used insulin therapy only, 19 used only oral therapy for diabetes while 12 patients used both oral therapy for diabetes and insulin therapy. However, in 14 patients with CFRD no use of either of the two treatments was reported.

INTRAVENOUS ANTIBIOTICS

In the year 2015, 38.9% (n = 424) of the patients received IV antibiotics; 28.3% (n = 142) amongst the children and 48.0% (n = 282) among the adults. The figures below show the proportion that received IV antibiotics at home and/or in hospital in 2014 (top) compared to 2015 (bottom). There are few patients below six years taking IV antibiotics at home. Half of the adults have IV antibiotics both at home and in hospital.

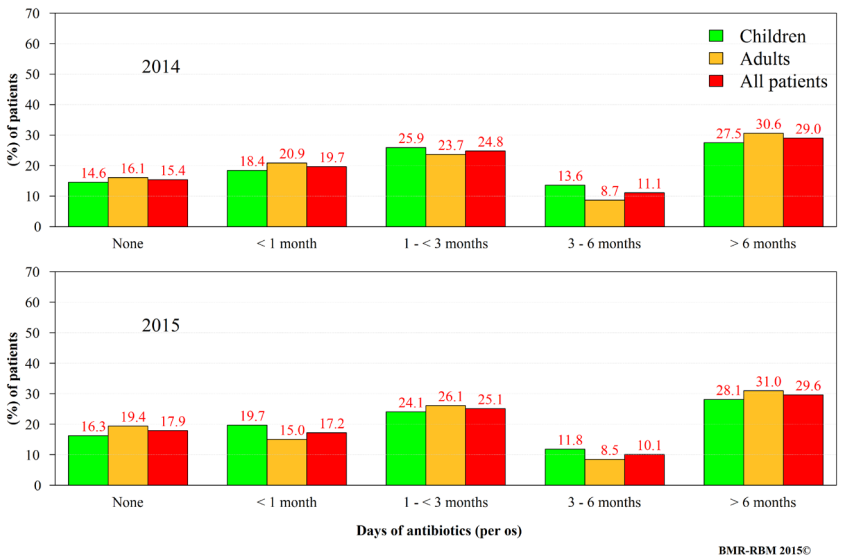
Figure 23 | Proportion that used IV antibiotic treatment by age category



ORAL ANTIBIOTICS

The figures below show the days of oral antibiotics used in 2014 (top) and compared to 2015 (bottom). Unknown days or missing data was excluded from this analysis. In 2015, 17.9% of the patients did not take any oral antibiotics; 16.3% of the children (n = 81) and 19.4% of the adults (n = 107). More than a quarter of both the children (28.1%) and adults (31.0%) used oral antibiotics for over six months.

Figure 24 | Days of oral antibiotics



CHAPTER 10: TRANSPLANTS AND CF

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, who have exhausted all other forms of conventional medical treatment and whose short term survival is compromised. For these patients, lung transplantation may offer prolonged survival and an improved quality of life; in some cases even a 'new' life.

The actuarial survival after lung transplantation for CF is steadily improving. At present the actuarial survival rate is more than 70 % at 3 years and more than 45% at 10 years after primary transplant[52]. 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 about 246 patients(6) with CF[54] (214 reported in the CF registry) have received a (heart)-lung transplant and approximately 10 lung transplants per year are now performed for CF. A few 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 2015, categorized by the year of first transplant.

TRANSPLANT STATUS

The registry records show that since inception of the registry in 1998, at least **230** patients, **111** male and **119** female, have benefitted from transplantation; either single or multiple. In 2015, 19 patients were on the waiting list, 22 had been evaluated but were not on the list with two patients each either refusing the transplant or being declined by the transplant centre.

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 (range) age of the transplant patients in the year of the first transplant was 28.3 (9.5) and 27.4 years (5.3 – 60.7) respectively. The oldest patient at first transplant was 60.7 years. About 11.3% (26 patients) had the first transplant done before age 18 years.

6 Source: Communication from Eurotransplant International Foundation

In 2015, there were **165** patients living with a recorded transplant. The mean (SD) and median (range) age of the transplant patients reported as alive in 2015 was 36.6 (10.4) and 35.8 (11.7 – 66.6) years respectively at the last consultation in 2015. 79 were male while 86 were female, while 97.6% of the transplanted patients in the 2015 data were adults. Eight transplanted patients died in 2015.

The data presented in table 18 concerns all recorded transplanted in the registry and also data of patients reported alive by the time of data collection for year 2015 (the numbers in the far right column). Slight differences may be noted with previous reports as we seek to consolidate the transplant data yearly. In the table, the numbers of transplants performed do not add up to the number of patients: - a patient can have several transplantations.

Multiple transplants are counted as separate transplant occasions. A total of 263 transplants on 230 patients are so far reported in the registry. There are 29 patients who have had a transplant on more than one occasion.

TYPE OF TRANSPLANT

The most frequent transplant done is the lung transplant, either single or with a liver or heart. So far, 210 isolated lung transplants have been carried out.

Table 18 | Type of transplant by year

Year	Type of transplant							Totals	
	Lung	Lung-Heart	Lung-liver	Liver	Kidney	Liver-Kidney	Heart	Transplants performed	Patients alive
1991	.	2	.	.	.	.	.	2	1
1992									-
1993	.	2	.	.	.	.	.	2	1
1994	.	3	.	.	.	.	.	3	1
1995	2	3	.	1	.	.	.	6	1
1996	.	1	.	.	.	.	.	1	-
1997	1	3	.	.	.	.	.	4	2
1998	9	1	.	.	.	.	.	10	3
1999	5	.	.	.	.	.	.	5	2
2000	10	.	.	.	.	.	.	10	3
2001	13	.	1	4	.	.	.	18	11
2002	10	.	.	2	.	.	.	12	7
2003	9	.	.	1	.	.	.	10	8
2004	11	.	.	.	.	.	.	11	8
2005	10	.	1	3	.	.	.	14	8
2006	14	.	.	1	1	.	1	17	10
2007	16	.	.	1	1	.	.	18	9
2008	16	.	.	.	3	.	.	19	12
2009	10	.	.	1	.	1	.	12	9
2010	13	.	2	1	.	.	.	16	11
2011	15	.	.	.	2	.	.	17	11
2012	12	.	.	.	.	.	.	12	9
2013	13	.	.	.	3	.	.	16	9
2014	6	.	.	.	3	.	.	9	5
2015	15	.	2	.	2	.	.	19	16
Total	**210**	**15**	**6**	**15**	**15**	**1**	**1**	**263**	**-**
Alive**	138	4	5	8	2	-	-	-	157*

* Total number of patients alive by end of 2015 by transplant year considering the first transplant
**Number of patients alive by end of 2015 considering type of first transplant

In figure 25, the total number of patients recorded each year is presented as a proportion of children and adults, with and without a transplant. The figure shows that while the proportion of adults is increasing, so is the number of adult patients living with a transplant.

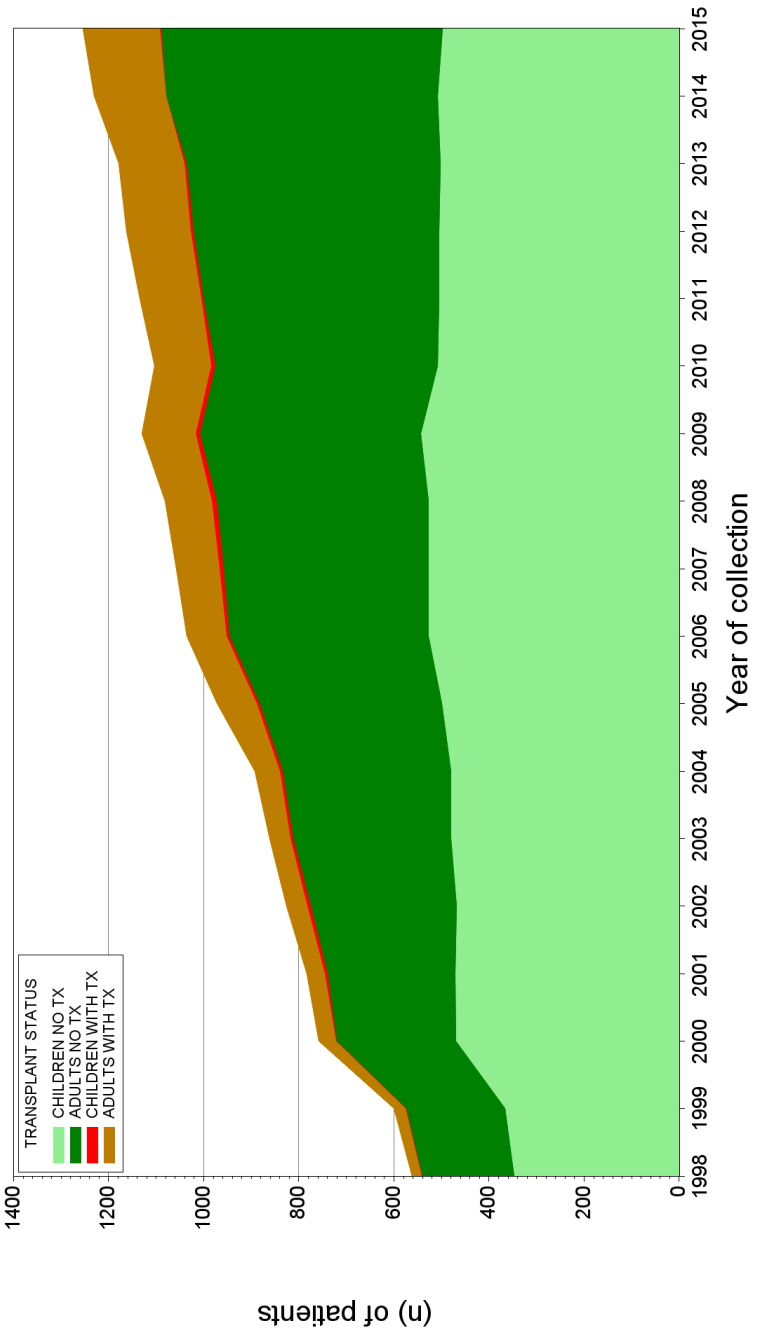


Figure 25 | Number of patients by age and transplant status

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 listed 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 some data. In some centers, this background data is automatically updated using the ConsultRN module by linking the CF registry data collection to the national registry database. The numbers may thus differ slightly from those previously reported due to this automatic update.

AGE AT DEATH

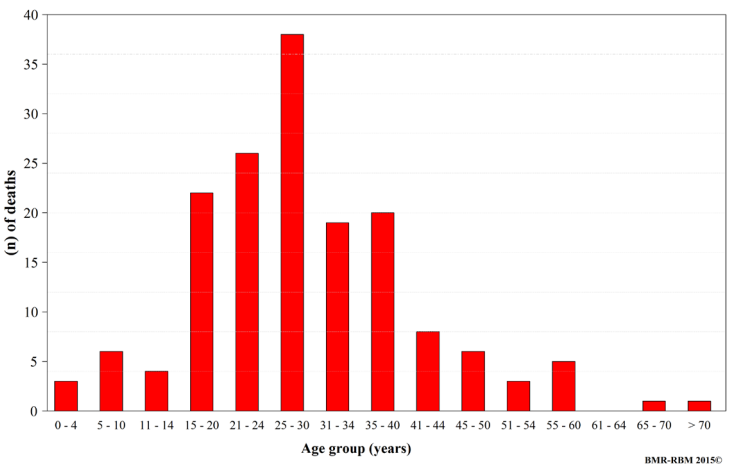
The data in the registry shows that there have been 162 reported deaths, 86 male and 76 female. Eighteen (11.1%) of the deaths were in children (below 18 years) while 8 (4.9%) of the deaths were in children younger than ten years. The mean (SD) and median (IQR) age at death for all reported cases is 29.7 (12.4) and 28.3 (13.8) respectively with the youngest at 0.6 years and the oldest case at 76.9 years. The table on the next page shows the year by age category at death for confirmed cases.

Table 19 | Categorized age at death

Year	Age at death															
	0 - 4	5 - 10	11 - 14	15 - 20	21 - 24	25 - 30	31 - 34	35 - 40	41 - 44	45 - 50	51 - 54	55 - 60	65 - 70	70 - 75	75 - 80	Total
1998	1	.	.	2	.	1	1	.	.	.	.	.	.	.	.	5
1999	.	.	.	5	2	4	.	1	.	.	.	.	.	.	.	12
2000	.	.	.	1	2	1	3	2	.	.	.	.	.	.	.	9
2001	.	2	.	1	3	2	.	2	.	.	.	.	.	.	.	10
2002	.	.	.	.	1	3	3	2	.	.	.	1	.	.	.	10
2003	.	1	1	3	4	3	1	1	.	1	.	.	.	.	.	15
2004	.	.	.	2	2	3	1	.	1	.	.	.	.	.	.	9
2005	1	.	.	.	1	1	.	.	.	.	.	.	.	.	.	3
2006	1	.	.	2	.	.	.	2	1	.	.	.	.	.	.	6
2007	.	1	1	1	.	2	.	1	1	1	.	.	.	.	.	8
2008	.	.	.	2	.	3	.	.	.	1	.	.	.	.	.	6
2009	.	.	1	1	2	2	2	.	1	1	.	.	.	.	.	10
2010	.	.	.	.	3	.	2	.	.	.	1	1	.	.	.	7
2011	.	1	.	.	2	3	1	.	1	1	.	.	.	.	.	9
2012	.	1	.	1	1	2	2	2	2	.	1	.	.	.	.	12
2013	.	.	.	1	2	3	.	.	.	.	.	.	.	.	.	6
2014	.	.	1	.	.	2	1	4	.	.	.	.	1	.	1	10
2015	.	.	.	.	1	3	2	3	1	1	1	3	.	.	.	15
Total	**3**	**6**	**4**	**22**	**26**	**38**	**19**	**20**	**8**	**6**	**3**	**5**	**1**	**.**	**1**	**162**

The figure below shows the number of reported and confirmed deaths in the CF registry since 1998. Most of the deceased patients were in the age category 25 – 30 years.

Figure 27 | Reported deaths by age category



PRIMARY CAUSE OF DEATH

Most of the reported deaths are attributable to multiple causes, some not listed in the table below. The other causes of death include and are not limited to: septic shock, multi-organ failure, terminal renal insufficiency, intoxication, hypoglycaemic coma and massive haemoptysis.

Table 20 | Primary causes of death for reported cases

Cause of death[1]	n	% *
Respiratory	67	*41.4*
Transplant	37	*22.8*
Other	28	*17.3*
Cancer	7	*4.3*
Cardiac	5	*3.1*
Liver	5	*3.1*
Suicide	3	*1.9*
Trauma	2	*1.2*
Unknown + missing	32	*19.8*

*based on the total reported deaths
[1]Causes of death are not mutually exclusive and these percentages are attributable to the specific cause of death

Note: The most common primary causes of death are associated with the respiratory system or are as a result of post-transplant complications.

CHAPTER 12: EDUCATION AND EMPLOYMENT

People with CF are living longer. According to the registry data the median patient age has increased from 14.9 in 1998 to about 22.0 in 2015 suggesting better life expectancy. This introduces new challenges and expectations alike. Despite their therapy burden, they are now studying, graduating and taking up a career either part-time or even full-time. They are thus taking up roles in society that were previously less attainable by cohorts decades back.

This section contains a summary of social and economic data, including education level of the people with CF registered in 2015. 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 21 | Education level

Education level	Children		Adults		Total	
	n	%	n	%	n	%
No school	49	*9.7*	65	*10.3*	114	*10.0*
Regular school / education attendance	453	*90.1*	118	*18.6*	571	*50.2*
Has finished school/education	1	*0.2*	448	*70.7*	449	*39.5*
Unknown	.	.	3	*0.5*	3	*0.3*
Subtotal	**503**		**634**		**1137**	
Missing	3	.	115	.	118	.
Total	**506**		**749**		**1255**	

SOCIAL ALLOWANCES AND EMPLOYMENT

Table 22 | Social allowances or benefits and employment

Description	Children		Adults	
	n	%	n	%
Additional child allowance	400	*79.1*	75	*10.0*
Income support (in adults)	.	.	152	*20.3*
Disability allowance	.	.	104	*13.9*
Preferential tariff (in adults)	.	.	343	*45.8*
Pension allowance (in adults)	.	.	7	*0.9*
Integration support (in adults)	.	.	188	*25.1*
Employment*				
Yes	.	.	250	*39.6*
No	.	.	233	*36.9*
Unknown or missing	.	.	148	*23.5*

*data excludes 118 adults still actively in school

Amongst the 250 patients who said they were employed, 106 (42.4%) worked full time, 88 (35.2%) part-time while for 56 patients this was unknown. Eighty three children and 176 adults had no information on social allowances.

CHAPTER 13: CF AND FERTILITY

With the improving trend in life-expectancy for people with CF, it is increasingly clear that social life and expectations other than education and employment come into play. Infertility in men with CF mainly arises from the failure of the vas deferens to develop properly[57]. A very small number (2 – 3%) are fertile[55, 56]. Many men with CF have moved into adolescence without being counselled on the certain possibility of being infertile[58]. This issue, including other aspects of their sexual functioning could be included and discussed openly in a transition care program as they move from the paediatric clinic to the adult clinic. Regular reproductive health education and a sperm analysis should be offered once they are at the adult clinic. Men can have children via assisted reproduction techniques including Percutaneous Epididymal Sperm Aspiration (PESA) or Testicular Sperm Aspiration (TESA) which are then used in either Intracytoplasmic Sperm Injection (ICSI) or in in-vitro fertilisation (IVF).

Despite most children with CF achieving near normal to normal growth, puberty and onset of other related physiological developments such as periods is often delayed in girls by one to two years. This is often a reflection of disease severity especially poor weight[60], or general ill health or CFRD. Most girls with CF have normal menstrual cycles but with a higher incidence of missed (amenorrhea) or irregular periods. When the egg is released, the thick mucus in the cervix may act as a barrier to sperm penetration thereby reducing fertility. Most women with CF have become pregnant without any difficulty. The fertility issues in women with CF should however be dealt with like any other normal women.

Mothers with CF are more likely to have pre-gestational diabetes, deliver preterm and have a primary caesarean delivery[61]. Issues of persistent decrement in lung function have also been documented. The use of contraception is thus advised to prevent unplanned pregnancies. Preconception care aimed at improving pulmonary function, eliminating pulmonary infections and exacerbations, improving the nutritional status as well as routine screening for signs of CFRD, including during gestation, will improve fertility before conception and the pregnancy outcome[62].

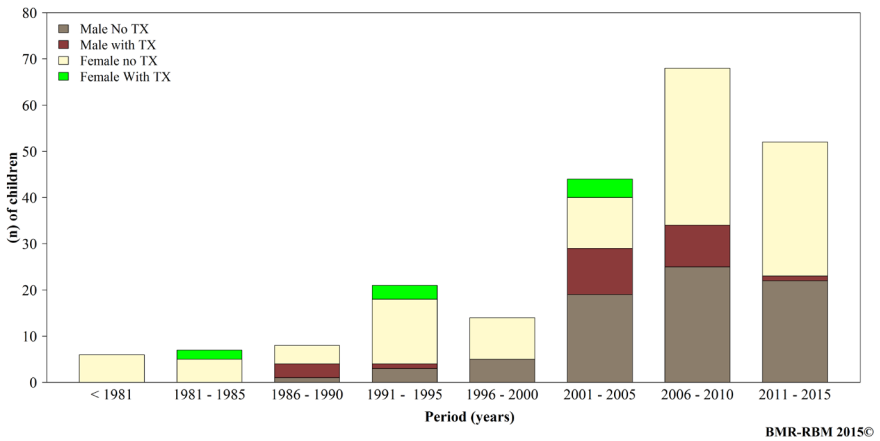
NUMBER OF BIRTHS REPORTED

Data from the registry shows that by 2015, there were at least 220 biological children reported from 162 patients (142 of them alive in 2015). More than half of those who have children were female (93, 57.4%). Among those with children, 22 (13.5%) are transplant patients. There were 58 (35.8%) parents homozygous for the F508del mutation. The mean age at which they had the first child was 29.2 years (median 29.0 years) with a range 17.0 – 49.0 years. The mean (median) was 31.9 (32.0) and 27.2 (27.0) years respectively for the male and female parents.

The mean number of children was 1.4 (median 1.0, range 1.0 – 4.0). 112 patients (69.1%) have one child while 44 (27.2%) have two children and 6 (3.7%) have three children or more. 17 parents had twins. There are four patients who have had a child before their 18th birthday. In 2015, three new births were reported.

Consistently more children have been born each year since 2009 when compared to the years before. The figure below shows the total number of births among CF patients.

Figure 28 | Number of reported births by period



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APPENDIX I: BCFR 2015 DIGITAL QUESTIONNAIRE NON TRANSPLANT PATIENTS

BMR-RBM 2015—Non-transplant patients

1. Background

Year of collection : .....
Treating physician : .....

1.1 - Identification

Patient ID (pseudo NISS) : .....
Date of birth : . . / . . / . . . .
Gender : ❑ Female ❑ Male
Place of residence : .....
Deceased? ❑ Yes ❑ No
Date of death : . . / . . / . . . .
Order in the family : .....
Country of origin father : .....
Country of origin mother : .....
Height father (cm) : ..... measured : ❑ Yes ❑ No
Height mother (cm) : ..... measured : ❑ Yes ❑ No
Received transplant : ❑ No ❑ Yes ❑ Missing data
Diagnosis confirmed : ❑ No ❑ Yes ❑ To be confirmed ❑ Unknown ❑ Missing data

1.2 - Diagnosis

Date of clinical diagnosis . . / . . / . . . .

Symptoms

Respiratory problems	❑
Nasal polyposis/chronic sinusitis	❑
Chronic dia-steatorrhea/malabsorption	❑
Meconium ileus	❑
Intestinal obstruction (other than mecon. 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 test ❑ unknown ❑ not done ❑ performed positive
❑ performed negative ❑ performed result unknown ❑ missing data

1.3 - Sweat test

Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.4 - Genotype

Legacy name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 ❑ Not applicable ❑ 5T ❑ 7T ❑ 9T ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 ❑ Not applicable ❑ 5T ❑ 7T ❑ 9T ❑ Missing data

cDNA name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 : .....
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 : .....

Protein name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
Chromosome 2 : .....
Chromosome 2 other : .....

1.5 - Nasal Transepithelial Potential Difference

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal ❑ Inconclusive ❑ Missing data
Date : . . / . . / . . . .

2. Observation

2.1 - Patient status

Patient status ❑ First registration in this center ❑ In follow-up ❑ Not seen patient
❑ Revoked diagnosis ❑ Moved to other center
❑ No information ❑ Missing data

2.2 - Cause of death

Cardiac ❑
Respiratory ❑
Hepatic ❑
Trauma ❑
Suicide ❑
Associated with cancer ❑
(type) .....
Associated with organ transplant ❑
(type) ❑ Chronic Lung Allograft Dysfunction (CLAD)
❑ Infection
❑ Other
Other cause ❑
(type) .....
Cause unknown ❑

2.3 - Last consultation of the year

Date consultation : . . / . . / . . . .

Anthropometry

Weight (kg) : .....
Height (cm) : .....

Lung function

Executed : ❑ No ❑ Yes ❑ Impossible ❑ Missing data
FVC (L) : .....
FEV_1 (L) : .....
FEF25-75 (L/s) : .....

2.4 - The best lung function of the year

Date of best LungFx : . . / . . / . . . .
FVC (L) : .....
FEV_1 (L) : .....
FEF25-75 (L/s) : .....
Weight (kg) : .....
Height (cm) : .....

3. Microbiology

3.1 - Microbiology: all cultures of the registration year

Microbiology executed	❑ Executed	❑ Not executed	❑ Missing data
Swabs	❑		
Sputum	❑		
Broncho-alveolar lavage (BAL)	❑		
Missing values	❑		

3.2 - Pathogen ever found during the registration year

Pseudomonas aeruginosa	❑
Burkholderia cepacia complex	❑
Stenotrophomonas maltophilia	❑
Achromobacter xylosoxidans (Alcaligenes)	❑
Methicillin resistant *Staphylococcus aureus* (MRSA)	❑
Methicillin sensible *Staphylococcus aureus* (MSSA)	❑
Haemophilus influenzae	❑
Aspergillus	❑
Scedosporium prolificans	❑
Atypical Mycobacterium (NTM)	❑
Other	❑
No pathogens	❑
Missing values	❑

3.3 - Colonisation

Number of exploitable months	❑ 0	❑ <4	❑ >=4	❑ Missing data
Pseudomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Burkholderia cepacia complex colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Stenotrophomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Achromobacter xylosoxidans colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
MRSA colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data

4. Complications

4.1 - Respiratory causes

Allergic bronchopulmonary aspergillosis ❑ No ❑ Yes ❑ Missing data
ABPA Treated ❑ No ❑ Yes ❑ Missing data
Treatment for ABPA ❑ Oral steroids and antifungal ❑ Omalizumab and antifungal ❑ Other ❑ Unknown ❑ Missing data
Pneumothorax ❑ No ❑ Yes ❑ Missing data
Nasal polyps (having required/requiring therapy) ❑ No ❑ Yes ❑ Missing data
Massive haemoptysis ❑ No ❑ Yes ❑ Missing data
Requiring embolization ❑ No ❑ Yes ❑ Missing data
Bronchiectasis ❑ No CT scan this year ❑ CT scan done, no bronchiectasis ❑ CT scan done, bronchiectasis ❑ CT scan done, result unknown ❑ Missing data

4.2 - Digestive causes

CF diabetes ❑ No ❑ IGT ❑ CFRD ❑ CFRD without fasting hyperglycemia ❑ CFRD with fasting hyperglycemia ❑ Missing data
OGTT done this year ❑ No ❑ Yes ❑ Missing data
Acute pancreatitis ❑ No ❑ Yes ❑ Missing data
Gastro-oesophageal reflux ❑ No ❑ Yes ❑ Missing data
Cirrhosis with portal hypertension ❑ No ❑ Yes ❑ Missing data
Gallstones ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : requiring surgery ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : not requiring surgery ❑ No ❑ Yes ❑ Missing data
Gastroparesis ❑ No ❑ Yes ❑ Missing data
Clostridium ❑ No ❑ Yes ❑ Missing data

4.3 - Other complications

CF related arthritis / arthropathy ❑ No ❑ Yes ❑ Missing data
Osteopenia / Osteoporosis ❑ z-score≥-1 ❑ z-score<-1 and >-2.5 ❑ z-score≤-2.5 ❑ Not done ❑ Missing data
Date of most recent DEXA . . / . . / . . . .
Psychiatric disease ❑ No ❑ Yes ❑ Missing data
Cancer ❑ No ❑ Yes ❑ Missing data
Type : .....
Hypertension treated ❑ No ❑ Yes ❑ Missing data
Other complications ❑ No ❑ Yes ❑ Missing data
Type : .....

4.4 - Surgery

Surgery ❑ No ❑ Yes ❑ Missing data
Type : .....
General anaesthesia ❑ No ❑ Yes ❑ Missing data

4.5 - New

Renal Function (last consultation of the year)
Date . . / . . / . . . .
Creatinine (mg/dl) . . . .

5. Therapy

5.1 - Therapy received during the registration year

Number of consultations	❑ 0	❑<4	❑ ≥4	❑ Missing data
Days in hospital	.....			

5.2 - Respiratory system

Systemic antibiotics	❑ No	❑ per os	❑ iv	❑ per os+iv	❑ Missing data
Days per os	.....				
Days iv at home	.....				
Days iv in hospital	.....				
Inhaled antibiotics	❑ No	❑ Yes	❑ Missing data		
Home O2-therapy	❑ No	❑ At night	❑ Day and Night		❑ Missing data
Inhalation therapy (except antibiotics)	❑ No	❑ Yes	❑ Missing data		
RhDnase	❑ No	❑ Yes			
Mucolytics	❑ No	❑ Yes			
Bronchodilators	❑ No	❑ Yes			
Corticosteroids	❑ No	❑ Yes			
Hypertonic saline	❑ No	❑ Yes			
Intranasal steroids	❑ No	❑ Yes	❑ Missing data		
Antiinflammatories p.o.	❑ No	❑ Yes	❑ Missing data		
NSAID	❑ No	❑ Yes			
Systemic Corticoids	❑ No	❑ Yes			
Azithromycine	❑ No	❑ Yes			

5.3 - Digestive system

Pancreatic sufficient	❑ No	❑ Yes	❑ Missing data
Pancreatic enzymes	❑ No	❑ Yes	❑ Missing data
Fat soluble vitamins (ADEK)	❑ No	❑ Yes	❑ Missing data
Ursodeoxycholic acid	❑ No	❑ Yes	❑ Missing data
Tube feeding	❑ No	❑ Yes	❑ Missing data
Gastrostomy	❑ No	❑ Yes	❑ Missing data
Parenteral feeding	❑ No	❑ Yes	❑ Missing data

5.4 - Miscellaneous

Oral therapy for diabetes	❑ No	❑ Yes	❑ Missing data
Insulin therapy	❑ No	❑ Yes	❑ Missing data
Prokinetics	❑ No	❑ Yes	❑ Missing data
PPI + H2 receptor blocker	❑ No	❑ Yes	❑ Missing data
Anticonceptive therapy	❑ No	❑ Yes	❑ Missing data
Psychopharmaca	❑ No	❑ Yes	❑ Missing data
Biphosphonates	❑ No	❑ Yes	❑ Missing data
Randomised drug trial	❑ No	❑ Yes	❑ Missing data
CFTR modulating therapy	❑ No	❑ Yes	❑ Missing data
Regular chest physiotherapy	❑ No	❑ Yes	❑ Missing data

6. Transplantation

Transplant 1

Transplant status ❑ Not evaluated ❑ Refused by transplant center ❑ Waiting list
❑ Received transplant ❑ Evaluated but not on waiting list ❑ Refused by patient
❑ Missing data

7. Social data

Pregnancy / Paternity
- Parenthood this year ❑ No ❑ Yes ❑ Missing data
- Birthdays of the biological children for this patient
  - Child 1 : . . / . . . . (month/year)
  - Child 2 : . . / . . . . (month/year)
  - Child 3 : . . / . . . . (month/year)
  - Child 4 : . . / . . . . (month/year)
  - Child 5 : . . / . . . . (month/year)
  - Child 6 : . . / . . . . (month/year)

School
- School status ❑ Unknown ❑ Regular school/education attendance ❑ Has finished school/education ❑ No school ❑ Missing data

Employment data
- Patient works ❑ No ❑ Yes ❑ Missing data
- Percentage ❑ Unknown ❑ Fulltime ❑Parttime ❑ Missing data

Financial benefits
- Additional child allowance ❑ No ❑ Yes ❑ Missing data
- Integration support ❑ No ❑ Yes ❑ Missing data
- Disability allowance ❑ No ❑ Yes ❑ Missing data
- Preferential tariff ❑ No ❑ Yes ❑ Missing data
- Pension ❑ No ❑ Yes ❑ Missing data
- Income support ❑ No ❑ Yes ❑ Missing data

Family composition
- Household composition ❑ Unchanged ❑ Changed ❑ First registration ❑ Missing data
- Number of siblings including the patient .....
- Number of siblings with CF .....
- Number of siblings deceased from CF .....
- General remark .....
  .....

APPENDIX II: BCFR 2015 DIGITAL QUESTIONNAIRE TRANSPLANT PATIENTS

BMR-RBM 2015—Transplant patients

1. Background

Year of collection : .....
Treating physician : .....

1.1 - Identification

Patient ID (pseudo NISS) : .....
Date of birth : . . / . . / . . . .
Gender : ❑ Female ❑ Male
Place of residence : .....
Deceased? ❑ Yes ❑ No
Date of death : . . / . . / . . . .
Order in the family : .....
Country of origin father : .....
Country of origin mother : .....
Height father (cm) : ..... measured : ❑ Yes ❑ No
Height mother (cm) : ..... measured : ❑ Yes ❑ No
Received transplant : ❑ No ❑ Yes ❑ Missing data
Diagnosis confirmed : ❑ No ❑ Yes ❑ To be confirmed ❑ Unknown ❑ Missing data

1.2 - Diagnosis

Date of clinical diagnosis . . / . . / . . . .

Symptoms

Respiratory problems	❑
Nasal polyposis/chronic sinusitis	❑
Chronic dia-steatorrhea/malabsorption	❑
Meconium ileus	❑
Intestinal obstruction (other than mecon. 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 test ❑ unknown ❑ not done ❑ performed positive
❑ performed negative ❑ performed result unknown ❑ missing data

1.3 - Sweat test

Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.4 - Genotype

Legacy name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 ❑ Not applicable ❑ 5T ❑ 7T ❑ 9T ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 ❑ Not applicable ❑ 5T ❑ 7T ❑ 9T ❑ Missing data

cDNA name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 : .....
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 : .....

Protein name

Date of genotype : . . / . . / . . . .
Chromosome 1 : .....
Chromosome 1 other : .....
Chromosome 2 : .....
Chromosome 2 other : .....

1.5 - Nasal Transepithelial Potential Difference

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal ❑ Inconclusive ❑ Missing data
Date : . . / . . / . . . .

2. Observation

2.1 - Patient status

Patient status ❑ First registration in this center ❑ In follow-up ❑ Not seen patient
❑ Revoked diagnosis ❑ Moved to other center
❑ No information ❑ Missing data

2.2 - Cause of death

Cardiac ❑
Respiratory ❑
Hepatic ❑
Trauma ❑
Suicide ❑
Associated with cancer ❑
(type) .....
Associated with organ transplant ❑
(type) ❑ Chronic Lung Allograft Dysfuntion (CLAD)
❑ Infection
❑ Other
Other cause ❑
(type) .....
Cause unknown ❑

2.3 - Last consultation of the year

Date consultation : . . / . . / . . . .

Anthropometry

Weight (kg) : .....
Height (cm) : .....

Lung function

Executed : ❑ No ❑ Yes ❑ Impossible ❑ Missing data
FVC (L) : .....
FEV_1 (L) : .....
FEF25-75 (L/s) : .....

2.4 - The best lung function of the year

Date of best LungFx : . . / . . / . . . .
FVC (L) : .....
FEV_1 (L) : .....
FEF25-75 (L/s) : .....
Weight (kg) : .....
Height (cm) : .....

2.5 - Best post-transplantation lung function (time interval between the 2 functions ≥ 3 weeks)

Date lung function 1	: . . / . . /	Date lung function 2	: . . / . . / . . . .
Weight (kg)	:	Weight (kg)	: .....
Height (cm)	:	Height (cm)	: .....
FVC (L)	:	FVC (L)	: .....
FEV_1 (L)	:	FEV_1 (L)	: .....

4. Complications

4.1 - Respiratory causes

4.2 - Digestive causes

CF diabetes ❑ No ❑ IGT ❑ CFRD ❑ CFRD without fasting hyperglycemia ❑ CFRD with fasting hyperglycemia ❑ Missing data

OGTT done this year	❑ No	❑ Yes	❑ Missing data
Acute pancreatitis	❑ No	❑ Yes	❑ Missing data
Gastro-oesophageal reflux	❑ No	❑ Yes	❑ Missing data
Cirrhosis with portal hypertension	❑ No	❑ Yes	❑ Missing data
Intestinal obstruction : requiring surgery	❑ No	❑ Yes	❑ Missing data
Intestinal obstruction : not requiring surgery	❑ No	❑ Yes	❑ Missing data
Gastroparesis	❑ No	❑ Yes	❑ Missing data
Clostridium	❑ No	❑ Yes	❑ Missing data

4.3 - Other complications

CF related arthritis / arthropathy	❑ No	❑ Yes	❑ Missing data
Osteopenia / Osteoporosis ❑ z-score≥-1	❑ z-score<-1 and >-2.5		
❑ z-score≤-2.5	❑ Not done		❑ Missing data
Date of most recent DEXA . . / . . /			
Psychiatric disease	❑ No	❑ Yes	❑ Missing data
Cancer	❑ No	❑ Yes	❑ Missing data
Type :			
Hypertension treated	❑ No	❑ Yes	❑ Missing data
Other complications	❑ No	❑ Yes	❑ Missing data
Type :			

4.4 - New

Renal Function (last consultation of the year)

Date . . / . . / . . . .

Creatinine (mg/dl) .....

Renal Function (1 month post-transplantation)

Date : . . / . . / . . . .

Creatinine (mg/dl) .....

Post-transplantation complications

Chronic lung allograft dysfunction (CLAD)

❑ No

❑ Bronchiolitis Obliterans Syndrome (BOS) :
- ❑ BOS 0-p
- ❑ BOS 1
- ❑ BOS 2
- ❑ BOS 3

❑ Restrictive allograft syndrome (RAS)

❑ Not possible to classify

Post-transplant lympho-proliferative disease ❑ No ❑ Yes ❑ Missing data

5. Therapy

5.1 - Therapy received during the registration year

Number of consultations	❑ 0	❑<4	❑ ≥4	❑ Missing data
Days in hospital	.....			

5.2 - Respiratory system

Home O2-therapy	❑ No	❑ At night	❑ Day and Night	❑ Missing data
Intranasal steroids	❑ No	❑ Yes		
Antiinflammatories p.o.	❑ No	❑ Yes	❑ Missing data	
Azithromycine	❑ No	❑ Yes		

5.3 - Digestive system

Pancreatic sufficient	❑ No	❑ Yes	❑ Missing data
Pancreatic enzymes	❑ No	❑ Yes	❑ Missing data
Fat soluble vitamins (ADEK)	❑ No	❑ Yes	❑ Missing data
Ursodeoxycholic acid	❑ No	❑ Yes	❑ Missing data
Tube feeding	❑ No	❑ Yes	❑ Missing data
Gastrostomy	❑ No	❑ Yes	❑ Missing data
Parenteral feeding	❑ No	❑ Yes	❑ Missing data

5.4 - Miscellaneous

Oral therapy for diabetes	❑ No	❑ Yes	❑ Missing data
Insulin therapy	❑ No	❑ Yes	❑ Missing data
Prokinetics	❑ No	❑ Yes	❑ Missing data
PPI + H2 receptor blocker	❑ No	❑ Yes	❑ Missing data
Anticonceptive therapy	❑ No	❑ Yes	❑ Missing data
Psychopharmaca	❑ No	❑ Yes	❑ Missing data
Biphosphonates	❑ No	❑ Yes	❑ Missing data
Randomised drug trial	❑ No	❑ Yes	❑ Missing data
CFTR modulating therapy	❑ No	❑ Yes	❑ Missing data
Regular chest physiotherapy	❑ No	❑ Yes	❑ Missing data

5.5 - Immunosuppressive treatments (> 3 months) (optional)

Calcineurin inhibitors			
Cyclosporine	❑ No	❑ Yes	❑ Missing data
Tacrolimus	❑ No	❑ Yes	❑ Missing data
Cell cycle inhibitors			
Azathioprine	❑ No	❑ Yes	❑ Missing data
Mycophenolate mofetil (MMF)	❑ No	❑ Yes	❑ Missing data
Other immunosuppressive treatments			
Steroids	❑ No	❑ Yes	❑ Missing data
Everolimus	❑ No	❑ Yes	❑ Missing data

Other immunosuppressive therapy, specify .....

.....

6. Transplantation

Transplant 1

Transplant status ❑ Not evaluated ❑ Refused by transplant center ❑ Waiting list
❑ Received transplant ❑ Evaluated but not on waiting list ❑ Refused by patient
❑ Missing data

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart
❑ Lung-liver ❑ Kidney ❑ Liver-Kidney ❑ Missing data

Year of transplant . . . . : . . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Precise date of Tx : . . / . . / . . . .

CMV status

Recipient ❑ pos. ❑ neg. ❑ unknown

Donor ❑ pos. ❑ neg. ❑ unknown

Induction therapy ❑ No ❑ Yes ❑ Missing data

Product ..... Duration (days): .....

Transplant 2

Transplant status ❑ Not evaluated ❑ Refused by transplant center ❑ Waiting list
❑ Received transplant ❑ Evaluated but not on waiting list ❑ Refused by patient
❑ Missing data

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart
❑ Lung-liver ❑ Kidney ❑ Liver-Kidney ❑ Missing data

Year of transplant . . . . : . . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Precise date of Tx : . . / . . / . . . .

CMV status

Recipient ❑ pos. ❑ neg. ❑ unknown

Donor ❑ pos. ❑ neg. ❑ unknown

Induction therapy ❑ No ❑ Yes ❑ Missing data

Product ..... Duration (days): .....

Transplant 3

Transplant status ❑ Not evaluated ❑ Refused by transplant center ❑ Waiting list
❑ Received transplant ❑ Evaluated but not on waiting list ❑ Refused by patient
❑ Missing data

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart
❑ Lung-liver ❑ Kidney ❑ Liver-Kidney ❑ Missing data

Year of transplant . . . . : . . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Precise date of Tx : . . / . . / . . . .

CMV status

Recipient ❑ pos. ❑ neg. ❑ unknown

Donor ❑ pos. ❑ neg. ❑ unknown

Induction therapy ❑ No ❑ Yes ❑ Missing data

Product ..... Duration (days): .....

7. Social data

Pregnancy / Paternity

Parenthood this year ❑ No ❑ Yes ❑ Missing data

Birthdays of the biological children for this patient

Child 1 : . . / . . . . (month/year)
Child 2 : . . / . . . . (month/year)
Child 3 : . . / . . . . (month/year)
Child 4 : . . / . . . . (month/year)
Child 5 : . . / . . . . (month/year)
Child 6 : . . / . . . . (month/year)

School

School status ❑ Unknown ❑ Regular school/education attendance
❑ Has finished school/education ❑ No school
❑ Missing data

Employment data

Patient works ❑ No ❑ Yes ❑ Missing data

Percentage ❑ Unknown ❑ Fulltime ❑ Parttime ❑ Missing data

Financial benefits

Additional child allowance ❑ No ❑ Yes ❑ Missing data
Integration support ❑ No ❑ Yes ❑ Missing data
Disability allowance ❑ No ❑ Yes ❑ Missing data
Preferential tariff ❑ No ❑ Yes ❑ Missing data
Pension ❑ No ❑ Yes ❑ Missing data
Income support ❑ No ❑ Yes ❑ Missing data

Family composition

Household composition ❑ Unchanged ❑ Changed
❑ First registration ❑ Missing data

Number of siblings including the patient .....
Number of siblings with CF .....
Number of siblings deceased from CF .....
General remark .....
.....

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