WETENSCHAPPELIJK INSTITUUT
VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE
DE SANTÉ PUBLIQUE

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

ANNUAL REPORT
BELGIAN CYSTIC FIBROSIS REGISTRY
2016

Annual report
Belgian Cystic Fibrosis Registry
2016

AUTHORS
Simeon Situma WANYAMA
Muriel THOMAS

PARTNERS AND COLLABORATORS

Scientific Institute of Public Health (WIV-ISP)
Operational directorate Public health and Surveillance
Unit Healthcare Services Research
Rue Juliette Wytsmanstraat 14 | 1050 Brussels | Belgium

March 2018 | Brussels, Belgium
PHS Report 2018-11
Depotnummer D/2018/2505/9

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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 pseudonymising 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

CONTRIBUTORS, MEMBERS OF THE BOARD OF THE BCFR

D. Baran (Hôpital Erasme, Bruxelles)
H. Boboli (CHR de la Citadelle, Liège)
F. De Baets (UZ Gent, Gent)
E. De Wachter (UZ Brussel, Brussel)
S. Gohy (Cliniques Universitaires St-Luc, Bruxelles)
L. Hanssens (HUDERF, Bruxelles)
C. Knoop (Hôpital Erasme, Bruxelles)
P. Lebecque (Cliniques Universitaires St-Luc, Bruxelles)
M. Lequesne (UZ Antwerpen, Antwerpen)
A. Malfroot (UZ Brussel, Brussel)
V. Nowé (GZA, Antwerpen)
U. Pypops (Belgian CF association)
V. Van Casteren (WIV-ISP, Brussel)
S. Van Biervliet (UZ Gent, Gent)
E. Van Braeckel (UZ Gent, Gent)
S. Verhulst (UZ Antwerpen, Antwerpen)
F. Vermeulen (UZ Gasthuisberg, Leuven)

REGISTRY MANAGEMENT

Scientific Institute of Public Health (WIV - ISP)
OD Public Health and Surveillance
Rue J. Wytsmanstraat, 14
1050 Brussels

V. Van Casteren : Head of unit
Tel. : 02/642.50.30 Fax : 02/642.54.10
M. Thomas : Project leader
Tel. : 02/642.50.23
S. S. Wanyama : Biostatistician
Tel. : 02/642.57.67
Y. Pirson : Administrative
Tel. : 02/642.57.41

Research funded by the National Institute for Health and Disability Insurance (RIZIV-INAMI)

Suggested reference:

Annual Data Report Belgian Cystic Fibrosis Registry (BCFR) 2016, Brussels, Belgium

ACCREDITED BELGIAN CF REFERENCE CENTRES

Mucoviscidose referentiecentrum UZ Brussel

UZ Brussel
Laarbeeklaan 101
1090 Brussel
A. Malfroot, E. De Wachter, E. Vanderhelst, S. Vincken

Muco-Referentiecentrum Antwerpen

St.-Vincentiusziekenhuis
St.-Vincentiusstraat 20
2018 Antwerpen
V. Nowé, I. Stappaerts

UZ Antwerpen
Wilrijkstraat 10
2650 Antwerpen
S. Verhulst, M. Lequesne, K. Van Hoorenbeeck

Referentiecentrum voor Mucoviscidose UZ Gent

UZ Gent
De Pintelaan 185
9000 Gent
F. De Baets, S. Van Daele, E. Van Braeckel

Muco-Referentiecentrum Gasthuisberg Leuven

UZ Leuven – Campus Gasthuisberg
Herestraat 49
3000 Leuven
K. De Boeck, F. Vermeulen, L. Dupont, M. Moens

Centre de référence de la Mucoviscidose UCL

Cliniques Universitaires St-Luc
Avenue Hippocrate, 10
1200 Bruxelles
P. Lebecque, S. Gohy, S. Berardis

Centre Liégeois de rééducation fonctionnelle pour la Mucoviscidose

CHR La Citadelle
Boulevard du 12ème de ligne, 1
4000 Liège
J.P. Sacré, H. Boboli

Clinique de l'Espérance
Rue St-Nicolas, 447-449
4420 Montegnée
F. Piérart

Institut de Mucoviscidose ULB

Hôpital Universitaire des Enfants Reine Fabiola
Avenue J.J. Crocq, 15
1020 Bruxelles
G. Casimir, L. Hanssens

Hôpital Erasme
Route de Lennik, 808
1070 Bruxelles
C. Knoop

ACKNOWLEDGMENTS

The annual data report of the Belgian Cystic Fibrosis Registry for the year 2016 is ready! We have faced a few of challenges in the recent past due to transition to a new data collection system including the migration of the registry and intergradation in the new Healthdata.be platform. Thanks to all our partners, we have been able to organize training on the new data collection system including the data correction and validation procedures, and we are proud to inform you that the lag in the publication of the reports has been resolved with the publication of this report. It is our hope that subsequently, the annual report will be published in time. Thank you all for your patience and collaboration.

We would like to most sincerely thank all our partners: - the physicians, nurses, administrative staff, physiotherapists and social workers who have spent long hours to complete the required registry data 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 2016. 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. In this edition, a brief analysis of anthropometry, spirometry, common complications and therapy in transplant patients has been added.

Since its establishment in 1998, the Belgium CF Registry (BCFR) has grown steadily and had 1275 patients registered in 2016. This number excludes five patients whose diagnosis for CF was revoked and fifteen without a confirmed diagnosis. There were 23 newly diagnosed patients in 2016, among them three adults, with a median age at diagnosis of 3.8 months with a range from birth to 52.3 years. All the newly diagnosed patients were genotyped; while 22 had sweat chloride values > 60 mmol/L.

Among the patients in follow-up in 2016, 52.0% were male and 61.2% adults with a median age of 22.5 years. This can be compared to the start of the registry 17 years ago when 39.0% were adults with a median age of 14.9 years. 46.7% of the patients are homozygous for the F508del mutation while 37.0% are F508del heterozygous. The main reasons for diagnosis of CF are acute or recurrent respiratory problems (42.1%) and failure to thrive (24.4%). About 18.0% were diagnosed via neonatal screening even though Belgium has no national neonatal screening program so far. Within the year, eight deaths were reported (four of them in transplanted patients) with age at death ranging from 20.5 to 44.8 years while 17 patients benefitted from a lung transplant. About 14.0% 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 11.7% in 2016; 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 53.7% and 13.6% respectively among the children and adults in 2016.

The overall annual prevalence of *Pseudomonas aeruginosa* reported in 2016 was 37.5% and has been declining compared to a prevalence of 42.4% in 2012. This prevalence has been below 40.0% since 2015. The prevalence of the *Burkholderia cepacia* complex on the other hand had remained stable over the years since 2014 at about 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. In 2016, CF related diabetes had a prevalence of 24.5% and 53.1% in non- transplanted and transplanted adults respectively. Other complications reported 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 2016, there were 1275 patients included in the registry with about 1400[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 [65-74] and several articles have been published[75-81].

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 has also contributed 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.

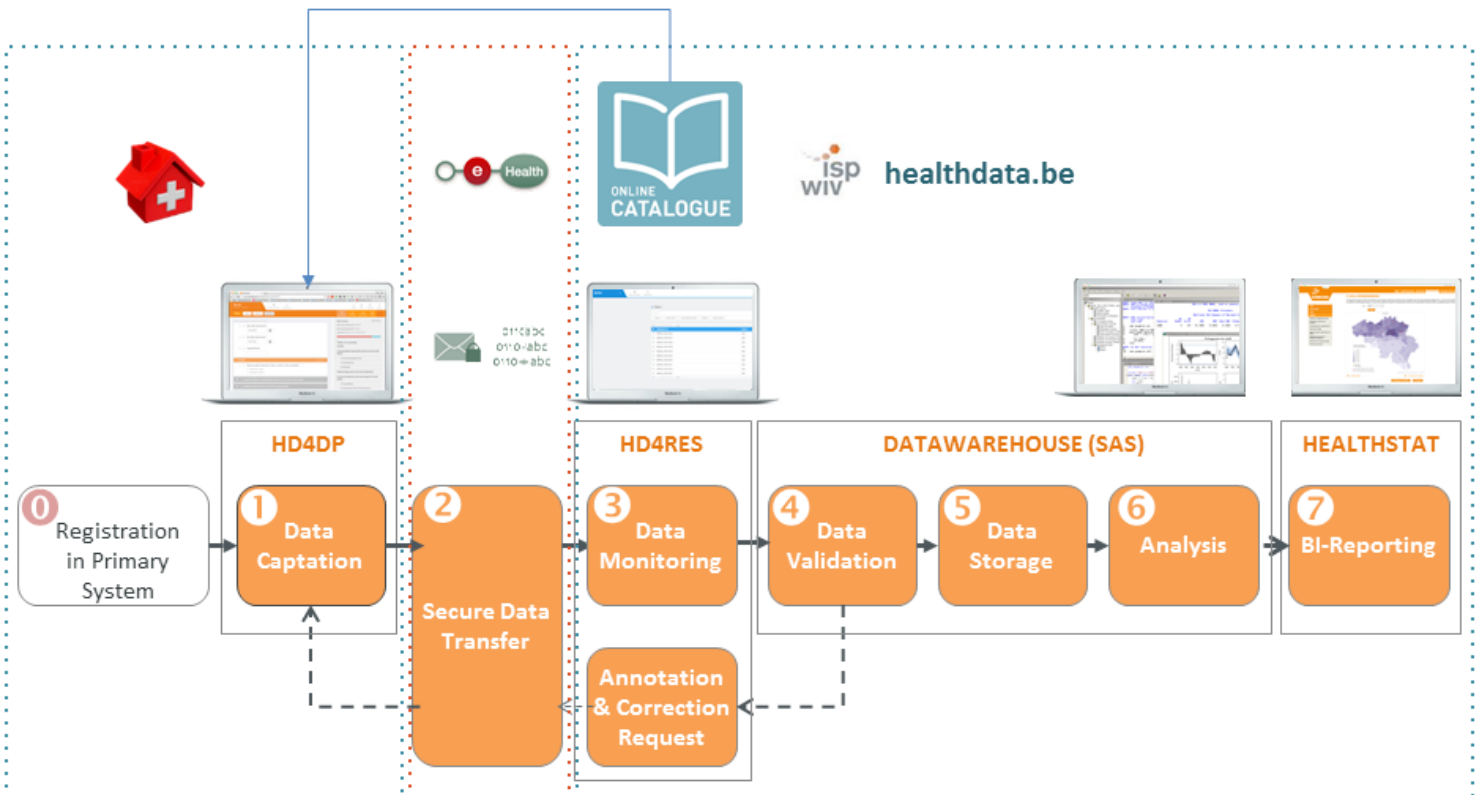
- **Analysis (6)**

  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 the latter 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 2013 - 2016

Table 1 | A comparison of demographic data for years 2013 - 2016

	2013	2014	2015	2016
Number of CF patients	1190	1230	1255	1275
Number of CF patients with complete records	1151	1194	1222	1243
Number of CF patients without observation[1]	39	36	33	32
Number of CF patients with a transplant	141	151	165	175
Number of CF patients who were not seen	18	24	27	29
New CF diagnoses[2]	28	36	25	23
Number of adults among the newly diagnosed patients	2	6	3	3
Number of patients without a confirmed diagnosis[3]	12	8	12	15
Number of patients with a revoked diagnosis[4]	9	2	1	5
Median patient age in years (range)[5]	20.6 (0.1 - 76.6)	21.3 (0.1 - 76.7)	22.0 (0.2 - 74.4)	22.5 (0.1 - 75.3)
Median patient age male (range)[5]	20.4 (0.1 - 66.2)	21.2 (0.2 - 67.3)	21.9 (0.3 - 68.3)	22.5 (0.5 - 69.2)
Median patient age female (range)[3]	20.8 (0.2 - 76.6)	21.5 (0.1 - 76.7)	22.0 (0.2 - 74.4)	22.6 (0.1 - 75.3)
Males (%)	621 (52.2%)	640 (52.0%)	654 (52.1%)	663 (52.0%)
Adults ≥ 18 years (%)	679 (57.1%)	720 (58.5%)	749 (59.7%)	780 (61.2%)
Median age at diagnosis (months)	5.9	5.7	5.7	5.7
Age range at diagnosis (years)	- 0.3 - 74.2	- 0.2 - 74.2	-0.2 - 65.2	- 0.2 - 65.2
Median age at diagnosis, male (months)[6]	5.9	5.9	5.9	6.0
Age range at diagnosis, male (years)	- 0.3 - 46.9	- 0.2 - 59.5	-0.2 - 59.5	- 0.2 - 59.5
Median age at diagnosis, female (months)	5.9	5.6	5.6	5.2
Age range at diagnosis, female (years)	- 0.2 - 74.2	- 0.1 - 74.2	-0.1 - 65.2	- 0.1 - 65.2
Median age at diagnosis new cases in years (range)	0.7 (0.0 - 25.7)	0.2 (0.0 - 60.0)	0.6 (0.1 - 55.0)	0.3 (- 0.1 - 52.3)
Number of transplants performed	16	11	20	17
Total number of deaths reported	6	10	15	8
Median age at death in years (range)	25.5 (17.6 - 30.5)	37.3 (11.5 - 76.9)	37.8 (22.4 - 60.8)	31.3 (20.5 - 44.8)
Number of deaths among transplant patients	2	4	8	4

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]

	2013	2014	2015	2016
SPIROMETRY: FEV_1 % PREDICTED				
Mean (SD) FEV_1 % predicted[36,37], Last of year	75.9 (25.7)	76.0 (26.1)	75.3 (25.3)	75.2 (25.2)
Male	78.3 (25.2)	78.4 (25.3)	77.9 (24.4)	77.7 (24.3)
Female	73.2 (26.0)	73.3 (26.7)	72.5 (26.0)	72.4 (26.0)
Children	90.8 (20.6)	92.1 (20.5)	90.9 (18.8)	90.8 (19.2)
Adults	64.9 (23.4)	65.3 (23.9)	65.4 (23.9)	66.2 (23.9)
Mean (SD) FEV_1 % predicted[36,37], Best of year	80.1 (25.0)	80.0 (25.0)	79.7 (25.1)	79.7 (25.0)
Male	82.3 (24.3)	82.5 (24.1)	82.5 (24.3)	82.0 (24.0)
Female	77.6 (25.7)	77.2 (25.6)	76.5 (25.7)	77.3 (25.8)
Children	95.5 (18.8)	96.4 (17.9)	96.0 (18.2)	96.5 (17.7)
Adults	68.9 (23.0)	69.4 (23.1)	69.5 (23.5)	70.2 (23.4)
ANTHROPOMETRY: BMI, HEIGHT AND WEIGHT (using CDC references)				
Median (range) BMI Z-score (last of year)	-0.4 (-4.3 - 2.7)	-0.4 (-3.9 - 2.3)	-0.4 (-3.7 - 2.5)	- 0.4 (- 4.0 - 2.5)
Median (range) Weight Z-score (last of year)	-0.6 (-6.5 - 2.4)	-0.5 (-4.2 - 2.6)	-0.5 (-4.0 - 2.8)	- 0.5 (- 4.1 - 2.6)
Median (range) Height Z-score (last of year)	-0.4 (-4.8 - 3.2)	-0.4 (-4.1 - 3.2)	-0.3 (-3.9 - 2.6)	- 0.3 (- 3.9 - 2.7)
INFECTIONS AND BACTERIOLOGY[8]				
Pseudomonas aeruginosa	426 (42.5%)	428 (41.3%)	405 (38.6%)	400 (37.5%)
Burkholderia cepacia complex	45 (4.5%)	38 (3.7%)	37 (3.5%)	36 (3.4%)
MRSA	66 (6.6%)	77 (7.4%)	64 (6.1%)	57 (5.3%)
Haemophilus influenzae	288 (28.7%)	279 (26.9%)	274 (26.1%)	249 (23.4%)
Stenotrophomonas maltophilia	119 (11.9%)	128 (12.3%)	123 (11.7%)	143 (13.4%)
Achromobacter xylosoxidans	107 (10.7%)	104 (10.0%)	109 (10.4%)	111 (10.4%)
Chronic *P. aeruginosa*	295 (29.4%)	289 (27.9%)	290 (27.6%)	274 (25.7%)
Chronic *B. Cepacia* complex	29 (2.9%)	34 (3.3%)	32 (3.0%)	27 (2.5%)
Chronic *S. maltophilia*	37 (3.7%)	40 (3.9%)	46 (4.4%)	41 (3.8%)
Chronic *A. xylosoxidans*	64 (6.4%)	68 (6.6%)	71 (6.8%)	73 (6.8%)
Chronic *MRSA*	45 (4.5%)	43 (4.1%)	38 (3.6%)	40 (3.8%)
COMPLICATIONS				
Allergic Bronchopulmonary Aspergillosis (ABPA)	96 (9.2%)	72 (6.7%)	70 (6.4%)	69 (6.3%)
Haemoptysis requiring embolisation	5 (0.5%)	5 (0.5%)	5 (0.5%)	3 (0.3%)
Pancreatic Insufficiency	838 (80.5%)	867 (80.4%)	880 (80.7%)	882 (80.2%)
CF related diabetes (CFRD)	160 (15.4%)	175 (16.2%)	167 (15.3%)	169 (15.4%)
Bronchiectasis[9]		307 (73.1%)	318 (75.9%)	403 (78.3%)

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 2016.

AGE ON DECEMBER 31 2016

Table 3 | Age on December 31 2016 by gender

Age years (on 31 Dec 2016)	Males			Females			All Patients		
	n	cum n	cum %	n	cum n	cum %	n	cum n	cum %
0 -< 5	54	54	*8.1*	54	54	*8.8*	108	108	*8.5*
5 -< 10	61	115	*17.3*	59	113	*18.5*	120	228	*17.9*
10 -< 15	65	180	*27.1*	85	198	*32.4*	150	378	*29.6*
15 -< 20	111	291	*43.9*	69	267	*43.6*	180	558	*43.8*
20 -< 25	82	373	*56.3*	68	335	*54.7*	150	708	*55.5*
25 -< 30	64	437	*65.9*	69	404	*66.0*	133	841	*66.0*
30 -< 35	67	504	*76.0*	67	471	*77.0*	134	975	*76.5*
35 -< 40	50	554	*83.6*	48	519	*84.8*	98	1073	*84.2*
40 -< 45	48	602	*90.8*	37	556	*90.8*	85	1158	*90.8*
45 -< 50	26	628	*94.7*	20	576	*94.1*	46	1204	*94.4*
≥ 50	35	663	*100.0*	36	612	*100.0*	71	1275	*100.0*
Total	**663**			**612**			**1275**		

The median age on 31, December 2016 was 22.5 years for both the male and female patients

The figures below compare the age distribution by gender for 2000 and 2016 data with an increase in the number of patients above age 40 years: 15.3% in 2016 compared to 1.2% in 2000.

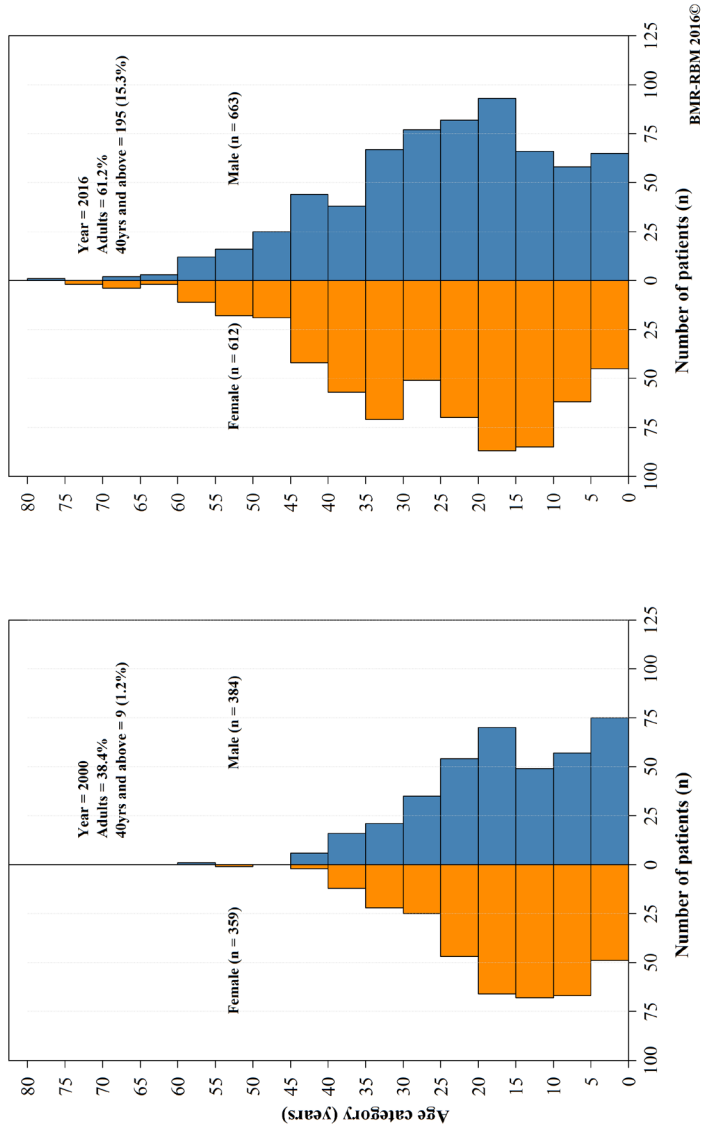
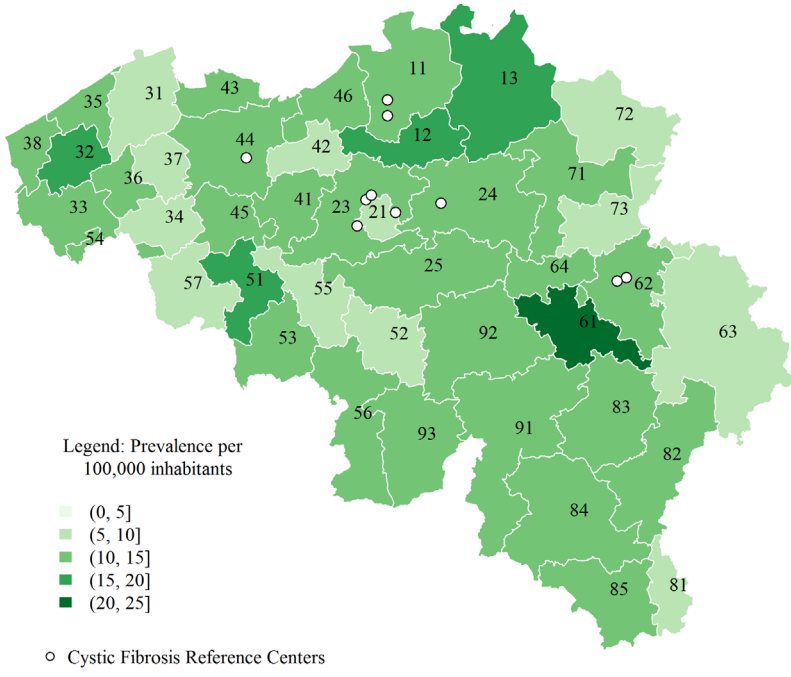


Figure 2 | Age distribution by gender in 2000 (left) and 2016 (right)

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 2016. 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 2016

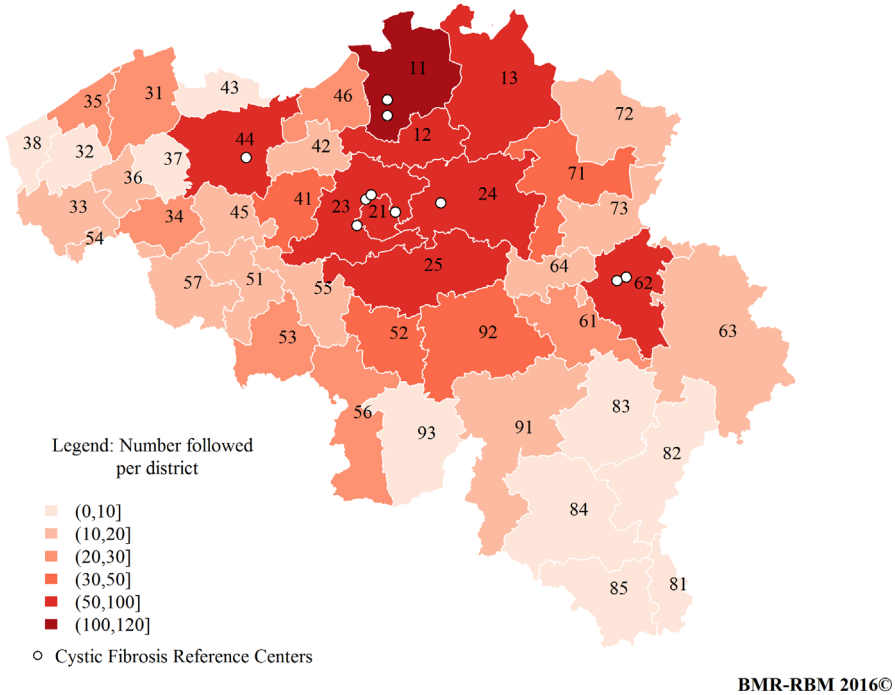


The figure above indicates that the top three districts with the highest prevalence are Huy (Hoei, code 61), with prevalence 21.1 and population of 113,568, Dixmuide (Diksmude, code 32) with prevalence 19.5 and population 51,191 and Turnhout (code 13) with prevalence 18.3 and population 453,301 at the beginning of the year respectively. The bottom three districts with the lowest prevalence are Verviers (code 63) with prevalence 6.6 and population 287,050, Arlon (Aarlen, code 81) with prevalence 6.5 and population 61,285 and lastly Tongeren (Tongres, code 73) which had the lowest prevalence of 5.4 in 100,000 in a population of 202,561 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 2016. 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 2016



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 113 patients in a population of about 1.039 million had a prevalence of 10.8 in 100,000 inhabitants and the capital city Brussels (Bruxelles, code 21) coming second with 100 patients in 1.19 million inhabitants and a prevalence of 8.4. The fewest patients lived in Arlon (Aarlen, code 81) with 4 patients in a population of 61,285 inhabitants and Bastogne (Bastenaken, code 82) with 5 patients and population 47,491 with prevalence 6.5 and 10.5 respectively.

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	113	*8.9*	61	Huy	24	*1.9*
12	Mechelen	61	*4.8*	62	Liège	78	*6.1*
13	Turnhout	83	*6.5*	63	Verviers	19	*1.5*
21	Brussel Hoofdstedelijk Gewest Région Bruxelles Capitale	100	*7.8*	64	Waremme	12	*0.9*
23	Halle-Vilvoorde	75	*5.9*	71	Hasselt	47	*3.7*
24	Leuven	54	*4.2*	72	Maaseik	16	*1.3*
25	Nivelles	56	*4.4*	73	Tongeren	11	*0.9*
31	Brugge	21	*1.6*	81	Arlon	4	*0.3*
32	Diksmuide	10	*0.8*	82	Bastogne	5	*0.4*
33	Ieper	11	*0.9*	83	Marche-en-Famenne	6	*0.5*
34	Kortrijk	26	*2.0*	84	Neufchâteau	9	*0.7*
35	Oostende	21	*1.6*	85	Virton	7	*0.5*
36	Roeselare	17	*1.3*	91	Dinant	13	*1.0*
37	Tielt	9	*0.7*	92	Namur	33	*2.6*
38	Veurne	9	*0.7*	93	Philippeville	8	*0.6*
41	Aalst	35	*2.7*				
42	Dendermonde	16	*1.3*				
43	Eeklo	9	*0.7*				
44	Gent	66	*5.2*				
45	Oudenaarde	15	*1.2*		**Subtotal**	**1262**	
46	Sint-Niklaas	27	*2.1*		**Foreign country**	**13**	***1.0***
51	Ath	15	*1.2*		**Missing**	**-**	**-**
52	Charleroi	34	*2.7*		**Total**	**1275**	
53	Mons	28	*2.2*				
54	Mouscron	11	*0.9*				
55	Soignies	14	*1.1*				
56	Thuin	22	*1.7*				
57	Tournai	12	*0.9*				

CHAPTER 4: DIAGNOSIS

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

SYMPTOMS AND CLINICAL REASONS SUGGESTING CF

In a patient with suggestive symptoms, a family history of 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 18.0% of the patients were diagnosed via neonatal screening test.

Table 5 | Symptoms and clinical reasons for CF diagnosis

			Newly diagnosed			
	Data 1998 – 2016		2015		2016	
	n	%	n	%	n	%
Acute or recurrent respiratory problems	513	*42.1*	12	*48.0*	6	*26.1*
Failure to thrive	298	*24.4*	12	*48.0*	6	*26.1*
Chronic diarrhea/steatorrhea/ malabsorption	229	*18.8*	1	*4.0*	0	*0.0*
Neonatal screening test	215	*17.6*	8	*32.0*	10	*43.5*
Meconium ileus	176	*14.4*	1	*4.0*	4	*17.4*
Family history	123	*10.1*	2	*8.0*	2	*8.7*
Nasal polyposis / chronic sinusitis	57	*4.7*	4	*16.0*	0	*0.0*
Rectal prolapse	32	*2.6*	0	*0.0*	0	*0.0*
Intestinal obstruction (other than meconium ileus)	26	*2.1*	1	*4.0*	0	*0.0*
Prenatal diagnosis	38	*3.1*	1	*4.0*	1	*4.3*
Dehydration / electrolyte imbalance	21	*1.7*	1	*4.0*	2	*8.7*
Neonatal jaundice / Prolonged icterus	2	*0.2*	0	*0.0*	0	*0.0*
Infertility	16	*1.3*	1	*4.0*	2	*8.7*
Diagnosis other	105	*8.6*	0	*0.0*	1	*4.3*
*No diagnosis reasons given	56	*4.6*	0	*0.0*	0	*0.0*

* The overall percentages are based on 1219, 56 patients did not have information on any of the above reasons given in the 2016 data and were excluded from the calculations.
There were 25 newly diagnosed in 2015, percentages are based on 25 patients.
There were 23 newly diagnosed in 2016, percentages are based on 23 patients.
Note: Reasons for diagnosis are not mutually exclusive.

DOCUMENTATION OF CF DIAGNOSIS

Table 6 | Documentation of CF at diagnosis

Procedure	Data 1998 – 2016		Newly diagnosed Patients 2016	
	n	%	n	%
Patients meeting inclusion criteria for the European CF Society Patient Registry				
Clinical symptoms and/or family history, sweat test and genotyping	668	*52.4*	11	*47.8*
Clinical symptoms and/or family history, sweat test, genotyping and abnormal TEPD	61	*4.8*	1	*4.3*
Clinical symptoms and/or family history and sweat test	20	*1.6*	.	.
Clinical symptoms and/or family history, sweat test and abnormal TEPD	3	*0.2*	.	.
Clinical symptoms and/or family history and genotyping	200	*15.7*	1	*4.3*
Clinical symptoms and/or family history, genotyping and abnormal TEPD	20	*1.6*	.	.
Neonatal screening test, sweat test and genotyping	118	*9.3*	6	*26.1*
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	63	*4.9*	4	*17.4*
Sweat test and genotyping	30	*2.4*	.	.
Sweat test, genotyping and abnormal TEPD	2	*0.2*	.	.
Clinical symptoms and/or family history, neonatal screening test and genotyping	12	*0.9*	.	.
Subtotal	**1202**	***94.3***	**23**	***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	38	*3.0*	.	.
Neonatal screening test and genotyping	2	*0.2*	.	.
Clinical symptoms and/or family history and neonatal screening test	16	*1.3*	.	.
Abnormal TEPD	1	*0.1*	.	.
Subtotal	**73**	***5.7***	**.**	**.**
Total	**1275**	***100.0***	**23**	***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.

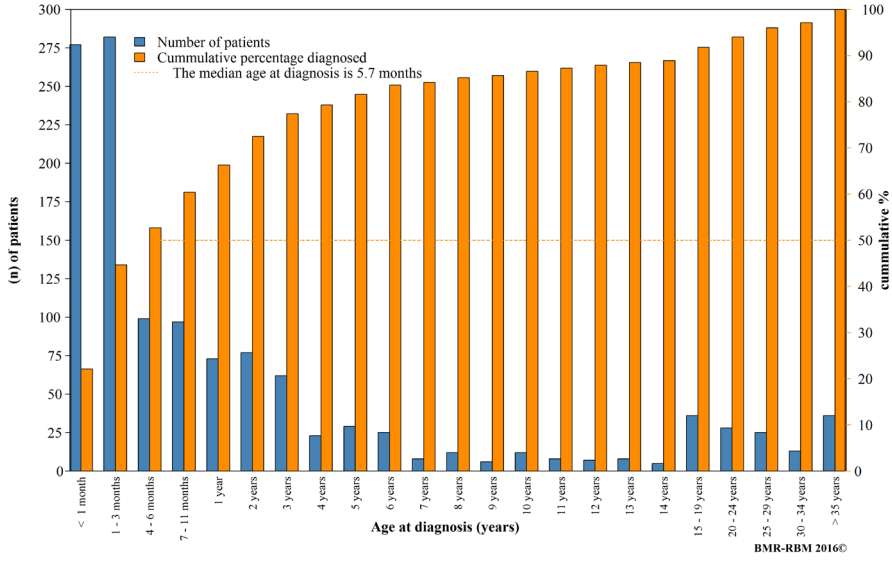
Inclusion criteria for patients into the European CF Society Patient Registry (ECFSPR)
For a patient to be included in the ECFSPR, at least one of the following three criterions must be met:

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 2016. The median age at diagnosis was 5.7 months; 6.0 months for male and 5.2 months for female patients respectively. At the age of 18 years 90.5% 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 3.0 months for the F508del homozygous patients, 9.3 months for the F508del heterozygous while for patients with other mutations it was 13.0 months.

Figure 5 | Age at Diagnosis



The median age at diagnosis for the 23 newly diagnosed patients in 2016 was 3.8 months; 7.9 months for male and 1.8 months for female patients respectively, with range of one month before birth to 52.3 years. There were three adult patients amongst the newly diagnosed.

GENOTYPE

All the 1275 patients have undergone a genetic analysis. However, 40 patients (3.1%) had at least one non-identified mutation. Almost half (46.7%) were homozygous for F508del (table 7) and 85.6% 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	596	*46.7*	*46.7*
F508del Heterozygous	472	*37.0*	*83.8*
F508del---NI	23	*1.8*	*85.6*
OTHER---OTHER	167	*13.1*	*98.7*
OTHER---NI	7	*0.5*	*99.2*
NI---NI	10	*0.8*	*100.0*
Total	**1275**		

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	1091	*85.6*	1687	*66.2*	5T*	6	*0.5*	6	*0.2*
G542X	66	*5.2*	74	*2.9*	621+1G->T	6	*0.5*	6	*0.2*
N1303K	58	*4.5*	62	*2.4*	E60X	6	*0.5*	6	*0.2*
3272-26A->G	44	*3.5*	44	*1.7*	G85E	6	*0.5*	6	*0.2*
1717-1G->A	37	*2.9*	37	*1.5*	G970R	6	*0.5*	6	*0.2*
S1251N	32	*2.5*	32	*1.3*	Q493X	6	*0.5*	6	*0.2*
A455E	31	*2.4*	31	*1.2*	3120+1G->A	5	*0.4*	6	*0.2*
2789+5G->A	30	*2.4*	30	*1.2*	711+1G->T	5	*0.4*	7	*0.3*
R117H*	28	*2.2*	30	*1.2*	L165S[$]	5	*0.4*	5	*0.2*
L927P	25	*2.0*	27	*1.1*	4218insT	4	*0.3*	4	*0.2*
3849+10kbC->T	19	*1.5*	19	*0.7*	G551D	4	*0.3*	5	*0.2*
2183AA->G	18	*1.4*	18	*0.7*	L227R	4	*0.3*	7	*0.3*
R553X	18	*1.4*	18	*0.7*	Q1313X	4	*0.3*	4	*0.2*
W1282X	17	*1.3*	17	*0.7*	R347H	4	*0.3*	4	*0.2*
I507del	10	*0.8*	10	*0.4*	R347P	4	*0.3*	4	*0.2*
R1162X	10	*0.8*	14	*0.5*	Y913C[$]	4	0.3	4	0.2
3659delC	8	*0.6*	8	*0.3*					
D1152H*	8	*0.6*	8	*0.3*					
W401X	8	*0.6*	8	*0.3*	Others	203	*15.9*	212	*8.3*
306insA	7	*0.5*	7	*0.3*	Not identified	40	*3.1*	50	*2.0*
G178R	7	*0.5*	7	*0.3*	**Subtotal**			**2550**	
R334W	7	*0.5*	7	*0.3*	**Missing**	-	-	-	-
394delTT	6	*0.5*	7	*0.3*	**Total**			**2550**	

The mutations detected in less than four patients were summarized into the "others" category for this purpose. According to the CFTR2 database – list 17/03/2017 - https://cftr2.org/, the mutations listed above are CF causing with few exceptions: - * = mutation with varying clinical consequence while those marked[$] are not yet annotated in the CFTR2 database.

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 **175 patients with a transplant (82 male, 93 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 2016 data from 1055 patients was analysed. The figure below shows a general trend for better median BMI over the years with the yearly profiles generally shifting upwards, even among the adult patients.

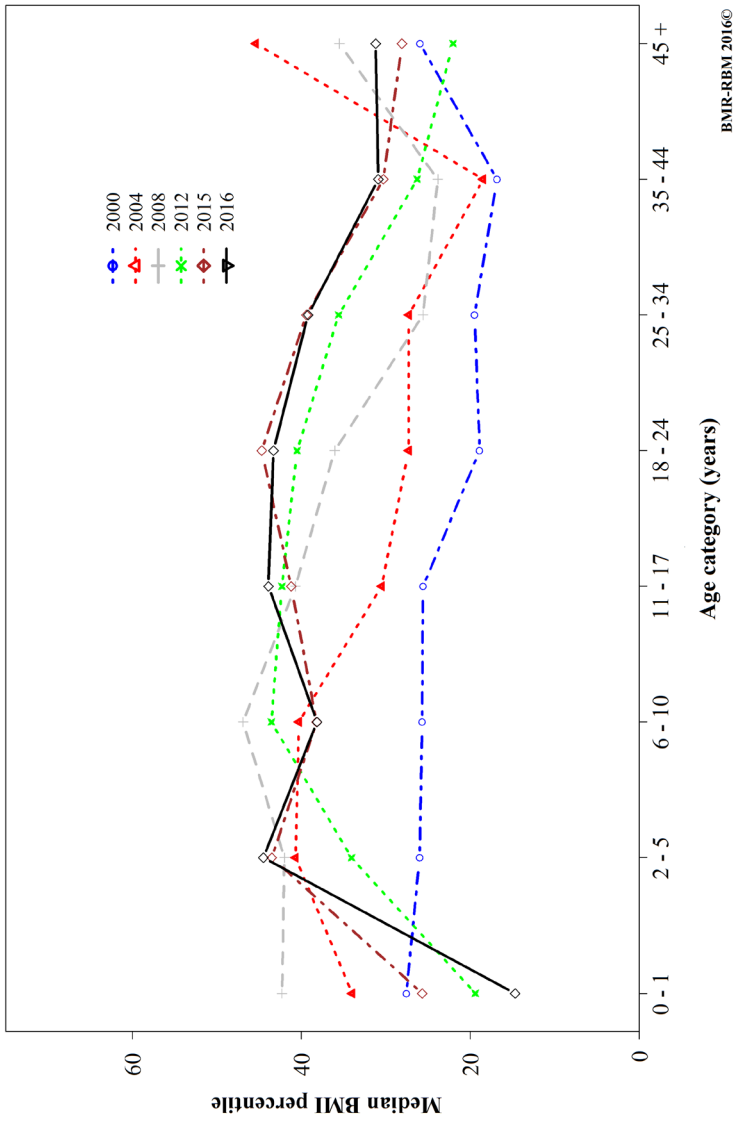
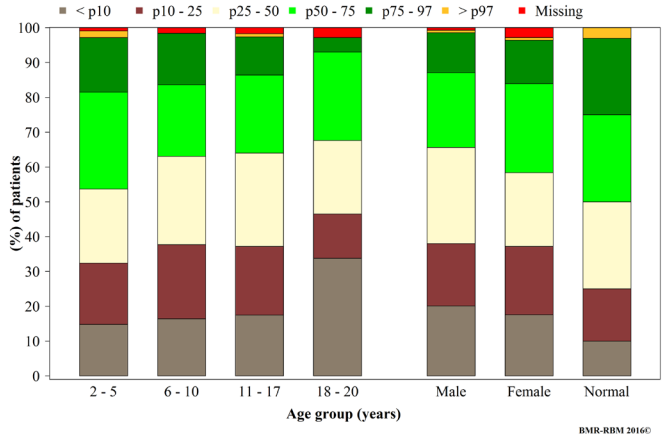


Figure 6 | Median BMI percentile by age group and year

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 2016 data from 520 patients was analysed. The figure below displays the proportion in each percentile category.

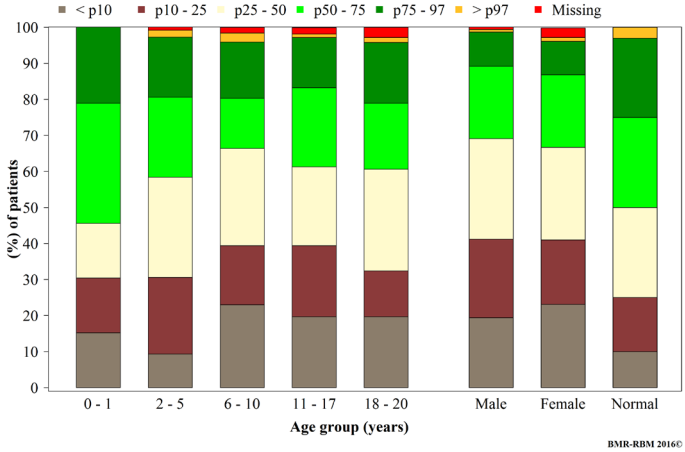
Figure 7 | CDC BMI percentiles by age



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 2016 data from 553 patients was analysed. The figure below indicates the proportion in each percentile category.

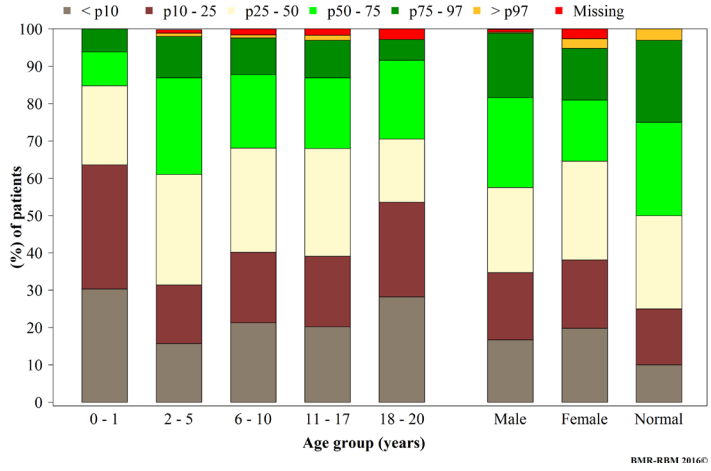
Figure 8 | CDC height percentiles by age



WEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover weight from 0.0 – 20.0 years. In 2016 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 has been observed in patients aged less than two 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 (**70 male, 71 female**) **was excluded** from the lung function analysis. **Those with a transplant (83 male, 92 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

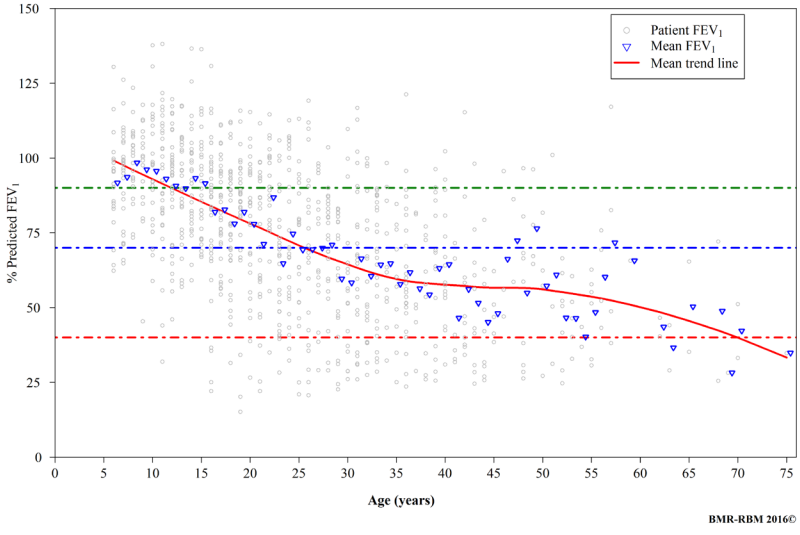
Wang's equations[36] were used for male, 6 – 17 years and female patients 6 – 15 years, while Hankinson's[37] were used for predictions for the male 18 years and above and female patients from 16 years onwards.

In 2016 data from 919 patients was analysed. The overall mean FEV_1 % predicted is 75.2 (SD = 25.2). The mean FEV_1 % predicted was 77.7 % (SD = 24.3) and 72.4 % (SD = 26.0) respectively for 484 male and 435 female patients. The mean FEV_1 % predicted was 90.8 % (SD = 19.2) and 66.2 % (SD=23.9) respectively for 337 children and 582 adult patients.

Amongst the 404 F508del homozygous, the means were 74.4% (SD = 24.6) and 71.3% (SD = 26.4) respectively for the 215 male and 189 female patients. The means were 89.7% (SD = 21.9) and 63.3% (SD = 22.2) respectively for the 148 children and 256 adults homozygous for the F508del mutation.

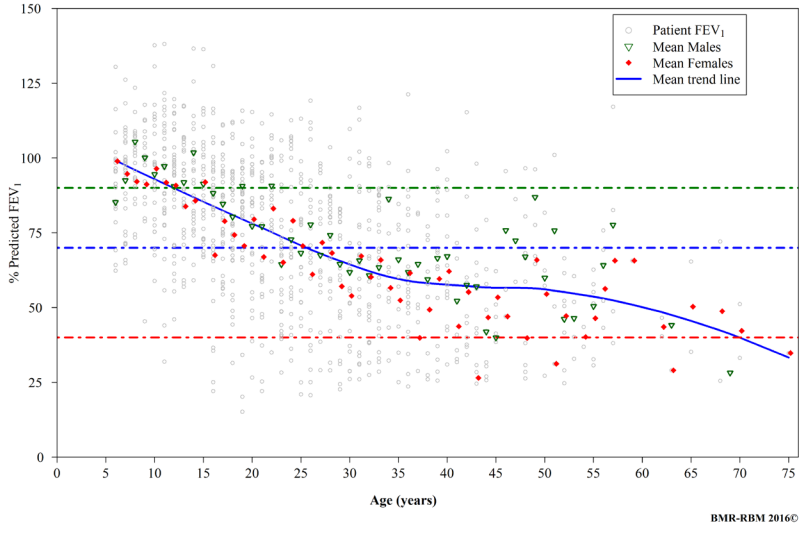
The figure below shows a scatter plot of the FEV_1 % predicted with the means calculated at yearly intervals. It shows on average declining values with age, with a steeper slope up to about 35 years of age when it levels off.

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 2016.

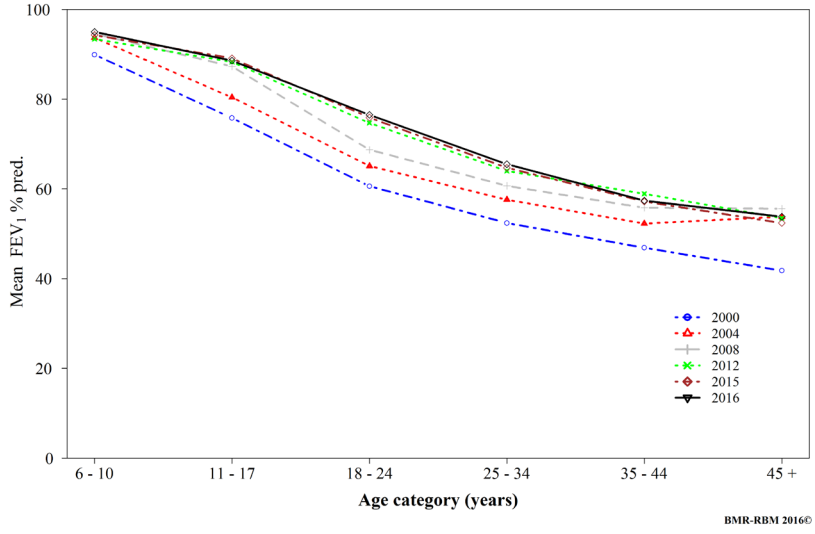
Table 9 | Proportions in each FEV_1 severity category for children and adults

Group	Children (6-17 years)		Adults (≥ 18 years)		Total	
	n	%	n	%	n	%
Normal : ≥ 90% predicted	190	*54.3*	106	*17.4*	296	*30.9*
Mild : 70% - 89% predicted	102	*29.1*	147	*24.1*	249	*26.0*
Moderate : 40% - 69% predicted	40	*11.4*	233	*38.3*	273	*28.5*
Severe : < 40% predicted	5	*1.4*	96	*15.8*	101	*10.5*
Missing	13	*3.7*	27	*4.4*	40	*4.2*
Subtotal	**350**		**609**		**959**	
Transplants	4		171		175	
< 6 years	141		-		141	
Total	**495**		**780**		**1275**	

The FEV_1 was 70.0% of predicted or higher in 56.9% of the patients: - in 83.4% of the children (6 – 17 years) and 41.5% of the adults (18 years and above). About 4.0% had missing FEV_1 data.

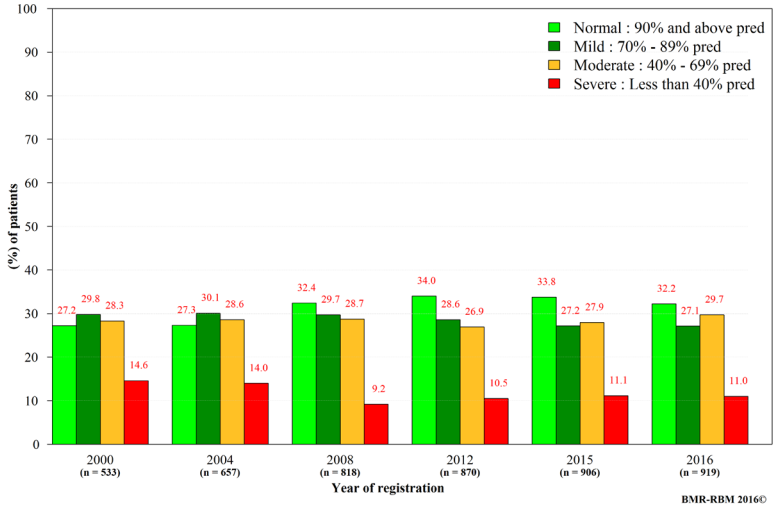
In the figure below, the mean FEV_1 % predicted calculated cross-sectional shows improving lung function over time in all age categories. There has however been a peak in these values since 2012 with the profiles less separated in that period.

Figure 12 | Mean FEV_1 % predicted by age group for selected years



The figure below represents the overall trend in lung function severity classification for both children and adults for selected years using the Wang – Hankinson equations. The highest proportion with FEV_1 of at least 90% was reported in 2012. When missing data is excluded, 11.1% of the patients had FEV_1 below 40% while 32.2% had FEV_1 of at least 90% in 2016.

Figure 13 | Trend in lung function severity



In the following figure, the proportion of patients in each severity group over selected years is presented for children and adults. There has been a general increase in the proportion of children with normal lung function peaking-off in 2012. After excluding missing data, 56.4% of the children and 18.2% of the adults patients had FEV1 of at least 90% in 2016. The proportion of adults with normal lung function has increased steadily from 10.5% in 2000 to 18.2% in 2016. The proportion of adults with severe lung function impairment has decreased since 2000 and is since 2008 within the range 16.0 – 17.0%.

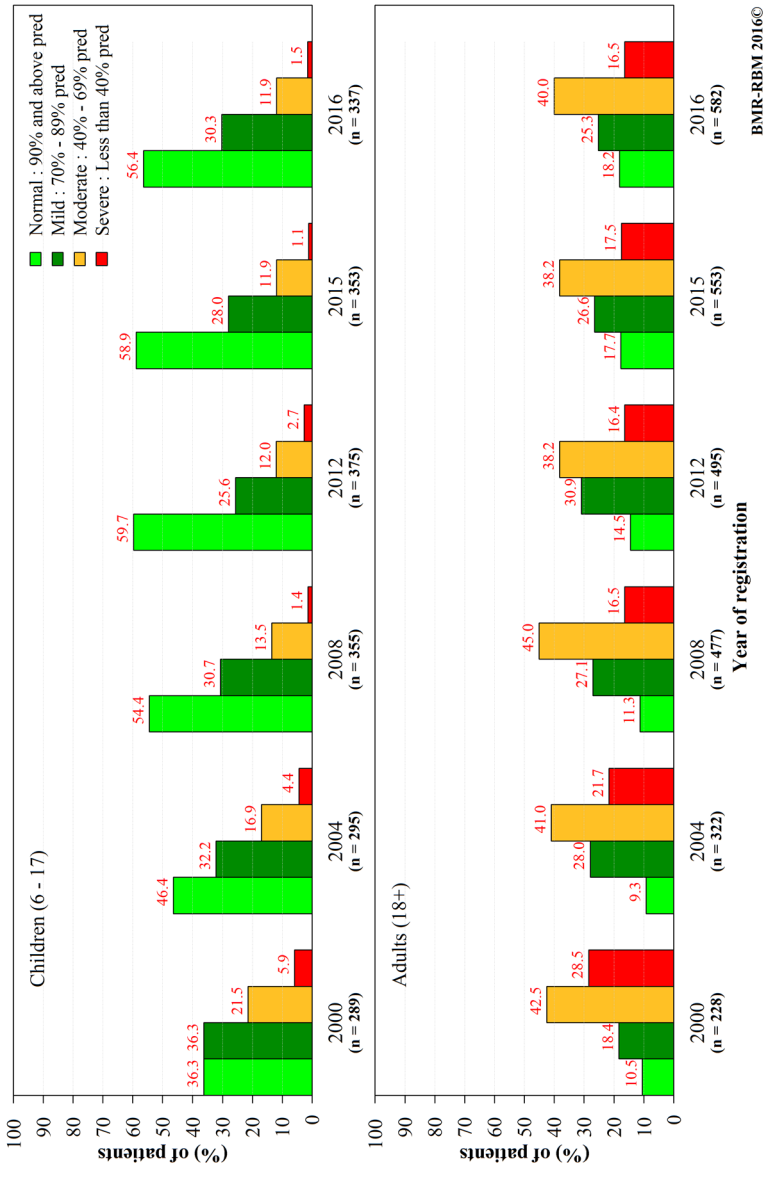


Figure 14 | FEV_1 % predicted groups in children and adults for selected years

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 2016, 485 children and 581 adults i.e. 99.1% of the 1100 non-transplant patients had at least one culture done. The largest proportion (82.1%) had at least four exploitable months during the year. Sputum samples were done in 833, throat swabs in 432 while 48 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 2013 - 2016

	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
Methicillin Sensitive Staphylococcus aureus (MSSA)	630	*62.4*	631	*60.8*	644	*61.3*	673	*63.1*
Haemophilus influenzae	288	*28.5*	279	*26.9*	274	*26.1*	249	*23.4*
Pseudomonas aeruginosa	426	*42.2*	428	*41.3*	405	*38.6*	400	*37.5*
Methicillin Resistant Staphylococcus aureus (MRSA)	66	*6.5*	77	*7.4*	64	*6.1*	57	*5.3*
Stenotrophomonas maltophilia	119	*11.8*	128	*12.3*	123	*11.7*	143	*13.4*
Achromobacter xylosoxidans	106	*10.5*	104	*10.0*	109	*10.4*	111	*10.4*
Burkholderia cepacia complex	45	*4.5*	38	*3.7*	37	*3.5*	36	*3.4*
Aspergillus	331	*32.8*	364	*35.1*	350	*33.3*	365	*34.2*
Scedosporium spp.	4	*0.4*	3	*0.3*	6	*0.6*	8	*0.8*
Atypical / Non – tuberculous mycobacteria (NTM)	8	*0.8*	11	*1.1*	22	*2.1*	18	*1.7*
Other pathogens	168	*16.7*	224	*21.6*	379	*36.1*	378	*35.5*

Percentages are based on 1009 , 1037 , 1050 and 1066 patients with a culture respectively for the years 2013 through 2016

While 24.1% of the children (n=117) and 48.7% of the adults (n=283) had a *Pseudomonas aeruginosa*, 4.7% (n=23) and 5.9% (n=34) respectively had a MRSA infection. *Burkholderia cepacia* complex infection was found in 8 (1.6%) children and 28 (4.8%) adults. The prevalence of *Stenotrophomonas maltophilia* has oscillated at about 12.0% since 2012. In 2016 it was 13.4 % (14.4% in children and 12.6% in the adults). There had been a steady increase of the prevalence of *Achromobacter xylosoxidans* from 5.9% in 2009 to 10.7 % in 2012 but has stabilized at about 10.0% since then. The prevalence of *Non-tuberculous mycobacteria* remains low at 1.7%. 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 2013 - 2016

	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
Chronic *Pseudomonas aeruginosa*	296	*29.3*	294	*28.4*	292	*27.8*	274	*25.7*
Chronic *Burkholderia cepacia* complex	29	*2.9*	34	*3.3*	32	*3.0*	27	*2.5*
Chronic *Stenotrophomonas maltophilia*	37	*3.7*	41	*4.0*	47	*4.5*	41	*3.8*
Chronic *Achromobacter xylosoxidans*	64	*6.3*	69	*6.7*	71	*6.8*	73	*6.8*
Chronic MRSA	45	*4.5*	45	*4.3*	38	*3.6*	40	*3.8*

Percentages are based on 1009 , 1037 , 1050 and 1066 patients with a culture respectively for the years 2013 through 2016

About 9.7% of the children (n = 47) and 39.1% of the adults (n = 227) had chronic *Pseudomonas aeruginosa* infection.

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 15 | Annual prevalence of selected pathogens by age group

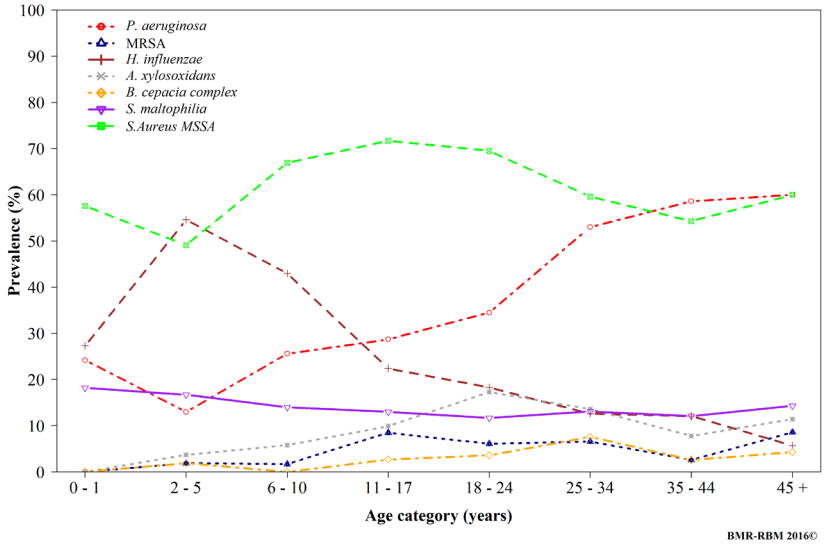
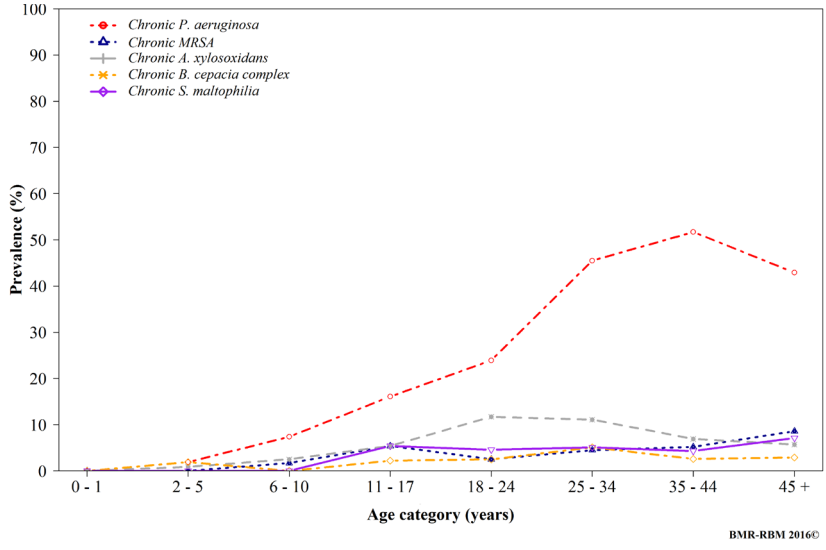


Figure 16 | Prevalence of chronic infections by age group



The figures 17 - 20 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 17 | Prevalence of *Burkholderia cepacia* complex infections by year and age

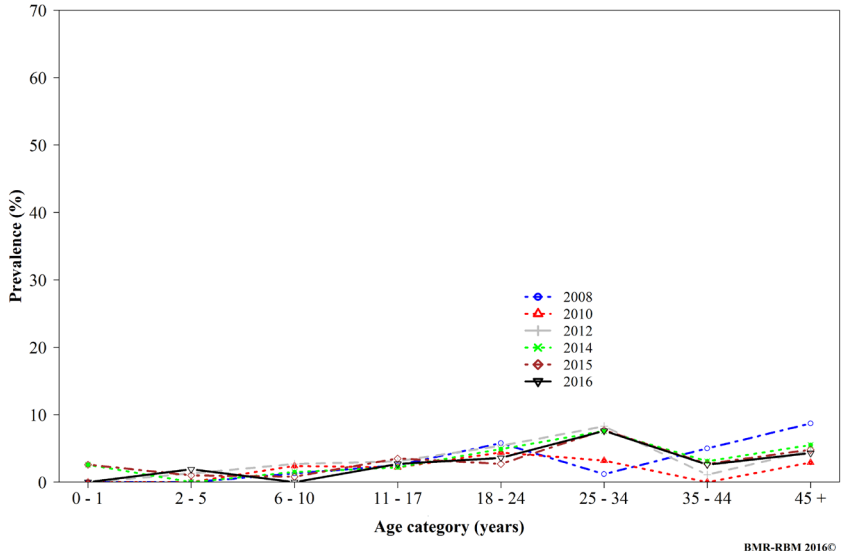


Figure 18 | Prevalence of *Pseudomonas aeruginosa* infections by year and age

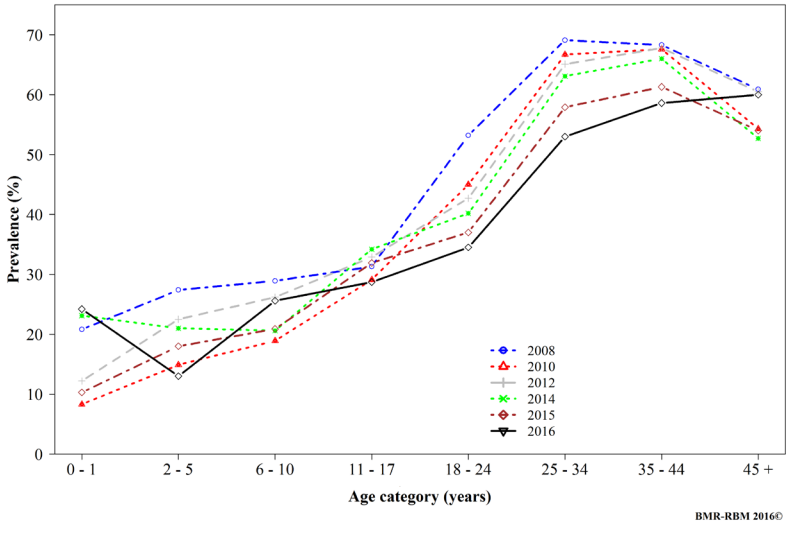
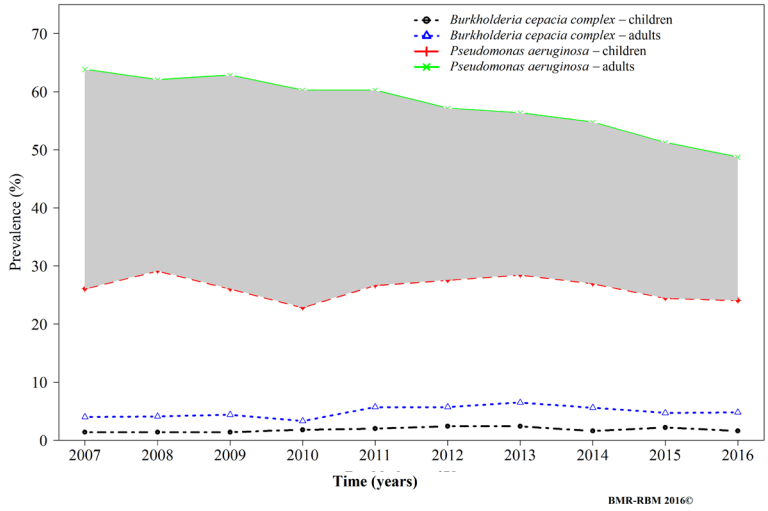


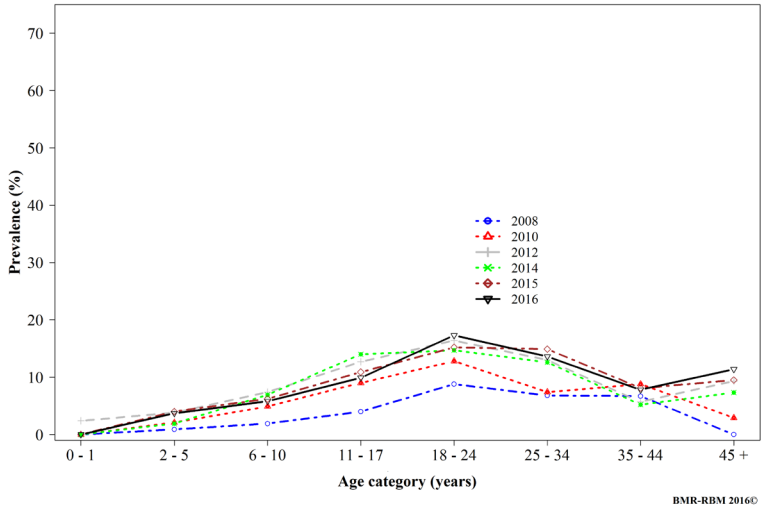
Figure 19 | Prevalence of *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex by age group and year



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 20, whose prevalence has been rising across most age categories, and especially so among the young adults 18 – 24, over the years.

Figure 20 | Prevalence of *Achromobacter xylosoxidans* by age group and year



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 175 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	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
Allergic bronchopulmonary aspergillosis (ABPA)	52	*5.1*	72	*6.7*	70	*6.4*	69	*6.3*
Pneumothorax	2	*0.2*	3	*0.3*	1	*0.1*	5	*0.5*
Nasal polyps	155	*15.2*	205	*19.0*	152	*13.9*	193	*17.5*
Massive haemoptysis	11	*1.1*	15	*1.4*	10	*0.9*	5	*0.5*
Massive haemoptysis requiring embolization	5	*0.5*	5	*0.5*	5	*0.5*	3	*0.3*
Bronchiectasis*			307	73.1	318	75.9	403	78.3

Percentages are based on 1017, 1079 , 1090 and 1100 non-transplant patients respectively for the years 2013 through 2016

*Only patients who had a CT scan considered

In this analysis, complications data from 491 children and 609 adults was used. ABPA is one of the most frequent major respiratory complications. In 2016 ABPA was reported in 23 (4.7%) children and 46 (7.6%) adults. Bronchiectasis was reported in 136 (61.3%) children and 267 (91.1%) 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	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
Exocrine pancreatic insufficiency	838	*82.4*	867	*80.4*	880	*80.7*	882	*80.2*
Acute pancreatitis	8	*0.8*	14	*1.3*	10	*0.9*	9	*0.8*
CF related diabetes (CFRD)	159	*15.6*	176	*16.3*	167	*15.3*	169	*15.4*
Impaired Glucose Tolerance (IGT)	66	*6.5*	77	*7.1*	90	*8.3*	114	*10.4*
Gastro-oesophageal reflux	188	*18.5*	265	*24.6*	271	*24.9*	313	*28.5*
Cirrhosis with portal hypertension	43	*4.2*	43	*4.0*	50	*4.6*	66	*6.0*
Gallstones	21	*2.1*	36	*3.3*	14	*1.3*	33	*3.0*
Intestinal obstruction (surgery)	5	*0.5*	2	*0.2*	1	*0.1*	8	*0.7*
Intestinal obstruction (no surgery)	52	*5.1*	37	*3.4*	55	*5.0*	55	*5.0*
Gastroparesis	3	*0.3*	2	*0.2*	1	*0.1*	3	*0.3*
Clostridium infection (treatment needed)	5	*0.5*	15	*1.4*	12	*1.1*	7	*0.6*

Percentages are based on 1017, 1079 ,1090 and 1100 non-transplant patients respectively for the years 2013 through 2016

In non-transplant patients, the data shows that 412 (83.9%) children and 470 (77.2%) adults are pancreatic insufficient. CFRD was reported in 20 (4.1%) children and 149 (24.5%) 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	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
CF-related arthritis / arthropathy	102	*10.0*	23	*2.1*	20	*1.8*	28	*2.5*
Cancer	3	*0.3*	4	*0.4*	2	*0.2*	3	*0.3*
Surgery	72	*7.1*	97	*9.0*	92	*8.4*	105	*9.5*
General anaesthesia	102	*10.0*	109	*10.1*	77	*7.1*	109	*9.9*
Psychiatric disease	36	*3.5*	41	*3.8*	33	*3.0*	30	*2.7*
Osteopenia	117	*11.5*	113	*10.5*	111	*10.2*	172	*15.6*
Osteoporosis	23	*2.3*	21	*1.9*	27	*2.5*	32	*2.9*
Hypertension requiring treatment	31	*3.0*	14	*1.3*	22	*2.0*	25	*2.3*
Others	161	*15.8*	170	*15.8*	126	*11.6*	132	*12.0*

Percentages are based on 1017, 1079, 1090 and 1100 non-transplant patients respectively for the years 2013 through 2016

*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 2016 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 491 children and 609 adults from a total of 1100 non transplant patients.

VISITS TO CF CARE CENTERS AND HOSPITALIZATION

In 2016, most of the patients (85.4%, n=940) 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 2016, 59.3% of the patients were not hospitalized: 63.7% of the children (n = 313) and 55.8% of the adults (n = 339). A small proportion (17 patients, 1.6%), was hospitalized for over two months. The median number of hospitalization days was about two weeks.

Figure 21 | Number of hospitalization days

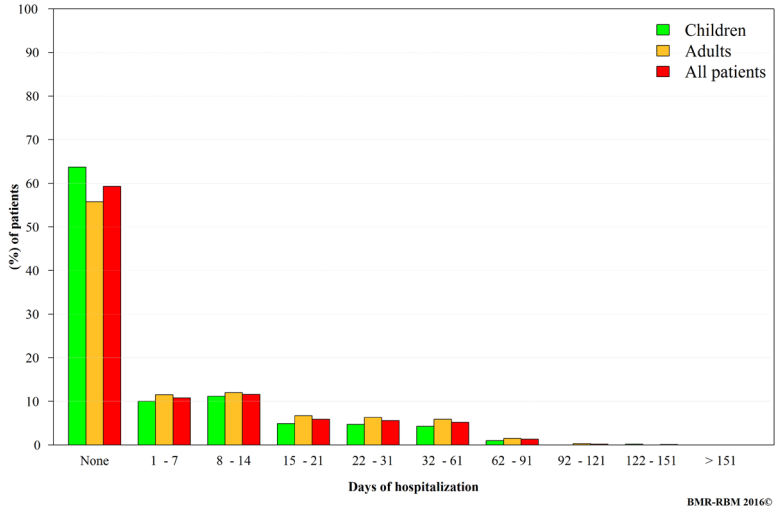
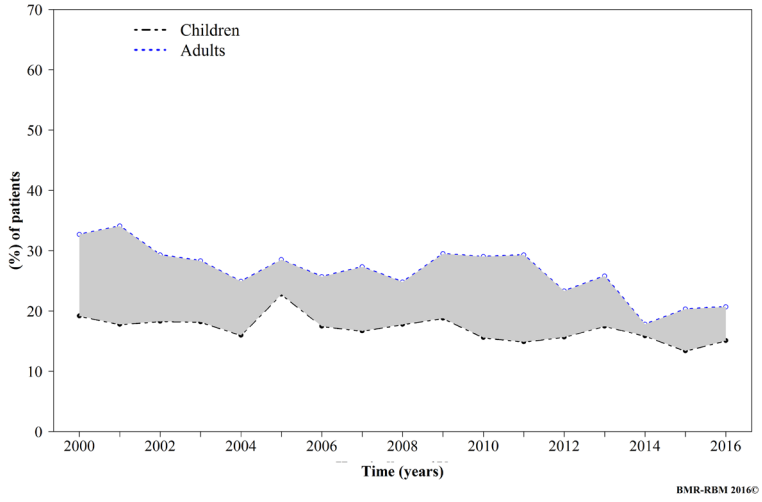


Figure 22 | Proportion of patients hospitalized for more than two weeks by age and year



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	486	*99.0*	587	*96.4*	1073	*97.5*
Antibiotics	440	*89.6*	532	*87.4*	972	*88.4*
Oral only	286	*58.2*	223	*36.6*	509	*46.3*
IV only	6	*1.2*	12	*2.0*	18	*1.6*
Oral and IV	133	*27.1*	273	*44.8*	406	*36.9*
Inhaled antibiotics	232	*47.3*	366	*60.1*	598	*54.4*
Inhalation therapy (excluding antibiotics)	471	*95.9*	558	*91.6*	1029	*93.5*
RhDnase	404	*82.3*	490	*80.5*	894	*81.3*
Other mucolytics	83	*16.9*	101	*16.6*	184	*16.7*
Hypertonic saline	291	*59.3*	385	*63.2*	676	*61.5*
Bronchodilators	371	*75.6*	441	*72.4*	812	*73.8*
Corticosteroids	198	*40.3*	382	*62.7*	580	*52.7*
Intranasal steroids	235	*47.9*	298	*48.9*	533	*48.5*
Oral anti-inflammatories	184	*37.5*	392	*64.4*	576	*52.4*
Azithromycin	182	*37.1*	378	*62.1*	560	*50.9*
Systemic corticosteroids	10	*2.0*	23	*3.8*	33	*3.0*
NSAID	2	*0.4*	35	*5.7*	37	*3.4*
Oxygen therapy	5	*1.0*	18	*3.0*	23	*2.1*

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 A, D, E and K 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	416	*84.7*	467	*76.7*	883	*80.3*
Fat soluble vitamins (A,D,E and K)	423	*86.2*	461	*75.7*	884	*80.4*
Proton pump inhibitor and/or H2 receptor blocker	226	*46.0*	316	*51.9*	542	*49.3*
Prokinetics	6	*1.2*	21	*3.4*	27	*2.5*
Ursodeoxycholic acid	119	*24.2*	126	*20.7*	245	*22.3*
Enteral feeding	22	*4.5*	8	*1.3*	30	*2.7*
Parenteral feeding	3	*0.6*	5	*0.8*	8	*0.7*
Gastrostomy tube	31	*6.3*	16	*2.6*	47	*4.3*

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

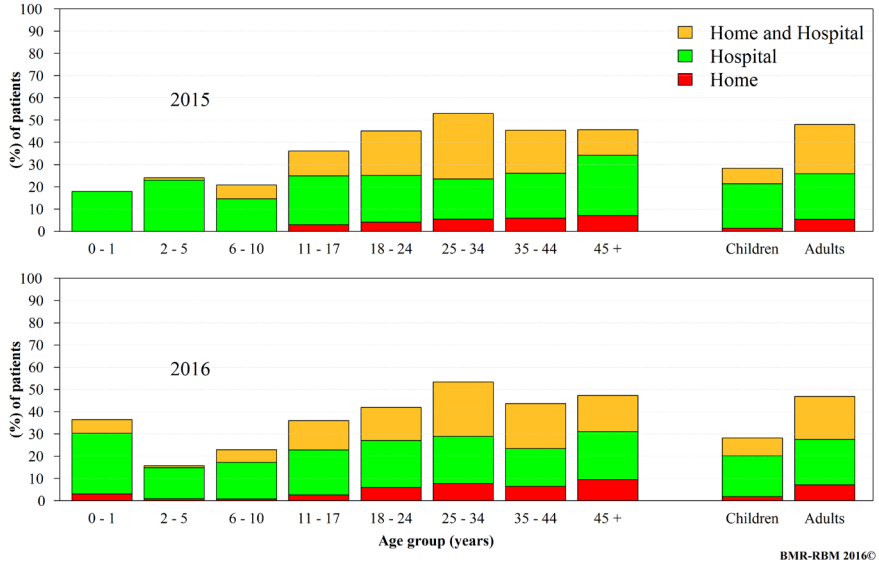
Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Insulin therapy	16	*3.3*	121	*19.9*	137	*12.5*
Oral therapy for diabetes	4	*0.8*	28	*4.6*	32	*2.9*
Bisphosphonates	.	.	21	*3.4*	21	*1.9*
Anti-conceptive therapy (females aged 12 and over)	8	*11.6*	111	*58.7*	119	*46.1*
Use of Psychopharmaca	10	*2.0*	63	*10.3*	73	*6.6*
CFTR Modulating Therapy	33	*6.7*	73	*12.0*	106	*9.6*

Note: Out of 1100 non transplant patients, 169 had CFRD. Among these, 125 used insulin therapy only, 15 used only oral therapy for diabetes while 11 patients used both oral therapy for diabetes and insulin therapy. However, in 18 patients with CFRD no use of either of the two treatments was reported.

INTRAVENOUS ANTIBIOTICS

In the year 2016, 38.5% (n = 424) of the patients received IV antibiotics; 28.3% (n = 139) amongst the children and 46.8% (n = 285) among the adults. The figures below show the proportion that received IV antibiotics at home and/or in hospital in 2015 (top) compared to 2016 (bottom). There are few patients below age ten years taking IV antibiotics at home. About one in five of the adults had IV antibiotics taken either in hospital only or both at home and in hospital.

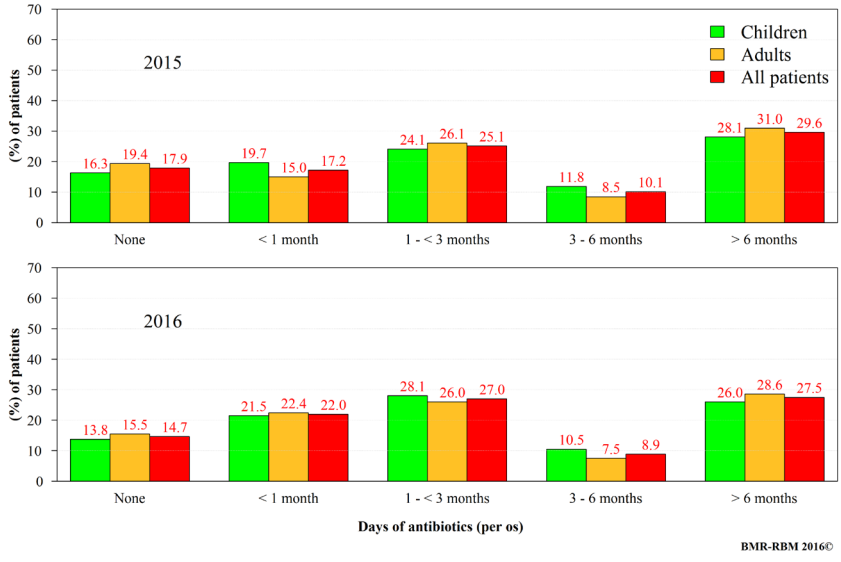
Figure 23 | Proportion that used IV antibiotic treatment by age category



ORAL ANTIBIOTICS

The figures below show the days of oral antibiotics used in 2015 (top) and compared to 2016 (bottom). Unknown days or missing data was excluded from this analysis. In 2016, 14.7% of the patients did not take any oral antibiotics; 13.8% of the children (n = 67) and 15.5% of the adults (n = 89). More than a quarter of both the children (26.0%) and adults (28.6%) 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 be an option. A lung transplant is indicated only for patients who have a severe lung disease, who have exhausted all other forms of conventional medical treatment and whose short term survival is severely compromised. For these patients, lung transplantation may offer prolonged survival and an improved quality of life; in some cases even a 'new' life. However, like other major surgeries, lung transplantation involves significant risks.

The actuarial survival after lung transplantation for CF is steadily improving. The actuarial survival rate estimated in the international lung transplant registry is more than 70 % at 3 years and more than 45% at 10 years after primary transplant[52]. Post-transplant survival, however, may vary considerably depending upon the transplant centers' experience, era of transplant, infection/colonization status (particularly in case of *B. cepacia complex*) and other concurrent comorbidities. 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 that time about 266 patients[1] with CF[54] (231 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 2016, categorized by the year of first transplant.

TRANSPLANT STATUS

The registry records show that since inception of the registry in 1998, at least 248 patients, 117 male and 131 female, have benefitted from transplantation; either single or multiple. In 2016, 12 patients were on the waiting list, 23 had been evaluated but were not on the list, one patient declined the transplant while two patients were refused 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

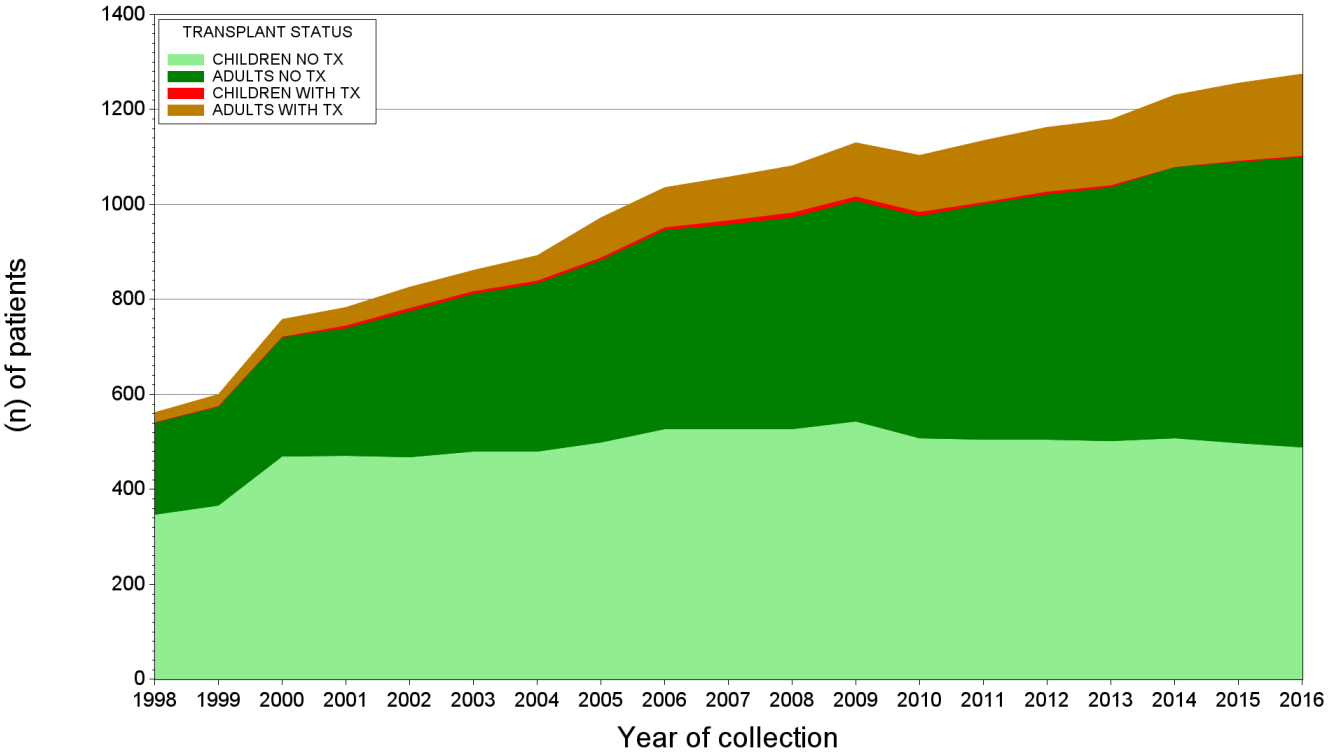
(range) age of the transplant patients in the year of the first transplant was 28.6 (9.6) and 27.6 years (5.3 – 60.7) respectively. About 10.9% (27 patients) had the first transplant done before age 18 years.

In 2016, there were 175 patients with a recorded transplant. The mean (SD) and median (range) age of the transplant patients reported as alive in 2016 was 36.9 (10.2) and 36.3 (12.6 – 67.7) years respectively at the last consultation in 2016. 82 were male while 93 were female, while 97.7% of the transplant patients in the 2016 data were adults. Eight transplant patients died in 2016.

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 2016 (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 283 transplants on 248 patients are so far reported in the registry. There are 31 patients who have had a transplant on more than one occasion.

Figure 25 | Number of patients by age and transplant status



In the figure above, 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.

TYPE OF TRANSPLANT

The most frequent transplant done is the lung transplant, either single or with a liver or heart. So far, 228 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	11
2009	10	.	.	1	.	1	.	12	9
2010	13	.	2	1	.	.	.	16	11
2011	15	.	.	.	2	.	.	17	11
2012	12	.	.	.	.	.	.	12	10
2013	13	.	.	.	3	.	.	16	9
2014	7	.	.	.	4	.	.	11	5
2015	16	.	2	.	2	.	.	20	17
2016	16	.	.	1	.	.	.	17	17
Total	**228**	**15**	**6**	**16**	**16**	**1**	**1**	**283**	**-**
Alive**	155	4	5	9	2	-	-	-	175*

* Total number of patients alive by end of 2016 by transplant year considering the first transplant
**Number of patients alive by end of 2016 considering type of first transplant

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

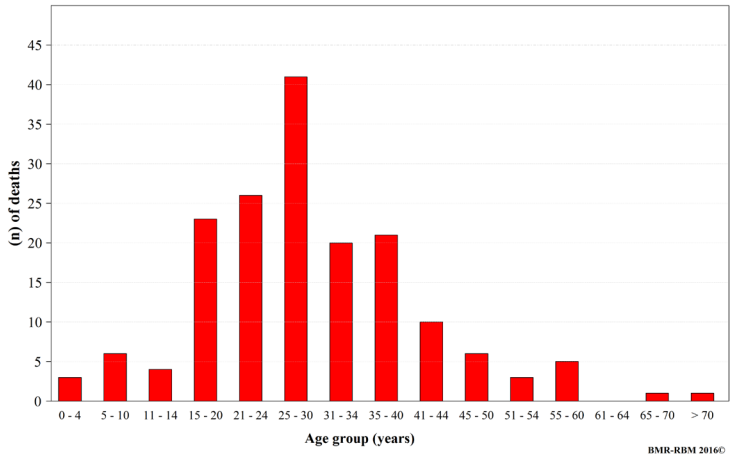
The data in the registry shows that there have been 170 reported deaths, 91 male and 79 female. Eighteen (10.6%) of the deaths were in children below 18 years while 8 (4.7%) of the deaths were in children younger than ten years. The mean (SD) and median (IQR) age at death for all reported cases is 29.9 (12.2) and 28.7 (14.0) respectively with the youngest at 0.6 years and the oldest case at 76.9 years. The table below 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	61 - 64	65 - 70	71+	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
2016	.	.	.	1	.	3	1	1	2	.	.	.	.	.	.	8
Total	**3**	**6**	**4**	**23**	**26**	**41**	**20**	**21**	**10**	**6**	**3**	**5**	**.**	**1**	**1**	**170**

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 26 | 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	73	*42.9*
Transplant	37	*21.8*
Other	29	*17.1*
Cancer	7	*4.1*
Cardiac	6	*3.5*
Liver	5	*2.9*
Suicide	3	*1.8*
Trauma	2	*1.2*
Unknown + missing	33	*19.4*

*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 22.5 in 2016 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 2016. 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	55	*11.2*	8	*1.1*	63	*5.1*
Regular school / education attendance	434	*88.6*	159	*21.3*	593	*48.0*
Has finished school/education	.	.	574	*76.9*	574	*46.4*
Unknown	1	*0.2*	5	*0.7*	6	*0.5*
Subtotal	**490**		**746**		**1236**	
Missing	5	.	34	.	39	.
Total	**495**		**780**		**1275**	

99% of the children between 3 and 18 years are attending regular school or education.

SOCIAL ALLOWANCES AND EMPLOYMENT

Table 22 | Social allowances or benefits and employment

Description	Children		Adults	
	n	%	n	%
Additional child allowance	391	*79.0*	70	*9.0*
Income support (in adults)	.	.	160	*20.5*
Disability allowance	.	.	110	*14.1*
Preferential tariff (in adults)	.	.	389	*49.9*
Pension allowance (in adults)	.	.	12	*1.5*
Integration support (in adults)	.	.	199	*25.5*
Employment*				
Yes	.	.	307	*49.4*
No	.	.	265	*42.7*
Unknown or missing	.	.	49	*7.9*

*data excludes 159 adults still actively in school

Amongst the 307 patients who said they were employed, 157 (51.1%) worked full time, 113 (36.8%) part-time while for 37 patients this was unknown. Eighty six children and 143 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].

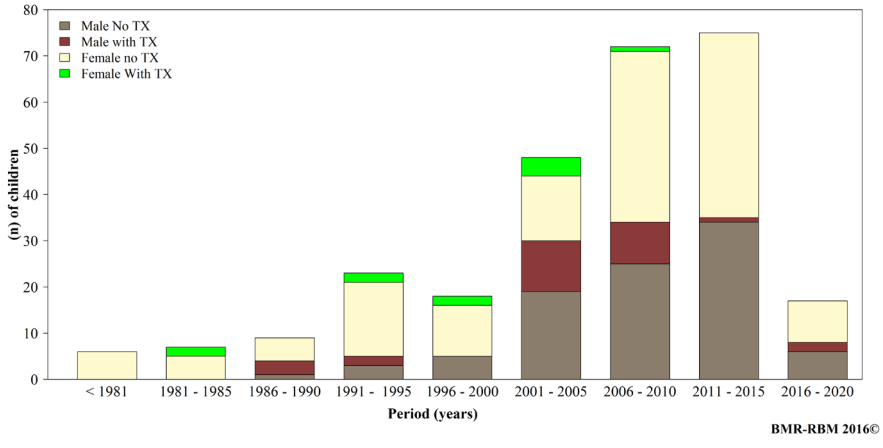
NUMBER OF BIRTHS REPORTED

Data from the registry shows that by 2016, there were at least 278 biological children reported from 170 patients (148 of them alive in 2016). More than half of those who have children were female (98, 57.7%). Among those with children, 20 (11.8%) are transplant patients. There were 62 (36.5%) parents homozygous for the F508del mutation. The mean age at which they had the first child was 28.9 years (median 29.0 years) with a range 16.0 – 49.0 years. The mean (median) was 31.5 (31.5) and 26.9 (27.0) years respectively for the male and female parents.

The mean number of children was 1.6 (median 1.5, range 1.0 – 6.0). 85 patients (50.0%) have one child while 68 (40.0%) have two children and 17 (10.0%) have three children or more. 15 parents had twins. There were three patients who have had a child before their 18th birthday. In 2016, seventeen new births were reported.

Consistently more children have been born each year since 2001 when compared to the years before. The figure below shows the total number of births among CF patients.

Figure 27 | Number of reported births by period



REFERENCES

1. Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008; 7:450-453.
2. Dequeker E, Accurso F, Cabeza S, Cassiman JJ, Corey M, Davidson A, Döring G, Heidet L, Heijerman H, Kotsimbos T, Mastella G, Morrison C, Pignatti PF, Strandvik B, Tsui LC, Dodge J. Classification of cystic fibrosis and related disorders. J Cyst Fibros 2002;1: 5-8.
3. Quinton PM. Physiological Basis of Cystic Fibrosis: A Historical Perspective. Physiological Reviews 1999; 79:S3-S22.
4. Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, Drumm ML, Iannuzzi MC, Collin, FS, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989; 245: 1066-1073.
5. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365:1663-1672.
6. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros 2014; 13:674-680.
7. Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F et al. Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. Dig Dis Sci 2016; 61:198-207.
8. Quittner A, Suthoff E, Rendas-Baum R, Bayliss MS, Sermet-Gaudelus et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. Health Qual Life Outcomes. 2015; 13:93. doi: 10.1186/s12955-015-0293-6.
9. Heltshe SL, Mayer-Hamblett N, Burns JL, Khan U, Baines A, Ramsey BW et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clin Infect Dis 2015; 60:703-712.
10. Bellin MD, Laguna T, Leschyshyn J, et al: Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. Pediatr Diabetes 2013; 14:417-421.
11. Tsabari R, Elyashar HI, Cymberknowh MC, Breuer O1, Armoni S, Livnat G, Kerem E, Zangen DH. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. J Cyst Fibros. 2016; 15:e25-7.
12. Hayes D Jr, McCoy KS, Sheikh SI. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. Am J Respir Crit Care Med. 2014; 190:590-1.
13. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, , Ratjen F, Sermet-Gaudelus I, Plant B, Munck A, Jiang Y, Gilmartin G, Davies JC. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). Lancet Respir Med 2014; 2: 902-910.
14. Sawicki GS, McKone EF, Pasta DJ, et al: Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med 2015; 192:836-842.

15. Davies JC1, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med 2013; 187:1219-1225.
16. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med 2013; 1:630-638.
17. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, Southern KW, Robertson S, Green Y, Cooke J, Rosenfeld M; KIWI Study Group. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med. 2016;4:107-15.
18. Hebestreit H, Sauer-Heilborn A, Fischer R, Käding M, and Mainz JG: Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation. J Cyst Fibros 2013;12:599-603.
19. Barry PJ, Plant BJ, Nair A, Bicknell S, Simmonds NJ, Bell NJ, Shafi NT, Daniels T, Shelmerdine S, Felton I, Gunaratnam C, Jones AM, Horsley AR. Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. Chest. 2014;146:152-8.
20. Taylor-Cousar J, Niknian M, Gilmartin G, Pilewski JM; VX11-770-901 investigators. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: Safety and efficacy in an expanded access program in the United States. J Cyst Fibros. 2016;15:116-22.
21. Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, Hong JS, Pollard HB, Guggino WB, Balch WE, Skach WR, Cutting GR, Frizzell RA, Sheppard DN, Cyr DM, Sorscher EJ, Brodsky JL, Lukacs GL. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. Mol Biol Cell. 2016;27:424-33.
22. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med. 2015; 373:1783-4.
23. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, Lubarsky B, Rubin J, Millar SJ, Pasta DJ, Mayer-Hamblett N, Goss CH, Morgan W, Sawicki GS. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017; 5:107-118.
24. Fajac I, De Boeck K. New horizons for cystic fibrosis treatment. Pharmacol Ther. 2017; 170:205-211.
25. Quon B, Rowe S. New and emerging targeted therapies for cystic fibrosis. BMJ. 2016;352:i859.
26. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016; 4:662-7.
27. http://www.inami.be/care/fr/revalidatie/convention/mucoviscidose/pdf/agreement.pdf.
http://www.inami.be/care/nl/revalidatie/convention/mucoviscidose/pdf/agreement.pdf.

28. http://www.inami.be/care/fr/revalidatie/convention/mucoviscidose/pdf/avenant.pdf.
http://www.inami.be/care/nl/revalidatie/convention/mucoviscidose/pdf/avenant.pdf.
29. http://www.ecfs.eu/projects/ecfs-patient-registry/information-about-ecfspr-cf-patients.
30. Castellani C1; CFTR2 team. CFTR2: How will it help care? Paediatr Respir Rev. 2013;14 Suppl 1:2-5.
31. Sosnay PR1, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, Ramalho AS, Amaral MD, Dorfman R, Zielenski J, Masica DL, Karchin R, Millen L, Thomas PJ, Patrinos GP, Corey M, Lewis MH, Rommens JM, Castellani C, Penland CM, Cutting GR. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013; 45:1160-7.
32. Kuczmarski RJ, Ogden CL, Guo SS. et al. CDC Growth Charts for the United States: Methods and Development. National Center for Health Statistics. Vital Health Statistics 2002; 11: 1-190.
33. Rolland-Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A. Body mass index variations: centiles from birth to 87 years. Eur J Clin Nutr 1991; 45: 13-21. *Rolland-Cachera MF: personal communication.
34. Schluchter MD, Konstan MW, Drumm ML, Yankaskas JR , Knowles MR. Classifying Severity of Cystic Fibrosis Lung Disease Using Longitudinal Pulmonary Function Data. Am J Respir Crit Care Med 2006; 174:780–786.
35. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study, Lancet 2003; 361:1671–1676
36. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993; 15:75-88.
37. Hankinson JL, Odencrantz RJ, Fedan KB. Spirometric Reference Values from a Sample of the General U.S. Population. Am. J. Respir. Crit. Care Med 1999; 159:179-187.
38. Cole TJ. The LMS method for constructing normalised growth standards. Eur J Clin Nutr 1990; 44: 45-60.
39. http://www.genet.sickkids.on.ca/cftr/SearchPage,$Form.direct.
http://www.cftr2.org/browse.php.
40. Hart CA, Winstanley C. Persistent and aggressive bacteria in the lungs of cystic fibrosis children. Br Med Bull 2002; 61: 81–96.
41. de Vrankrijker AM, van der Ent CK, van Berkhout FT, Stellato RK, Willems RJ, Bonten MJ, Wolfs TF. Aspergillus fumigatus colonization in cystic fibrosis: implications for lung function? Clin Microbiol Infect. 2011; 17:1381-6.
42. Flume PA. Pulmonary Complications of Cystic Fibrosis, Respir Care 2009; 54:618–625.
43. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman Harry GM, Robberecht E, Doring G. Nutrition in patients with cystic fibrosis: a European Consensus, J Cyst Fibros 2002; 1:51–75.
44. Goodin B. Nutrition Issues in Cystic Fibrosis, Practical Gastroenterology 2005; 27:76 – 94.

45. McCallum TJ, Milunsky JM, Cunningham DL, Harris DH, Maher TA, Oates RD. Fertility in Men With Cystic Fibrosis: An Update on Current Surgical Practices and Outcomes. Chest 2000; 118:1059-62.
46. Lyon A, Bilton D. Fertility Issues in Cystic Fibrosis. Paediatr Respir Rev 2002; 3:263-240.
47. Kioumis IP, Zarogoulidis K, Huang H, Li Q, Dryllis G, Pitsiou G, Machairiotis N, Katsikogiannis N, Papaiwannou A, Lampaki S, Porpodis K, Zaric B, Branislav P, Mpoukovinas I, Lazaridis G, Zarogoulidis P. Pneumothorax in cystic fibrosis. J Thorac Dis. 2014; 6(Suppl 4):S480-7
48. Stevens DA, Moss RB, Kurup VP et al. Participants in the Cystic Fibrosis Foundation Consensus Conference. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis. 2003; 37 Suppl 3:S225-64.
49. Schuster SR, McLaughlin FJ, Matthews WJ Jr, Strieder DJ0, Khaw KT, Shwachman H. Management of pneumothorax in cystic fibrosis, Journal of Pediatric Surgery 1983; 4:492-497.
50. Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Cochrane Database of Systematic Reviews 2013; Issue 7. Art. No.: CD003884. DOI: 10.1002/14651858.CD003884.pub4.
51. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: Challenges to disease self-management, J Cyst Fibros 2009; 8:91-96.
52. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung ransplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016;35:1170-1184.
53. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: 29th Adult Lung and Heart-Lung Transplant Report-2012. J Heart Lung Transplant. 2012; 31:1073-86.
54. Van Raemdonck D. on behalf of the Thoracic Committee of the Belgian Transplantation Society. (Heart-)Lung transplantation in Belgium. Annual report 2012.
55. Barreto C, Pinto LM, Duarte A, et al. A fertile male with cystic fibrosis: molecular genetic analysis. Journal of Medical Genetics 1991; 28:420-421.
56. Dreyfus DH, Bethel R, Gelfand EW. Cystic fibrosis 3849+10kb C > T mutation associated with severe pulmonary disease and male fertility. Am J Respir Crit Care Med 1996; 153:858-860.
57. Kaplan E, Shwachman H, Perlmutter AD, et al. Reproductive failure in males with cystic fibrosis. New N Engl J Med 1968; 279:65-91.
58. Sawyer SM, Farrant B, Cerritelli B, et al. A survey of sexual and reproductive health in men with cystic fibrosis: new challenges for adolescent and adult services. Thorax 2005; 60:326-330.
59. Ujhelyi R, Treszl A, Vasarhelyi B, et al. Bone mineral density and bone acquisition in children and young adults with cystic fibrosis: a follow-up study. J Pediatr Gastroenterol Nutr 2004; 38:401-406.
60. Stallings VA, Tomezsko JL, Schall JI, et al. Adolescent development and energy expenditure in females with cystic fibrosis. Clinical Nutrition 2005; 24:737-745.

61. Jelin AC, Sharshiner R, Caughey AB. Maternal co-morbidities and neonatal outcomes associated with cystic fibrosis, Journal Matern Fetal Neonatal Med 2017; 30:4-7.
62. Janice E Whitty, Cystic fibrosis in pregnancy, Clinical Obstetrics and Gynecology 2010; 53:369-76.
63. Schindler T. Nutrition Pre and Post Lung Transplant. Nutrition in Cystic Fibrosis 2015; pp 207-217 Nutrition and Health. Humana Press, Cham.
64. Laporta Hernández R, Lázaro Carrasco MT, Varela de Ugarte A, Ussetti Gil P. Long-term follow-up of the lung transplant patient. Arch Bronconeumol 2014; 50:67-72.

Registry related publications and abstract presentations

Abstracts and presentations

65. Dewulf J, Vermeulen F, Wanyama S, Thomas M, De Boeck K. Treatment burden in patients with CF and at least one class 4 or 5 mutation. J Cyst Fibros, 2014, 13 [Suppl 2], S8. (Oral presentation at 37th ECFS Conference, Gothenburg, Sweden, June 2014).
66. De Keyzer L, Haerynck F, Schelstraete P, Van Daele S, Thomas M, Wanyama S, De Baets F. ABPA in CF: effect on FEV1 decline and infectious exacerbations, a case control study.Tijdschrift Belgische Kinderarts, 2014, 16: 439. (Poster Belgische Vereniging Kindergeneeskunde (BVK-SBP), March 2014).
67. De Baets F, Wanyama S, De Keyzer L, Haerynck F, Schelstraete P, Thomas M, Van Daele S. ABPA syndrome (ABPAs) in CF: FEV1 decline, infectious exacerbations and BMI before and after the year of diagnosis (index year), a case control study. J Cyst Fibros, 2016, 15 [Suppl 1], S32.
68. Thomas M, Munck A, Gulmans V, Lemonnier L, de Monestrol I, Middleton PG, Wanyama S, De Boeck K. How different is the cohort of young CF children included in national registries of countries with and without newborn screening? J Cyst Fibros, 2014, 13 [Suppl 2], S8. (Oral presentation at 37th ECFS Conference, Gothenburg, Sweden, June 2014).
69. Willekens J, Wanyama S, Thomas M, De Wachter E, De Schutter I, Malfroot A. Burkholderia cepacia complex acquisition: a threat in all CF patients ? J Cyst Fibros, 2015, 14 [Suppl 1], S54. (Poster at 38th ECFS Conference, Brussels, Belgium, June 2015).
70. Willekens J, Wanyama S, Thomas M, De Wachter E, De Schutter I, Malfroot A. CF patients with a declining FEV1: at risk for acquisition of Burkholderia cepacia complex infection? J Cyst Fibros, 2015,14 [Suppl 1], S74. (Poster at 38th ECFS Conference, Brussels, Belgium, June 2015).
71. De Wachter E, Thomas M, Wanyama S, Vanderhelst, E, De Schutter, I, Malfroot, A. Characterizing Belgian CF-registry (BCFR)-patients with a rare CFTR-mutation (RM): topwards better identification of the role of RM in disease liability. J Cyst Fibros, 2016, 15 [Suppl 1], S35.

72. Libeert D, Wanyama S, Declercq D, Thomas M, Van Daele S, De Baets F, Van Biervliet S. Characteristics at baseline of tube-fed cystic fibrosis (CF) patients with matched controls: a registry study. J Cyst Fibros, 2017, 16 [S1] S147.
73. Libeert D, Wanyama S, Declercq D, Thomas M, Van Daele S, De Baets F, Van Biervliet S.
74. The impact of tube feeding in children and adults with cystic fibrosis. J Cyst Fibros, 2017, 16 [S1] S9. (Oral presentation at 39th ECFS Conference, Sevilla, Spain, June 2017).

Articles

75. De Boeck K, Vermeulen F, Wanyama S, Thomas M, Members BMR-RBM. Effect of inhaled corticosteroids on lung function decline in children and adults with cystic fibrosis. Eur Respir J 2011;1091-5.
76. Thomas M, Lemonnier L, Gulmans V, Naehrlich L, Vermeulen F, Cuppens H, Castellani C, Norek A, De Boeck K. Is there evidence for correct diagnosis in cystic fibrosis registries? J Cyst Fibros. 2014 May;13(3):275-80. doi: 10.1016/j.jcf.2013.10.010. Epub 2013 Nov 22.
77. Dewulf J, Vermeulen F, Wanyama S, Thomas M, Proesmans M, Dupont L, De Boeck K. Treatment burden in patients with at least one class IV or V CFTR mutation. Pediatr Pulmonol. 2015 Dec;50:1230-6. doi: 10.1002/ppul.23313. Epub 2015 Nov 5.
78. De Boeck K, Munck A, de Monestrol I, Gulmans V, Lemonnier L, Middleton PG, Wanyama S, Thomas M. Does newborn screening influence the young cystic fibrosis cohort included in national registries? Eur Respir J. 2017 Jan 11; 49(1). pii: 1600686. doi: 10.1183/13993003.00686-2016
79. Bosch B, Bilton D, Sosnay P, Raraigh KS, Mak DY, Ishiguro H, Gulmans V, Thomas M, Cuppens H, Amaral M, De Boeck K. Ethnicity impacts the cystic fibrosis diagnosis: A note of caution. J Cyst Fibros. 2017 Feb 20. pii: S1569-1993(17)30023-1. doi: 10.1016/j.jcf.2017.01.016.
80. De Wachter E, Thomas M, Wanyama SS, Seneca S, Malfroot A. What can the CF registry tell us about rare CFTR-mutations? A Belgian study. Orphanet J Rare Dis. 2017 Aug 22;12(1):142. doi: 10.1186/s13023-017-0694-1.
81. Libeert D, Declercq D, Wanyama S, Thomas M, Van daele S, De Baets F, Van Biervliet S. The effect of enteral tube feeding in cystic fibrosis: A registry based study, J Cyst Fibros, Available online 1 February 2018, ISSN 1569-1993, https://doi.org/10.1016/j.jcf.2018.01.004.

APPENDIX I: BCFR 2016 DIGITAL QUESTIONNAIRE NON TRANSPLANT PATIENTS

BMR-RBM-BCFR 2016 – 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 decreased from CF .....
- General remark .....
  .....

APPENDIX II: BCFR 2016 DIGITAL QUESTIONNAIRE TRANSPLANT PATIENTS

BMR-RBM-BCFR 2016 – transplant patients

1. Background

Patient code (BMR-RBM) : .....
Year of collection : .....
Treating physician : .....

1.1 - Identification

Patient ID (NISS) : .....
Name : .....
Firstname : .....
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
Date of sweat test : . . / . . / . . . .

1.3 - Sweat test

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

Legacy name

1.4 - Genotype

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 : .....

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal

1.5 - Nasal Transepithelial Potential Difference

❑ 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 decreased from CF .....
General remark .....
.....

L'Institut Scientifique de Santé Publique (ISP) est la référence scientifique dans le domaine de la santé publique.

Nous apportons notre soutien à la politique de santé grâce à nos recherches innovantes, nos analyses, nos activités de surveillance et grâce aux avis d'experts que nous rendons.

De cette manière, nous travaillons pour permettre à chacun de ***vivre longtemps en bonne santé****.*

Het Wetenschappelijk Instituut Volksgezondheid (WIV) is de wetenschappelijke referentie voor de volksgezondheid.

Wij ondersteunen het gezondheidsbeleid door innovatief onderzoek, analyses, surveillance en expertadvies.

Zo dragen wij bij tot ***een langer gezond leven voor iedereen****.*

OPERATIONAL DIRECTORATE PUBLIC HEALTH AND SURVEILLANCE
Unit Health Services Research
Juliette Wytsmanstreet 14 | 1050 Brussels | Belgium
www.wiv-isp.be

Responsible Editor : Dr. Sneyers Myriam
Legal Deposit D/2018/2505/9