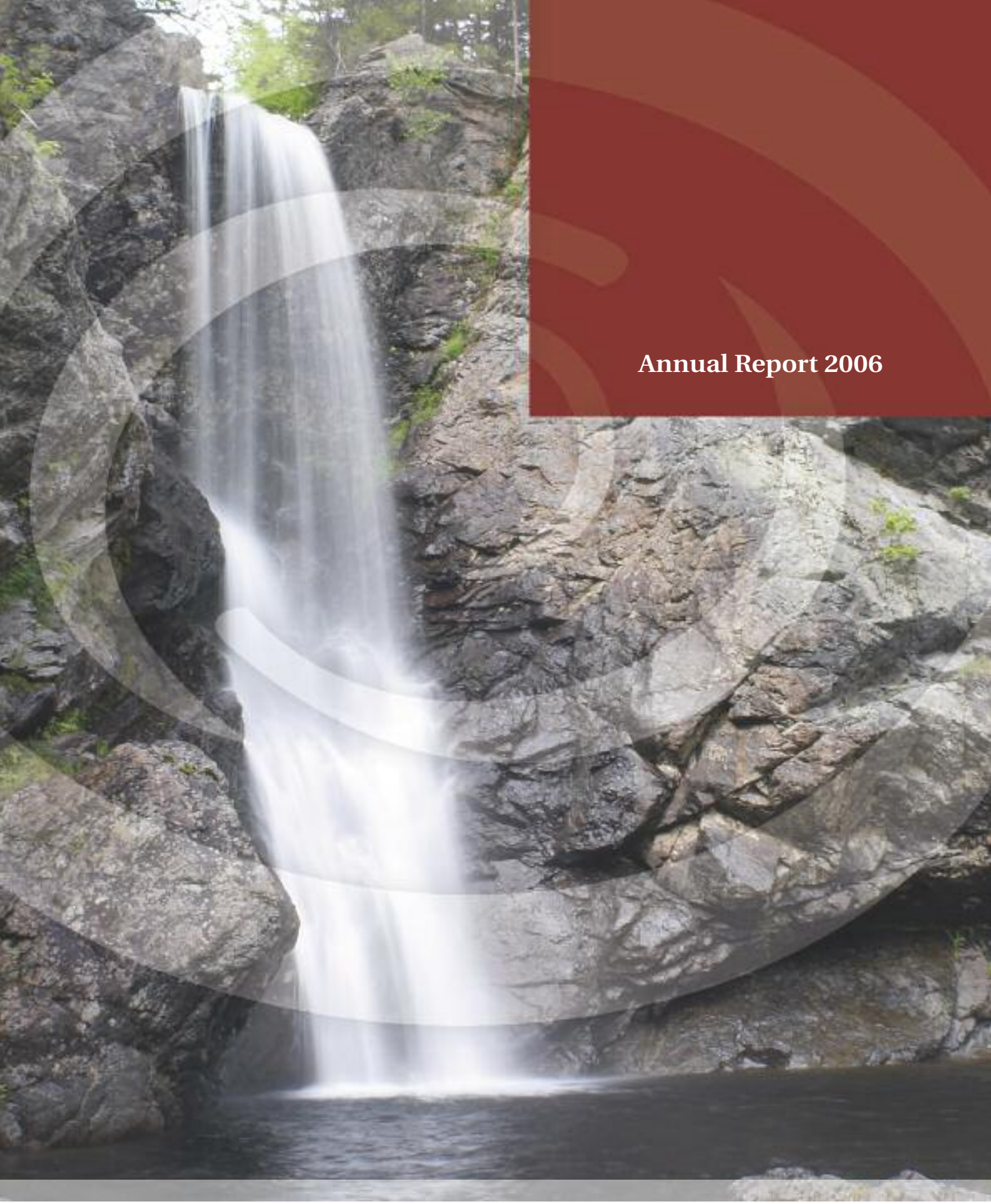

Annual Report 2006

The Cystic Fibrosis Registry of Ireland

CFRI
The Cystic Fibrosis Registry of Ireland

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Glossary (commonly used abbreviations in this report)

AA	Annual Assessment
AB	Antibiotics
CFAI	Cystic Fibrosis Association of Ireland
CFRI	Cystic Fibrosis Registry of Ireland
NBS	Newborn Screening (for CF)
PWCF	Persons with Cystic Fibrosis

Hospital Abbreviations

CUH	Cork University Hospital, Wilton, Cork
MWRH	Midwest Regional Hospital, Limerick
MMUH	Mater Misericordiae University Hospital
NCH or AMNCH	National Children's Hospital at the Adelaide & Meath Hospital, Tallaght, Dublin 24
OLCH	Formerly Our Lady's Hospital for Sick Children; now re-named as Our Lady's Children's Hospital
OLLH	Our Lady of Lourdes Hospital, Drogheda, Co Louth
SVUH	St Vincent's University Hospital
UCHG	University College Hospital Galway

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Executive Summary

The worldwide trend in CF registry methodology is to create web-enabled databases. In Europe, we are moving towards this target, and will achieve it within the next two years. Beyond Europe, there will be progression towards merging sets of data from various continents within the next decade. Assisted by larger and larger sets of data, researchers will be able to make more definitive statements about CF and answer more questions about treatments. These conclusions will have impact for PWCF all over the world. Analyses will be done faster and results known sooner when data is pooled from many national databases.

Ireland was the first country to launch a web-based registry. We are now in our third year to summarise and present data from the registry and we continue to enrol new patients. However, full "ascertainment", or enrolment is an issue for the CFRI (Cystic Fibrosis Registry of Ireland). Each PWCF should consider whether he/she would like to enrol. Publications such as the Patient Information Booklet and the 'Frequently Asked Questions' section on the registry website, www.cfairegistry.org are designed to assist people to make this decision.

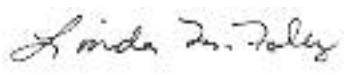
Each potential enrolee should be comfortable that their information is confidential and secure; and, that it will be used to answer fundamental questions about CF. We have taken extra steps to assure the security of the CFRI, through the use of an exclusive server at the Internet Service Provider and advanced encryption techniques.

The question, "Can CF registries help to analyse information that will result in improved treatments and a better quality of life for PWCF?" should be the fundamental query that we are striving to answer. My belief is that CF registries are an effective tool with the potential to accomplish this. Improved treatments will mean prolonged life.

Irish data from the CFRI demonstrates that over half of the CF population are diagnosed after 3 months of age. As a general principle, earlier diagnosis leads to improved growth and reduced therapy needs. That means that over 50% of our CF population is at a disadvantage at the very start. Newborn screening for CF would transform that situation. Furthermore, screening combined with early enrolment on the CFRI would mean that PWCF would be monitored from birth. Monitoring can detect negative trends and alert the clinician to make changes or intensify therapy.

This 2006 Annual Report presents data from nearly 60% of our CF population. If more PWCF were enrolled we could increase our knowledge about CF in Ireland as well as uncover many more interesting facets of our unique population.

Thus, my message this year is to encourage your friends and fellow travellers to register or to contact the CFRI for more information. Enrolment on the CFRI will help everyone.



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Cystic Fibrosis Centres

County	Hospital	Consultant	Type of Centre
Cork	Cork University Hospital (CUH)	Dr. Michael Henry	Adult
		Dr Muireann Ní Chróinín	Paediatric
Dublin	Beaumont Hospital	Prof NG McElvaney	Adult
	St Vincent's University Hospital (SVUH)	Dr Charles Gallagher/ Dr Ed McKone	Adult
	The Children's University Hospital	Dr Dubhfeasa Slattery	Paediatric
	National Children's Hospital (AMNCH)	Dr Peter Greally/Dr B Elnazir	Paediatric
	Our Lady's Children's Hospital	Dr Gerry Canny	Paediatric
	Mater Misericordiae University Hospital (MMUH)	Dr Jim Egan	Post-Transplant
Galway	University College Hospital Galway	Prof BG Loftus/ Dr E Moylett/Dr A Khan	Paediatric
	Merlin Park Hospital, Galway	Dr JJ Gilmartin/Dr A O'Regan	Adult
Kerry	Kerry General Hospital	Dr Fergus Leahy/ Dr RB Fitzsimons	Paediatric
Limerick	Midwestern Regional Hospital (MWRH)	Dr MJ Mahony	Paediatric
		Dr Eithne Mulloy/Dr TH Peirce	Adult
Louth	Our Lady of Lourdes Hospital	Dr David Vaughan	Paediatric
		Dr John Kiely	Adult
Mayo	Mayo General Hospital	Dr Michael O'Neill	Paediatric
Sligo	Sligo General Hospital	Dr R Tummaluru	Paediatric
Waterford	Waterford Regional Hospital	Dr A Altaf	Paediatric

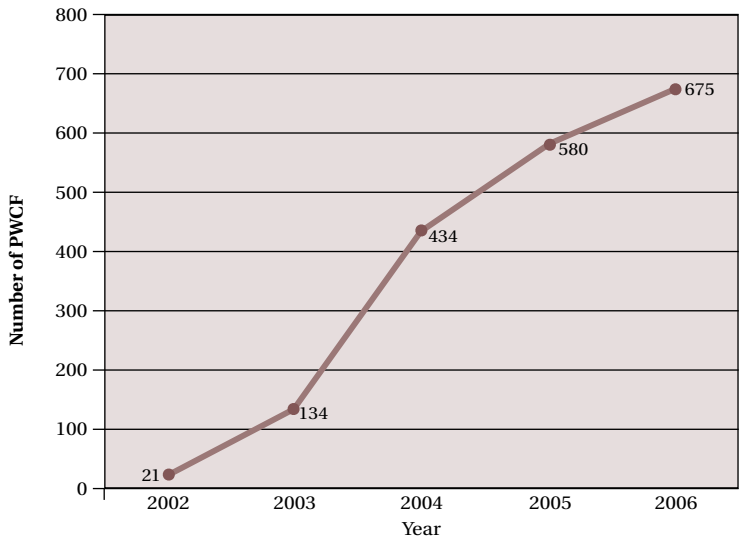
Registry Management Committee

Professor N.G. McElvaney	Professor of Medicine, Royal College of Surgeons in Ireland. Beaumont Hospital and R.C.S.I., Dublin	Chairman of the Registry Management Committee
Mrs. Linda Foley	Director, CF Registry of Ireland	
Dr. Charles Gallagher	Consultant in Respiratory Medicine, St. Vincent's University Hospital, Dublin	Committee Member
Dr. Peter Greally	Consultant in Paediatric Respiratory Medicine, National Children's Hospital in Tallaght, Dublin	Committee Member
Dr. Gerry Canny	Consultant in Paediatrics, Respirology, Our Lady's Children's Hospital, Dublin	Committee Member
Dr. R Tummaluru	Consultant Paediatrician, Sligo General Hospital, Sligo	Committee Member
Ms. Gerardine Leen	CF Nurse Specialist, National Children's Hospital in Tallaght, Dublin	Committee Member
Ms. Anne Marie Lyons	CF Nurse Specialist, Beaumont Hospital, Dublin	Committee Member
Mr. Carl Rainey	Vice Chairperson, Cystic Fibrosis Association of Ireland	Committee Member
Mr Godfrey Fletcher	CEO, Cystic Fibrosis Association of Ireland	Committee Member
Mr. Martin Wickham	IT Director, BT Ireland and Representative of CFAI	Committee Member

Introduction

The population of the Cystic Fibrosis Registry (CFRI) continues to grow (Figure 1). We began the project in mid-2001 with a set of objectives to build a comprehensive database that would be accessible to all Irish CF consultants through the internet. Now, at the end of 2006, we have achieved many of our original targets and what remains is the completion of enrolment, along with some secondary development. This is the third report in which we have been able to use patient data to describe the CF population in Ireland. At the end of each year, the data that is held as of the 31st of December is closed off, copied, and migrated to a different area of the server so that it is available for interrogation for the annual report. The original web address remains live and can still accept data so that it continues to display its full functionality for the user.

Figure 1: CFRI Enrolment 2002-2006 (n=675)



Each year enrolment progress is marked against a census that is compiled through the thirteen CF centres. We are now 43% short of the mark of total ascertainment. If, however, we gauge our target at 80% of the total as is the case with most of the other major registries such as the USA, UK, and Germany, we are only 23% short. At the end of 2006, 675 PWCF have been registered on the CFRI (Figure 1). In October 2006, the independent census showed that 1186 PWCF are attending centres throughout the country. Each year we make a rough comparison of age groups (<18's vs. ≥18's) between the census and the CFRI. In all the years to date, the CFRI proportions are similar to the whole population in terms of age and geographic distribution. So, the data that is presented in the annual report reflects a fairly accurate picture of the entire CF population. We have shown for instance, the pattern of change in the CF population; that is, what was once primarily a paediatric condition is moving in the direction of an adult-dominated population and this brings new challenges in terms of complications, treatments, and essential resources. It is very important to be able to predict the growth and location of the population as this may affect resource decisions.

The effectiveness of the CFRI relies on up-to-date data entry. Since the database is accessible through the internet, this provides universal availability to all CF Centres. All reports may be printed out immediately after data entry, or may be accessed at a later date for printing. Reports

are accessible for any number of exercises, such as for clinic visits or hospital admissions. A continuous record of one's infections and treatments/ antibiotics, plus pulmonary function test results can be very useful to the clinician. The updating of records is presently being done through the central CFRI office, but it can be localised provided there are personnel on site to achieve this. There is a resource issue for the central office to enter annual assessment data for all 675 PWCF each year while continuing to enrol new PWCF, and this results in a continuous data entry backlog. Data entry training is minimal because the CFRI is so intuitive. Future plans for the CFRI include disseminated data entry through the CF centres, with quality control and training operating from the central office. As general resources for CF improve, the balance of data entry will hopefully shift onto the CF centres. This will promote the value of the registry to the clinician.

Although we have been hampered somewhat by delay in accruing data, we have still been able to demonstrate a 'gender gap' defined by the 'age at diagnosis'. Our analysis has revealed that there are some females who are not diagnosed as early as males, even though they may have the same set of mutations as their male counterparts. This is in agreement with reports from the USA, and researchers have not yet determined the reason(s) for this. The challenge for us now is to show whether this delay in diagnosis will affect long-term outcomes for females; or, whether early-diagnosed males may have a long-term advantage. The longitudinal aspect of the CFRI is ideally suited to the study of this question. We have the ability to follow similar groups of PWCF along their clinical course and relate it back to early interventions or complications. Many studies have shown that early diagnosis has been linked to better outcomes for both sexes. Newborn screening would, of course, eliminate any potential gender differences as everyone would be diagnosed at a very early stage.

NEWBORN SCREENING (NBS)

In Ireland, studies have estimated an incidence of 1 CF child in every 1,461 births (the highest reported incidence in the world), yielding approximately 40 newborns with CF each year. If each child was tested at birth (along with other routine screening tests) the vast majority of these children would be diagnosed early and reap the benefits of early diagnosis. These include early nutritional support and may also lead to reduced numbers of hospitalisations, and improved survival. The report of the Newborn Cystic Fibrosis Screening Working Group recommended the implementation of screening in Ireland (March, 2004).

If Ireland adopted NBS, CF infants would be diagnosed at birth and they could also be enrolled on the CF Registry of Ireland at that time, so that an accurate record of the course of their condition could be created. CFRI reports provide an excellent summary of a person's clinical course, combining information from different hospitals. The CFRI would be an ideal companion to a NBS programme while also contributing to continuous assessment records of all PWCF.

These are just some examples of the value of a comprehensive registry/database. Eventually the CFRI will help to predict the likelihood of complications and hospitalisations of individuals. With predictability comes the confidence of introducing interventions at an early stage which may prolong a stable clinical course for PWCF.

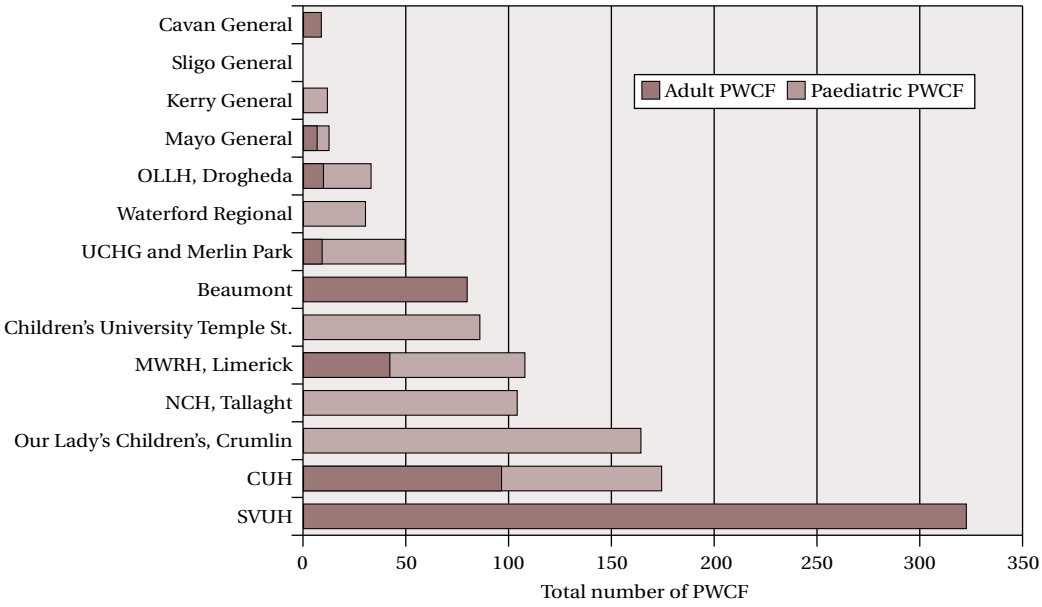
We are still developing the website report section and hope to adapt the functionality so that individual CF Centres may create their own reports.

Demographic Comparison: CF Centre Census, vs. CFRI Enrolment

A census of PWCF attending CF Centres is completed each year. Not all PWCF reported in this census are enrolled on the CFRI, so it provides the CFRI with an enrolment target.

The CF census for 2006 has changed slightly (+ 0.34%) compared with 2005. This is less than would be expected taking into consideration the assumed incidence of CF in Ireland. However, this variation is more likely due to a change in the "definition of attendance at a particular clinic", rather than real change. That is, the 2006 census reveals a reduction in the number of PWCF who are counted in two separate centres, a situation which may have prevailed in earlier surveys. Because this census is used only as a target/guide for CFRI enrolment, and does not require names of PWCF, sex, nor other identifiers, its accuracy cannot be directly compared with the CFRI. Figure 2 shows the distribution of PWCF by CF Centre attendance and shows that in Dublin, adults and paediatric PWCF are segregated into separate hospitals; while in Cork, Limerick, Galway, Drogheda and Mayo, both age groups are seen in the same CF Centre. Note also that eleven PWCF attend Sligo General Hospital, but they also attend a Dublin centre, so their numbers have been accrued in the Dublin centre census.

Figure 2: CF Centre Census, 2006 (n=1186)

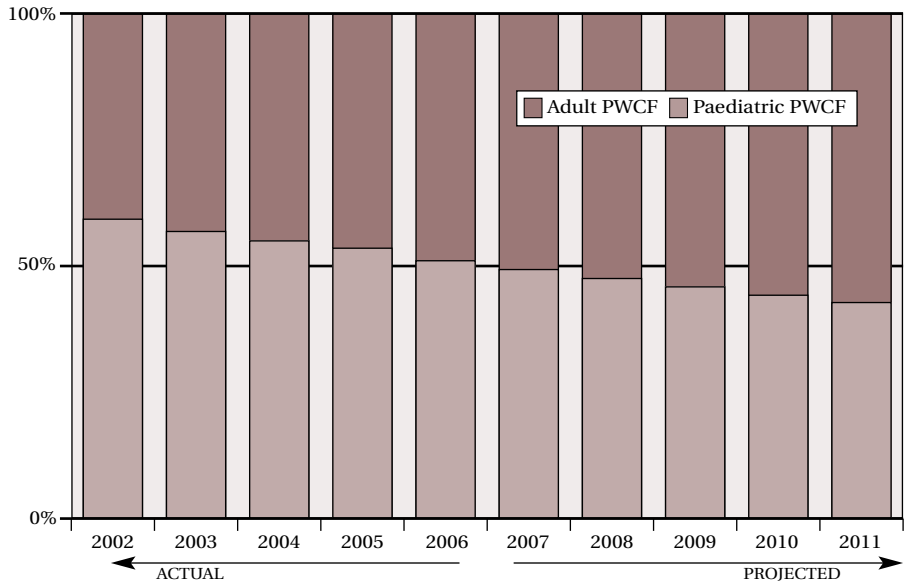


Another major difference between the CF Centre Census and the records in the CFRI is the age distribution. For the purposes of the CF Centre Census, a person is grouped in the paediatric group if they are still attending a paediatric centre. That is, they may well be over 18 years of age, but they are still grouped with the paediatric sector. In contrast, the data from the CFRI is fully accurate in terms of age and hospital attendance; it will show us the precise number of PWCF who are over 18 years and still attending paediatric centres.

But despite these drawbacks, the CF Centre Census can be useful for projecting the age group growth in order to estimate resource needs into the future. Once we have full enrolment on the CFRI, the need for the CF Centre Census will diminish. All projections will be done using data

from the CFRI. The additional information such as sex, genotype, infection status, plus many other items of information will contribute to much more accurate estimates of resource requirements which is essential for budget forecasting. At present, using the CF Census figures of the past 5 years, the projection shows that the adult population will become more numerous by the end of 2007(See Figure 3).

Figure 3: Projected ratio of adult to paediatric population to 2011



This gives us some indication regarding the need to put into place comprehensive adult CF medical facilities, especially hospital resources. Our projections in previous years indicated that this dominance of adult PWCF would not take place until 2009/10, but this projection is now based on more extensive data with less reliance on estimated figures. This data will also be useful when plans are created for new paediatric CF facilities. The paediatric sector will remain relatively stable in numbers: the number moving to the adult sector at age 18 will roughly equal the number of new diagnoses in each year coming into the paediatric segment. But, the adult group will continue to grow and their needs will become much more clearly defined. This is where the CFRI will be very useful, because along with their age, genotype and geographic area of residence, we will be tracking complications, infections, and antibiotic usage. All of this information will contribute towards forecasting definitive hospital needs for the growing group of CF adults.

At present, using the two independent censuses we can compare where PWCF reside with where PWCF attend for specialist care. Using CFRI information, we can examine the geographic distribution of our PWCF population by looking at which HSE Areas they reside in. Figure 4 shows that 39% actually live within the HSE Eastern Region. But, because of the number of hospitals located there, the Eastern Region actually treats 64% of all PWCF in Ireland (Figure 5). The Southern, Midwestern, Western, and North-eastern Areas combined, treat another 33% of all PWCF. But there are a sizeable number of PWCF from each of these regions who travel to Eastern Region hospitals. Nine percent of PWCF reside in either the Midland Area or the North-Western Area, but there are no centres in these regions so they attend CF Centres outside of their immediate area. The Eastern Region (64%), Mid-Western Area (9%), and Southern Area (16%) cater for 89% of all PWCF. The Western Area, South Eastern Area and North-Eastern Area care for the remaining 11% of PWCF.

Figure 4:
Geographic distribution by residence

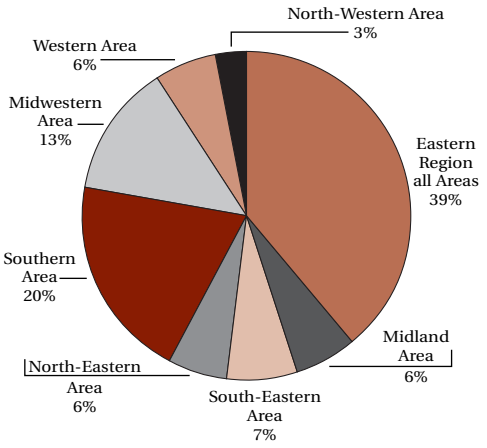
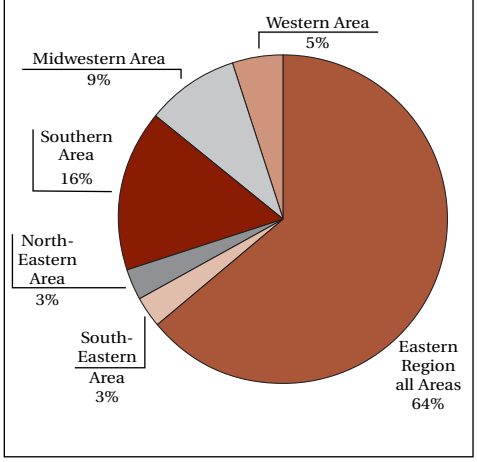
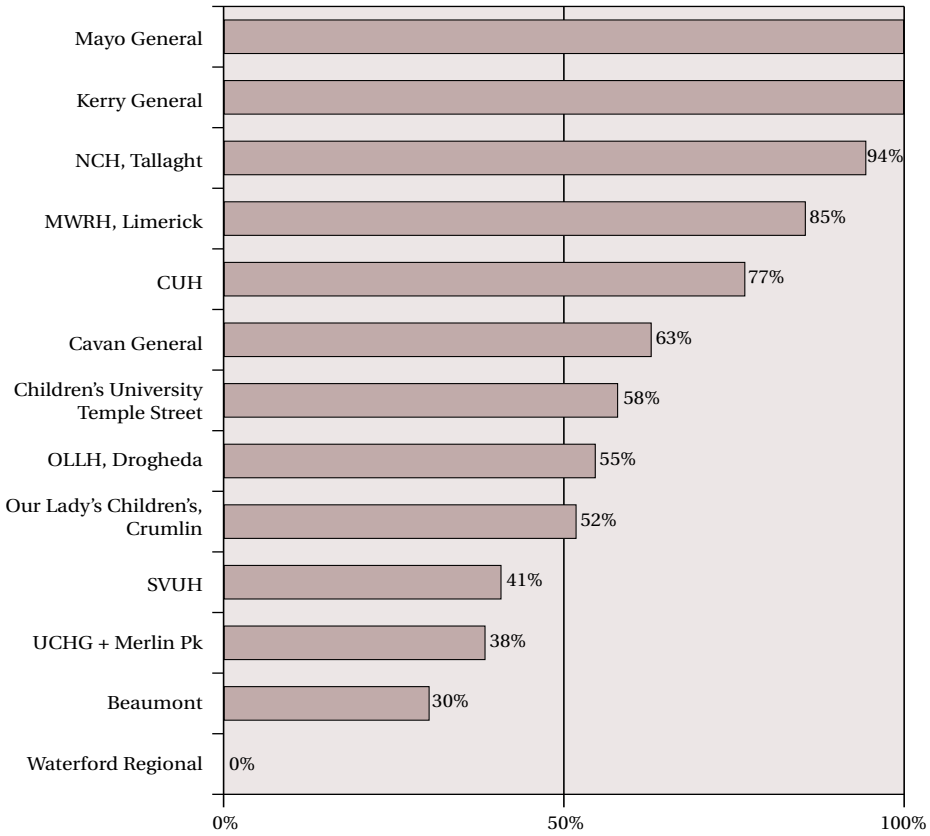


Figure 5:
Geographic distribution by CF care centres



It would appear that the majority of PWCF who travel outside of their own HSE Area, generally travel to Dublin for their care; certainly for their annual assessment. This information can be very useful when making resource decisions; be they decisions regarding bed allocation and isolation requirements or the need for further CF personnel.

Figure 6:
Informed consents for CFRI by CF Centre

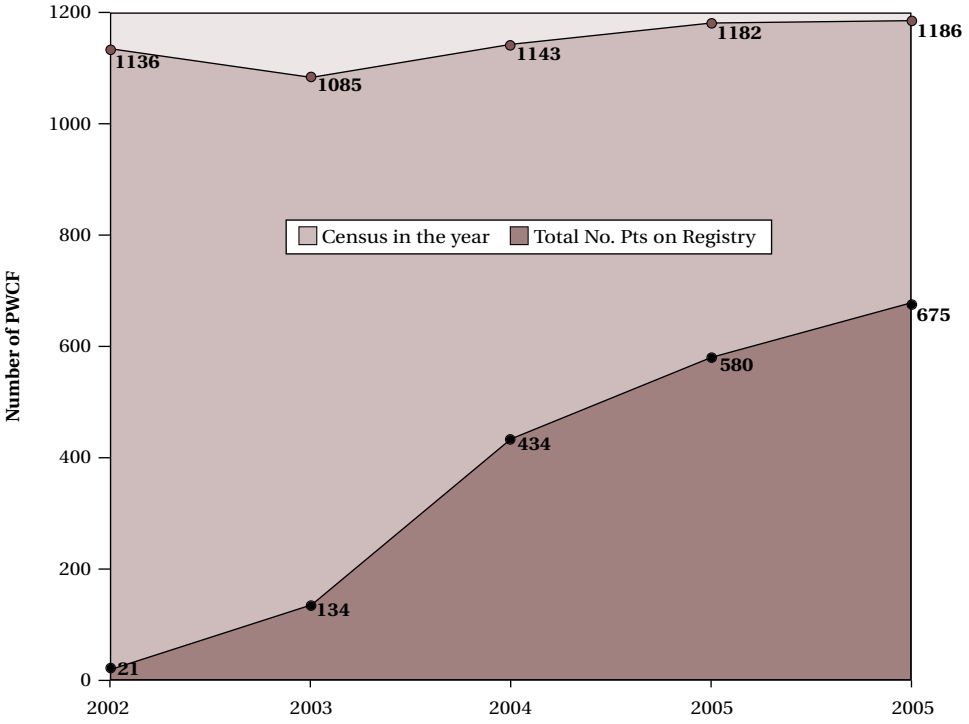


One further useful comparison between the CF Census and the CFRI ascertainment level is that of the number of Informed Consents that are signed and on file in the CFRI office versus the census for the hospital. Figure 6 shows that the majority of hospitals have over 50% of their

patients signed up to the CFRI. This describes the target for 2007 for enrolment. Part of the problem preventing complete ascertainment resides with those hospitals that are less than 50% enrolment: SVUH, Beaumont and Our Lady's Children's Hospital. If these hospitals could be brought up to 75% enrolment, we would be at a very high level of completeness. This will be a target for 2007 and we will continue to pursue 100% enrolment in later years.

Figure 7 shows the narrowing gap between the total census (top line) and the enrolment line (Total number of PWCF on Registry). If a large majority of PWCF were enrolled, this would lend credence and strength to conclusions drawn from research using CFRI data.

Figure 7: Gap in CFRI enrolment and CF Centre census

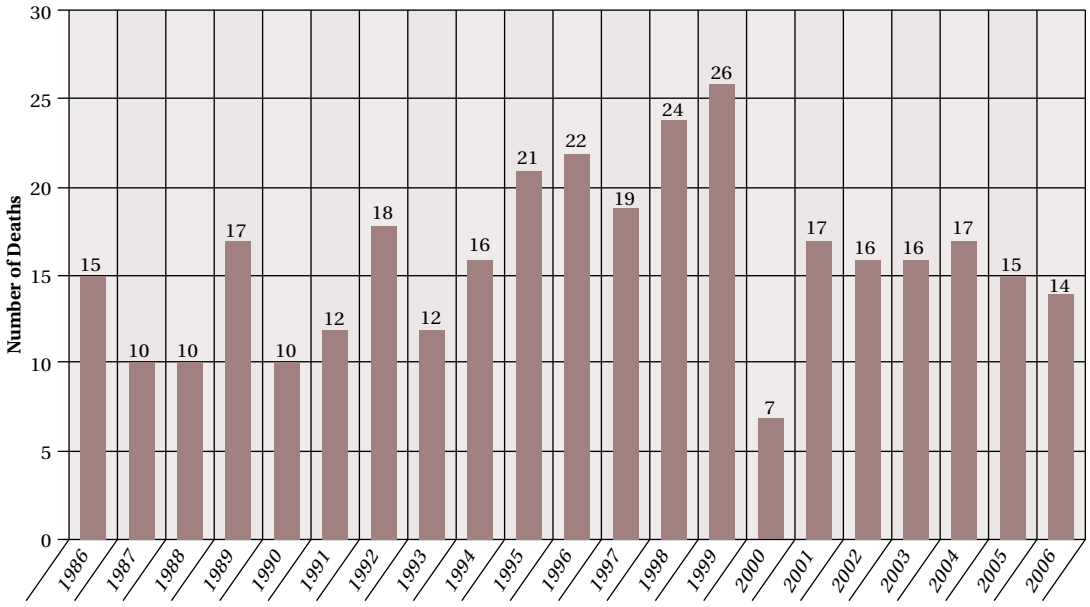


Descriptive Data from CFAI

The CF Association of Ireland (CFAI), a patient support group, has been in existence since 1963. In 1986 they began to record information regarding the number of PWCF who died each year; now, they have over 20 years of records for those who are/were members of the CFAI. The CFAI has kindly granted the CF Registry of Ireland (CFRI) permission to use this data in the present report. It is estimated that 85-95% of all PWCF (and/or their parents) belong to the CFAI. Descriptive data regarding cause of death of those who were enrolled on the CFRI will be shown later in this report but there are some interesting points that can be made regarding the CFAI information (which records the age and date of death only).

First of all, the total number of deaths per year may be dropping slightly from a high of 26 deaths in 1999 (Figure 8).

Figure 8: Number of deaths of CF patients, 1986-2006 (n=334)



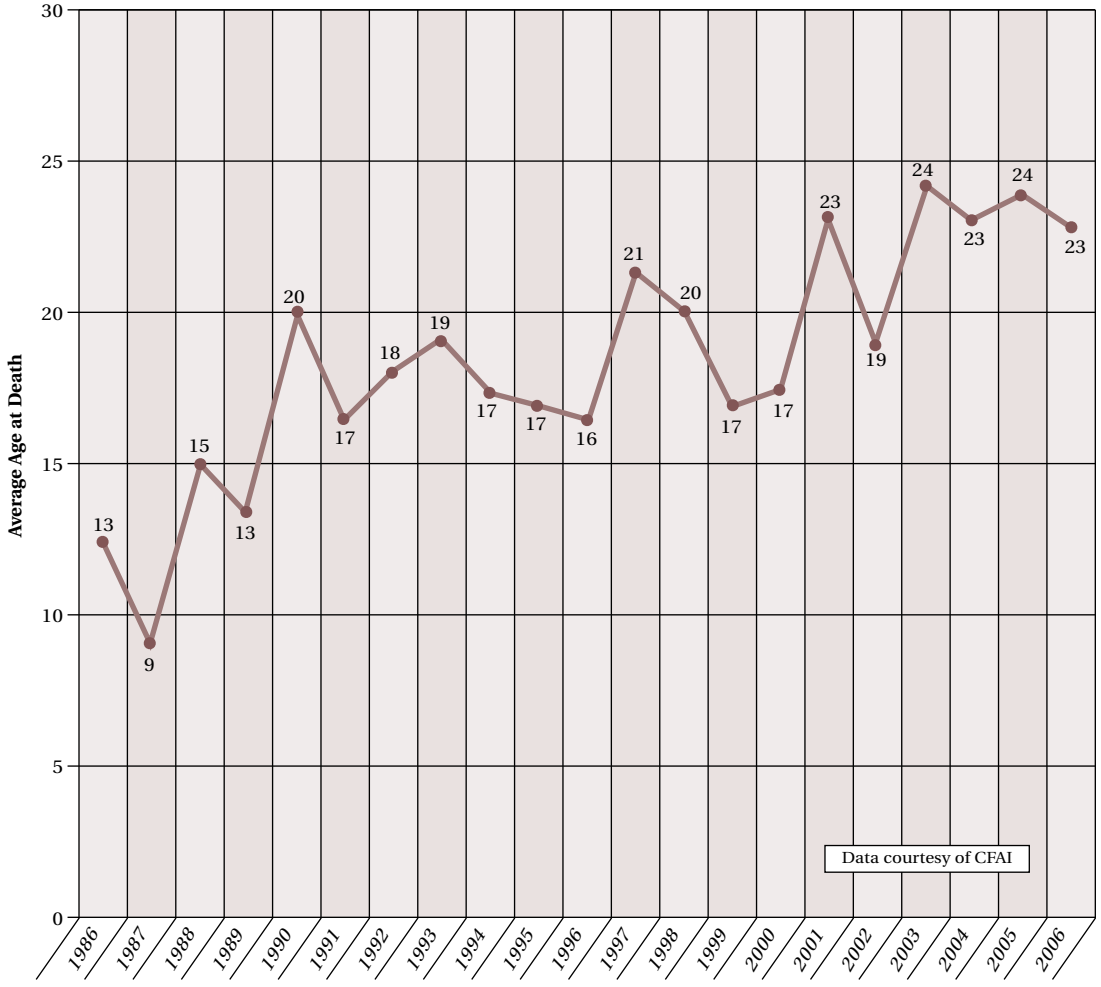
Data courtesy of CFAI

There was a five year period from 1995 to 1999 when the number of deaths in each year was over 19 (annual range 19-26). For the nine year period prior to that (1986-1994) the average number of deaths was 13.3 per year; during the 'peak' period of 1995-1999, the average was 22.4 and for the most recent period, 2000-2006 the average went back down to 14.6 deaths per year. The overall average number of deaths during the entire period of 1986-2006 is 15.9. There may have been some significant medical or social factors influencing the rise in the '95-'99 period and this may be a point of investigation for the future. What we can now say is, that apart from that peak period ('95-'99) the average number of deaths since 1986 has remained relatively static; and this is despite the fact that the entire CF population has been growing steadily throughout the period. In other words, the "death rate" appears to be decreasing, albeit in small increments. But, because we do not have PWCF census figures going back to 1986 we cannot calculate the precise death rates.

There are other interesting points that can be considered regarding the description of those PWCF who died during that period. During the period, 1986-2006, the average age at death

appears to be increasing (Figure 9). Also, according to this data, the total number of deaths in the "under-18" age group has fallen and continues to fall. So, more PWCF are progressing from the "under-18" age group to the adult group; and, those who are in the adult group are living longer. It is unlikely that this positive trend can be linked to any one factor, but it is encouraging that, overall, positive change can be seen. Some of the factors that undoubtedly influenced this positive trend are the development of new antibiotics and new treatment strategies. We would expect this positive trend to continue with the expansion of specialist medical teams and the establishment of purpose built CF centres in the major regions.

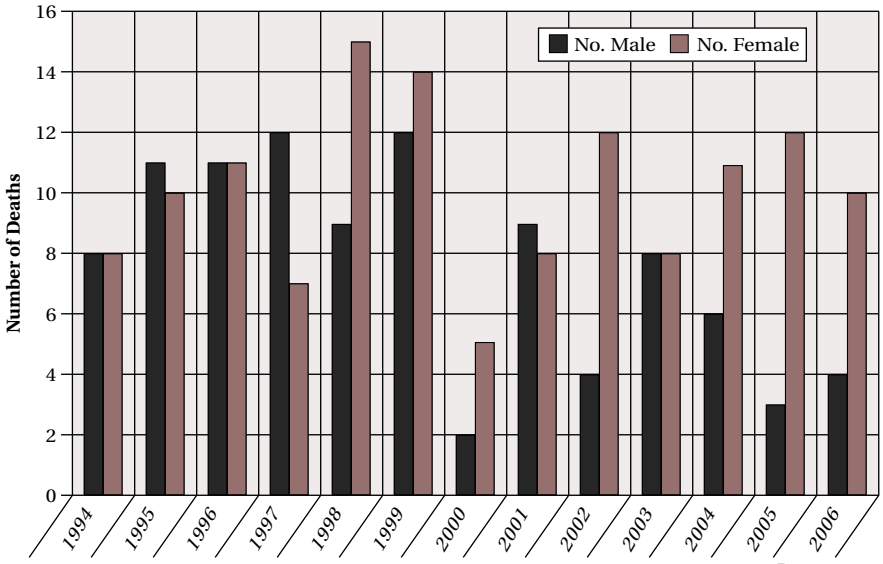
Figure 9: Average age at death, 1986-2006



Please note that Figure 9 is NOT a 'survival curve', nor 'median survival'. A 'survival curve' is a statistical measure which gives you the 'likelihood' of a person surviving to a certain age. Generally speaking, survival curves tend to be higher than actual 'age at death' graphs (Figure 9). A survival curve is a statistical prediction based on the age of death (historical data) of **all** people in the group who have died. We do not have survival data for Ireland. Consequently, this data should NOT be compared with other countries' data that quote "median age of survival"; or "predicted median survival". In Ireland, we will not be in a position to derive "median survival" for several more years. In order to create survival curves for the Irish CF population, we need to have everyone enrolled on the CFRI and this is why it is so important to join the CFRI.

Another interesting aspect of this data is the sex distribution of the deaths of PWCF in Ireland. Over the past 13 years the total number of female deaths outnumbered the total number of male deaths, with the exception of 3 years: 1995, 1997, and 2001 (Figure 10). This gender difference is an aspect that warrants further investigation. It may simply be an artefact; that is, a chance occurrence, but it should be looked at further, especially in more recent years where we have have some CFRI data that can be analysed alongside the death data. Whether this finding relates to a difference in the age at diagnosis, genotype, or other factors remains to be tested.

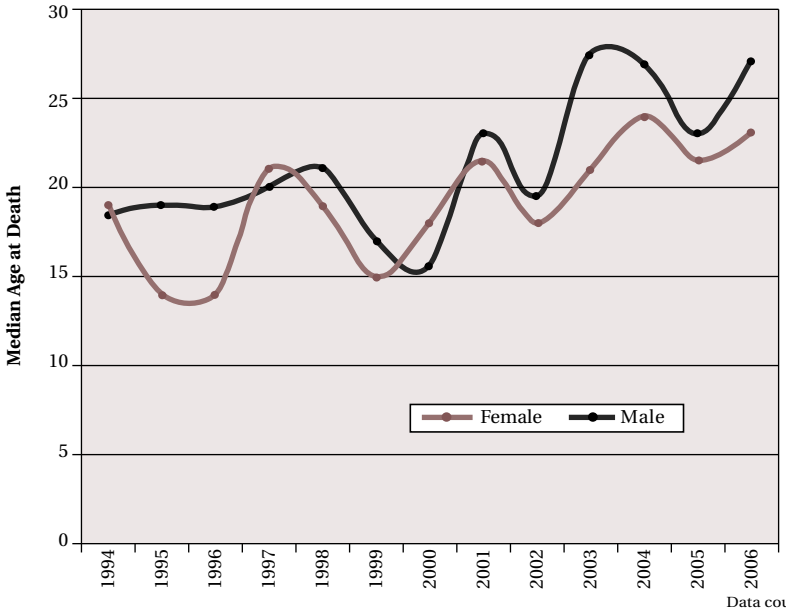
Figure 10: Number and gender of CF deaths, 1994-2006



Data courtesy of CFAI

There is further evidence that there may be some factors related to sex that affect long-term survival and this is represented by the 'Median Age at Death' separated into males and females (Figure 11). Studies from other countries have shown a 'gender gap' in terms of survival and Figure 11 shows the pattern in Ireland.

Figure 11: Median age at death of CF patients (males vs. females), 1994-2006



Data courtesy of CFAI

The problem with our data is that the number of deaths in each year is relatively small, so that we may need to accumulate many more years' data before it can be fully analysed. That is, the numbers in our sample are too small to derive any statistically significant conclusions.

Median Age at Death

The Median Age at Death means that 50% of the group who died in that year were above that age; and 50% of the group were below that age. So, taking 2006 and looking at the male point of '27' means that of the 4 males (Figure 10) who died in 2006, 2 of them were above age 27 and 2 were below 27; similarly for the 10 females who died in 2006, 5 were above the age of 23 and 5 were below the age of 23 when they died.

Thus far, we are seeing trends that point to both a slightly larger number of deaths in the female population and they may be dying at a slightly earlier age than their male counterparts. This data requires further study and verification.

Using this mortality data of the entire CF population in Ireland as background, we can now examine the CFRI data in detail.

Demographics of the CFRI

The following table can be seen every time one accesses the registry database. It is 'up-to-date' and 'live' data. Every time a patient is fully registered, the numbers change.

Table 1: Summary data from CF Registry of Ireland (CFRI)

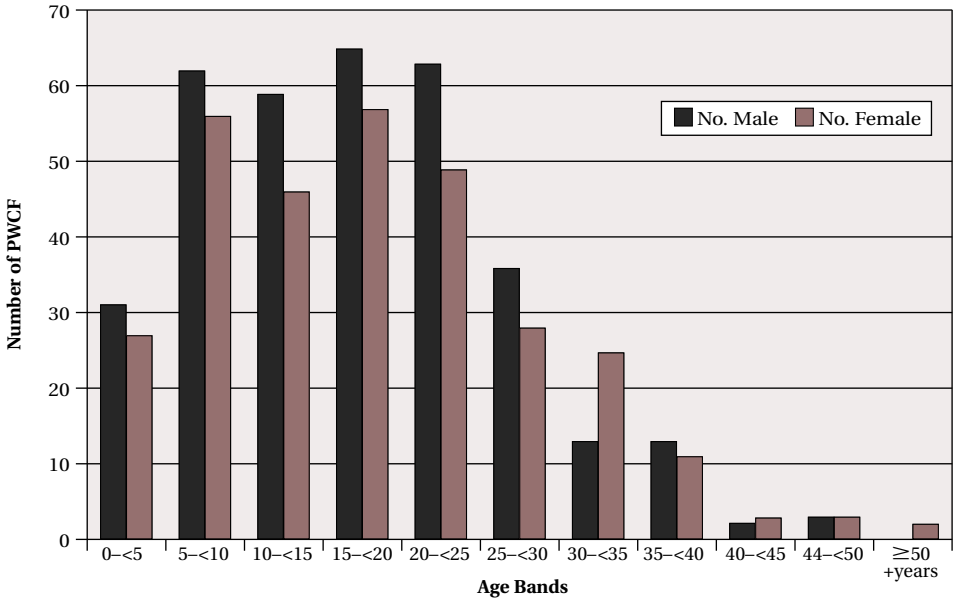
General Data

Year:	2002	2003	2004	2005	2006	Total	%age
PWCF Registered in the Year	21	113	300	146	95	675	
Age Range					1–54		
Mean Age [yrs]					17.4		
Median Age [yrs]					17		
No. Males					354		52.4%
No. Females					321		47.6%
No. < 18 yrs					358		53%
No. ≥ 18 yrs					317		47%
No. Males ≥ 18					163		24.1%
No. Females ≥ 18					154		22.8%
Deaths during year	0	6	5	6	4	21	3.1%
Total no. PWCF on Registry who are alive at end of Year					654		96.9%

At the end of 2006, the total number of PWCF who have been enrolled is 675 (Table 1). Of these, 52% are male, and 53% are less than 18 years of age. Nearly one-quarter of the population on the database is male **and** over 18 years of age. The 'mean' (or average age) of all enrolees is 17.4 years of age; while the 'median' age is 17. The age range of all participants is from less than one year to 54 years old.

The age and gender distribution, broken down into 'age bands', can be seen in Figure 12.

Figure 12: CFRI, age and gender distribution by age bands



Nine per cent of the males enrolled are over 30 years of age; while 14% of the females are over 30 yers of age. Overall, there is an even distribution of males and females on the registry.

The gender and age breakdown on the CFRI are shown in Figures 13 & 14.

Figure 13:
Proportion male & female PWCF on CFRI

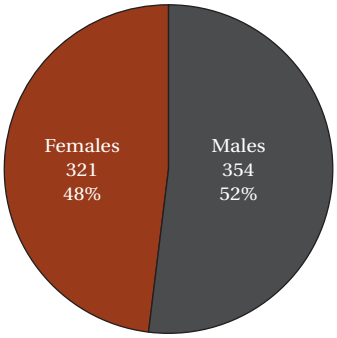
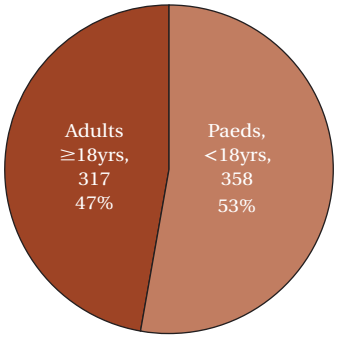


Figure 14:
Proportion paediatric & adult PWCF on CFRI



These are representative of the Irish CF population as a whole, and show that we have over 55% of the CF population enrolled.

Geographically, the CFRI reflects the major population centres of the country.

A detailed breakdown of PWCF and their county of residence is available from the CFRI (Table 2).

This shows the number and percentage of PWCF who were enrolled and are alive at the end of 2006; and their county of residence. The distribution is as expected with the majority of PWCF coming from the larger urban areas. A better picture will emerge when all PWCF are enrolled and we will then be able to see if there are any pockets of CF population that need further attention in terms of resources. But, the table is reflective of the entire CF population, and these percentages are unlikely to change markedly as the CFRI increases enrolment.

Table 2: PWCF by county of residence

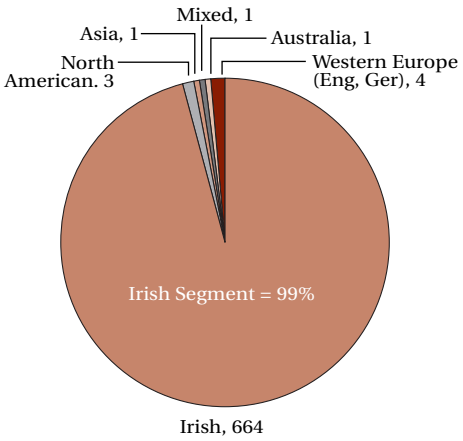
County of Residence		
County	**No. of PWCF in residence**	**Percentage**
Dublin 1–24	131	20.0%
Cork	99	15.1%
Dublin County	56	8.6%
Limerick	45	6.9%
Kerry	33	5.0%
Kildare	32	4.9%
Wicklow	28	4.3%
Clare	26	4.0%
Mayo	22	3.4%
Wexford	18	2.8%
Meath	18	2.8%
Sth Tipperary	16	2.4%
Nth Tipperary	16	2.4%
Westmeath	15	2.3%
Galway	14	2.1%
Laois	10	1.5%
Louth	10	1.5%
Sligo	9	1.4%
Waterford	8	1.2%
Cavan	8	1.2%
Kilkenny	7	1.1%
Offaly	7	1.1%
Donegal	7	1.1%
Carlow	5	0.8%
Monaghan	5	0.8%
Roscommon	5	0.8%
Longford	2	0.3%
Leitrim	2	0.3%
Total PWCF	654	100%

Ethnicity

The CF population in Ireland is quite homogeneous (Figure 15). The Irish segment composes 99% of the PWCF enrolled to date. The other ethnic/national groups represented are North America, Western Europe, Australia, Asia, and those of Mixed heritage. Ethnic information is missing for one PWCF. There will undoubtedly be more groups represented in the future as the overall population of this country becomes more varied, influenced by the present trend of immigration from other countries.

It will be interesting to follow the clinical outcomes of our PWCF, against the background of their ethnic origins and genotype. Because the overwhelming segment of Irish PWCF were born here and have been treated here, their clinical course may be said to have been influenced primarily by genotype, and CF Centre attendance. This may not be the case for other CF populations. There is a "uniqueness" about the Irish CF population that might reveal unexpected findings.

Figure 15:
Ethnic groups represented in CFRI



Siblings

As well as the homogeneousness of the origin of the CF population here, Ireland has a high proportion of siblings with CF (Table 3). With just over half of the PWCF enrolled, 21% of enrolees also have a sibling on the CFRI. When all of the PWCF are finally enrolled, we would expect that percentage to increase. This provides an excellent environment for some creative studies of how infection may spread within families, for example.

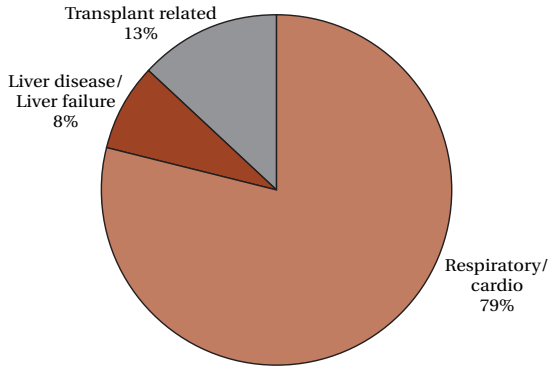
Table 3: PWCF families and siblings

Irish CF Families	
Total number of PWCF enrolled	675
Families Represented	604
Total number of children represented by 604 families	2371
Average Number of children per family (with and without CF)	3.9
Average number of children with CF per family	1.1
Number of families with 2 siblings with CF (includes 3 sets of twins)	63
Number of families with 3 siblings with CF	4

Deaths

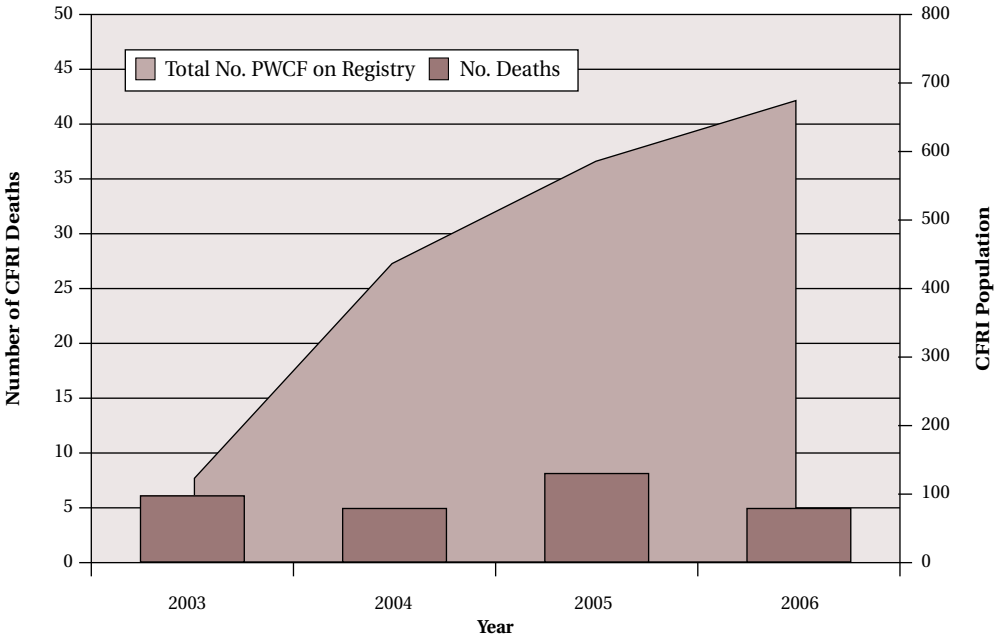
There have been 24 deaths of PWCF who were enrolled on the CFRI since 2003. Seventy-nine percent of the individuals died from 'Respiratory / Cardiac' problems (Figure 17). Two deaths were attributed to 'Liver disease/liver failure' and three deaths were 'Transplant related'. The ratio of male deaths to female deaths of those enrolled on the CFRI is 1 : 2.4.

Figure 16: Proportional cause of death, Summary 2002-06



It is interesting to note that the number of deaths has not increased in relation to the number of people enrolled. Figure 17 shows the growth of the CFRI in the solid background; while the number of deaths for each year 2003-2006, are represented by the bars in the foreground. The bars are a similar height throughout time, while the database has grown significantly.

Figure 17: Number of deaths against background of enrolment on CFRI

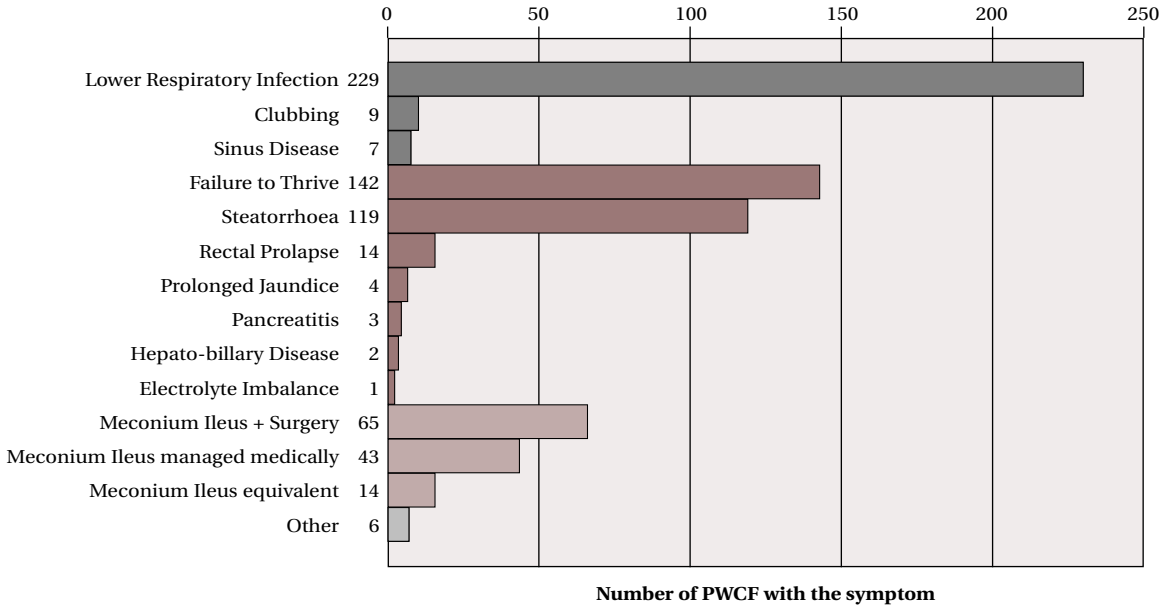


Symptoms at Diagnosis

The information that is recorded in the CFRI in the 'diagnosis' section falls into two categories. The first category includes all of the clinical symptoms or conditions (e.g., meconium ileus) that the person displayed prior to diagnosis. The second category includes items that were applied after an initial suspicion that CF may be present, in order to arrive at a diagnosis. This latter category includes 'Screening' and 'Sweat test'. In addition, the genotype for each PWCF is recorded on the CFRI, if it is available. Not all enrolees have symptoms or genotype recorded; and many enrolees have multiple symptoms recorded.

We will discuss the first category, symptoms leading to further investigation, in more detail. Each person may have more than one condition or symptom attributed to them, so the total number of symptoms out-numbers the total number of PWCF on the database. The clinical symptoms may be summarised under three headings: 'Respiratory' (RESP), 'Gastrointestinal' (GI), and 'Meconium Ileus' (MI). Figure 18 shows the frequency of the symptoms as recorded on the database. There are 81 PWCF for whom we do not have any diagnostic-symptom information. The most frequently reported symptom is 'lower respiratory infection/persistent lower respiratory symptoms', recorded by 229 PWCF; and falls into the 'Respiratory' category. The next most frequently recorded symptoms are gastrointestinal in nature, being 'failure to thrive and/or malnutrition' and 'steatorrhoea and/or abnormal stools'. Finally, all of the meconium conditions account for approximately 20% of all diagnoses. The meconium conditions, 'managed medically', 'requiring surgery', and 'equivalent' most often appear in the antenatal period. They account for the majority of PWCF who are diagnosed within the first three months. However, eleven of the 14 PWCF who have the symptom 'meconium ileus equivalent' recorded were diagnosed after their first month of life (Median Age at diagnosis of 1.87 months). In contrast, the median age of the PWCF who had 'MI managed medically' or 'MI needing surgery' was less than two weeks (Median Age at diagnosis of 0.43 months). Those who are attributed with the symptom 'MI equivalent' may be assumed to be slightly less severe than the other two groups, as the median age at diagnosis was 1.87 months in contrast to less than one month for the other two meconium categories.

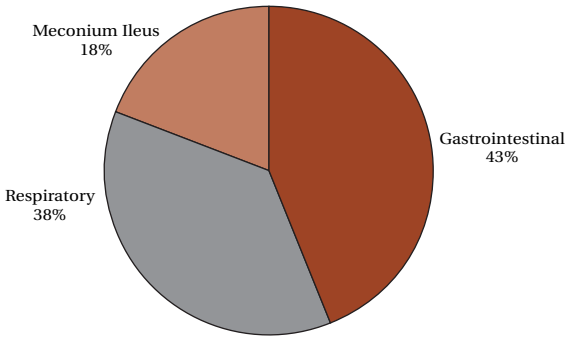
Figure 18: Symptoms at diagnosis from 594 PWCF



Among the GI symptoms, the 'failure to thrive' and 'steatorrhoea' symptoms occur with a similar frequency. 'Rectal prolapse', while not occurring as frequently, is associated with a delay in diagnosis. The median age at diagnosis for the 14 PWCF who record 'rectal prolapse' is 33.5 months (range 19.8 months – 64 months). [Interestingly, of the 14 PWCF with 'rectal prolapse' as the presenting symptom, four are male and all carry the △F508 mutation (7 are homozygous, 5 are △F508/G551D and 1 is △F508/E60X).] A diagnosis beyond 24 months is rather late; nutritional status and general health parameters may be affected by such a late diagnosis. The negative consequences of a late diagnosis are difficult to reverse. This set of PWCF are a particular puzzle and it would be worthwhile to discover why they weren't picked up earlier, especially in the context of their genotype.

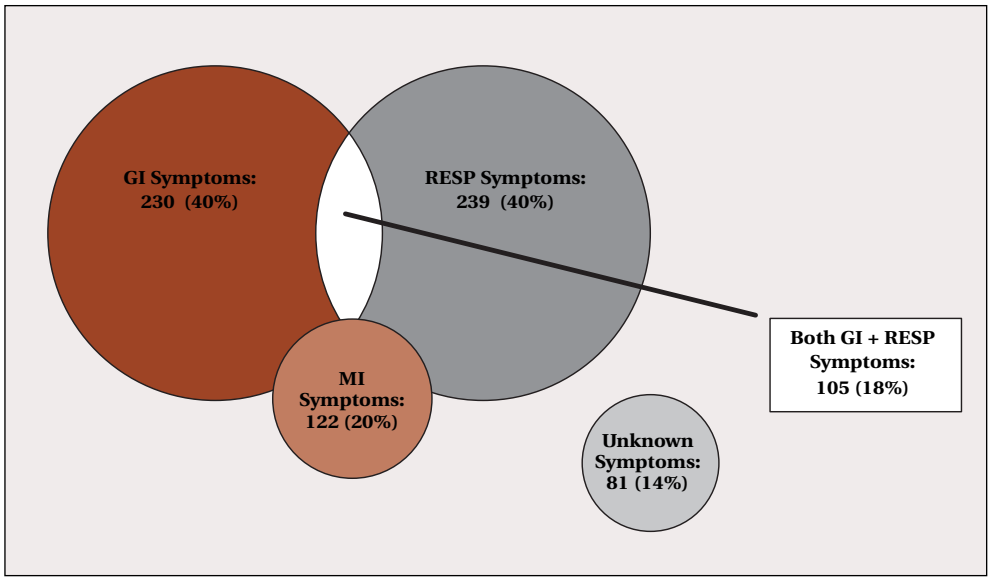
Another interesting exercise is to examine the proportions of 'Gastrointestinal', 'Respiratory' and 'Meconium' symptoms within the overall number of symptoms. It appears that MI symptoms will occur 20% of the time in Ireland, while GI and RESP symptoms occur with equal frequency at about 40% each. The GI symptoms can be further sub-divided into 'steatorrhoea' and 'failure to thrive'; and these are reported with roughly equal frequency.

Figure 19:
Proportion of symptom distribution at diagnosis



Rather than considering the symptoms first, if we look at the PWCF first, and then their symptoms, we can count the number of people who have multiple clinical symptoms at diagnosis and note their median age at diagnosis. A Venn diagram (Figure 20) shows the number of PWCF who have at least one GI, or RESP, or MI symptom and also demonstrates the number of people who have more than one type of symptom at diagnosis. There is a reasonably strong overlap between GI and RESP symptoms.

Figure 20: Venn diagram of symptoms at diagnosis



Age at Diagnosis

In previous reports we have been examining 'Age at Diagnosis' differences between males and females. This year we have looked at the differences in terms of both symptoms and genotypes and present these comparisons. Primarily, we are attempting to perceive if there are any gender differences in the 'age at diagnosis'; and if so, what factors might influence this. We have an 'age at diagnosis' for the majority (96%) of PWCF on the CFRI (Table 4). Overall, nearly half 298, (46%) of all PWCF are diagnosed clinically at less than 3 months of age. A large proportion of those present with meconium ileus; and the percentage is similar for both sexes.

Table 4: Age at diagnosis of PWCF

	Females	%	Males	%	Total
Total in set	311		338		649
Total diagnosed in < 3 mos	136	44%	162	48%	298
Total diagnosed in ≥3 mos	175	56%	176	52%	351
Total MI	63	20%	55	16%	118
Total GI	109	35%	128	38%	237
Total RESP	110	35%	123	36%	233
Total RESP + GI	45	14%	57	17%	102
Diagnosed in < 3mos with MI	58	43%	50	31%	108
Diagnosed in <3 mos with GI	32	24%	41	25%	73
Diagnosed in <3 mos with RESP	19	14%	27	17%	46
Diagnosed in <3 mos with both RESP + GI	10	7%	11	7%	21
Diagnosed in <3 mos Other reasons	27	20%	44	27%	71
Symptoms at Diagnosis Guide:					
MI = Meconium Ileus GI = Gastrointestinal RESP = Respiratory					

The remainder of this early diagnosis group have various symptoms at diagnosis, but the larger percentages are in the GI group of symptoms. From this data it would appear that those PWCF with gastrointestinal symptoms are more likely to be diagnosed before they are 3 months old than those with respiratory symptoms or a combination of gastrointestinal and respiratory symptoms. As we saw above, 'failure to thrive' and 'steatorrhoea' occur with equal frequency and are also key signs of negative developmental progress. Although 'lower respiratory infection' is a very frequent occurrence as a diagnostic symptom, it still takes time to develop and oft-times repetitive infections occur before they are clinically investigated for CF. In other words, respiratory damage may require a period of several months to profess, while the signs of malnutrition are more likely to be evident from birth, such as at the six-week check-up and at later regular healthcare interventions such as primary childhood vaccine administration. Thus, it might be more likely that the GI symptoms will trigger further and earlier investigation than the respiratory symptoms unless the RESP symptoms are severe from an early age. The data in the table mirrors these assumptions and shows that there do not appear to be differences between the genders if we look at those diagnosed in less than 3 months of age.

But, if we **exclude** those who have been diagnosed in less than 3 months, and concentrate on the sub-groups of those who are older when they are diagnosed, then some differences begin to appear between the genders. Table 5 shows the 'Median Age at Diagnosis' for both males and females in the different sub-categories. The median age of females in those categories that may be significant are shown in bold. All ages are noted in months; and the 'Mean Age at Diagnosis' is also given for reference purposes. All PWCF who were diagnosed in less than 3 months are excluded from the calculations in this table.

Table 5: Median age at diagnosis in Months

	Females	n	Males	n
Median Age @ Diag Excl MI	5.82	248	5.59	283
Median Age at Diag excl < 3 mos	17.87	170	13.18	171
SYMPTOMS				
Median Age at Diag GI	4.93	59	5.82	71
Median Age at Diag RESP	**24.69**	66	10.14	66
Median Age at Diag RESP+GI	**12.015**	46	6.41	57
Mean age @ diag excl <3 mos	54.6	170	36.45	171
GENOTYPE				
Median Age DF508 homzygous	2.86	184	2.99	201
Median Age DF508 +G551D	7.79	28	9.105	32
Median Age DF508+ R117H	**71.51**	13	5.605	6
Symptoms at Diagnosis Guide:				
MI = Meconium Ileus GI = Gastrointestinal RESP = Respiratory				

The median age at diagnosis for females and males who present with GI symptoms is similar, 4.93 months for females and 5.82 months for males. Differences appear to arise when we select those who presented with respiratory symptoms **only** or those who had GI + RESP symptoms. In both cases, the median age at diagnosis for females is twice that of males (Table 5 & Figure 21).

We have also looked at the 3 sub-groups of genotypes which appear with greatest frequency in the CFRI (Figure 22). There are no differences between males and females if they have the △F508 mutation on both chromosomes, or if they have the △F508 mutation on one chromosome and the G551D on the other. But, if they have the △F508 mutation on one chromosome and the R117H on the other, then there is a large difference in the median age at diagnosis. The age range for the females having this genotype is 2.2 months old for the youngest diagnosed, and 23 **years** (277.3 months) old for the eldest; while for the males, it is 2.3 months old for the youngest diagnosed, and 12 **years** (148.6 months) old for the eldest. Caution is imperative when interpreting these findings as the number of PWCF in both groups (△F508/R117H) is small. But this comparison could reveal a clue for interpreting differences in genetic expression in males and females affected by this genotype. Those PWCF who have the △F508/△F508 genotype tend to be diagnosed very early and manifest the most obvious symptoms. But, what is of most concern is the fact that more than half of all males and females

are diagnosed after they are 3 months of age and most of them carry the △F508/△F508 genotype. By then it may be too late to reverse nutritional disadvantage. The CFRI affords us the ability to look at the clinical course for all such variations of diagnosis and measure and predict later outcomes. This is the advantage of a comprehensive clinical database. It will be possible to correlate pulmonary function test results with genotype or presenting diagnostic symptoms, but we will need to obtain more data before performing such an extensive exercise.

Figure 21:
Median age at diagnosis for males and females by symptom category

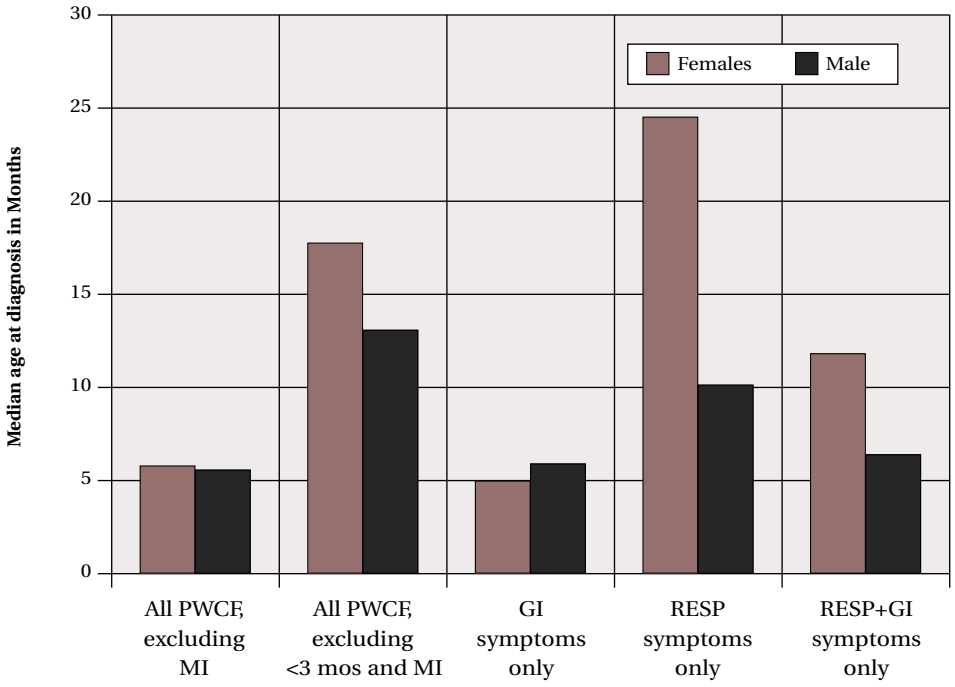
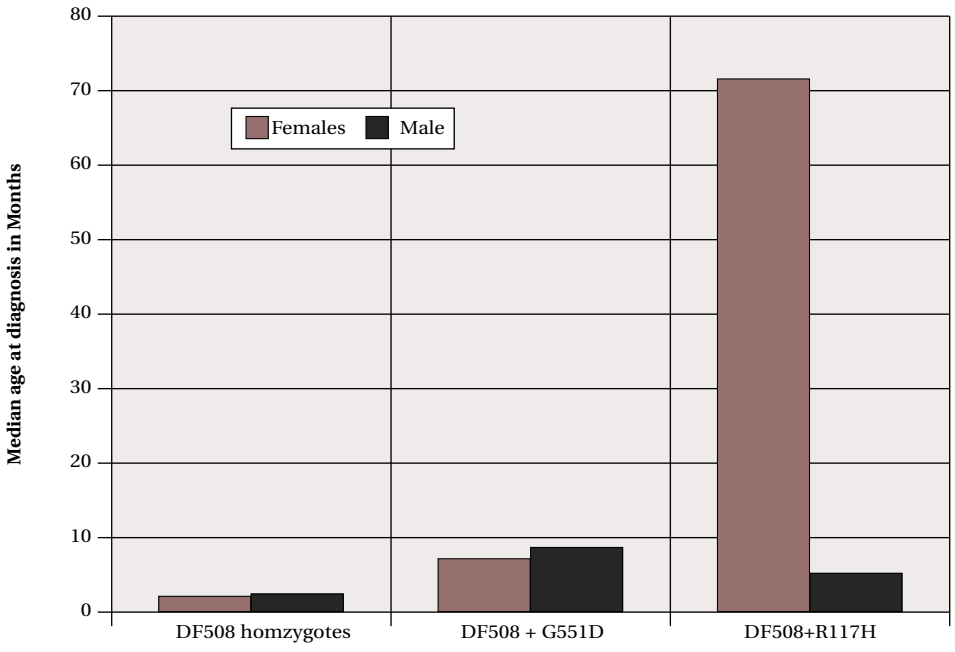


Figure 22:
Median age at diagnosis for males and females by most frequently occurring genotypes



Genotype

The genotype data is accumulating with each year. We now have genetic data from 654 PWCF, or 97% of those on the database. Results are still pending for 80 alleles, but even so we can make some observations regarding the Irish CF population as a whole. We have found that 89% of PWCF carry the △F508 mutation on at least one chromosome; while 61% have △F508 on both chromosomes. This would appear to be higher than most other Western Europe and North American populations. Two other mutations are of interest as they occur with the next highest frequencies to △F508; they are G551D and R117H. The G551D occurs on at least one chromosome of 11% of the CFRI population; while the R117H mutation occurs in 5% of the CFRI population. Although the G551D mutation is viewed as one of the more severe genotypes, the R117H is generally associated with a milder course.

Tables 6 & 7 list the mutations that have been detected in the Irish population. Table 6 shows the more frequent mutations, while Table 7 expands into greater detail, the 'Other' mutations found on the last line (highlighted in grey) of Table 6. Six additional mutations are noted in the Irish population to the mutation list published in the 2005 annual report: R553X, 3849+10KbC->T, E60X, 3272-26A->G, 3659delC, and G85E.

Table 6: Frequency of 14 common CF mutations in CFRI

Most Frequent CF Mutations								
	Allele 1							
Allele 2	**Result Pending**	**Δ1507**	**ΔF508**	**G551D**	**R117H**	**R560 T/K**	**Other**	**TOTAL**
Result Pending	38		33	3	4		2	80
Δ1507			5					5
ΔF508			399					399
G551D			60	2		1		63
R117H		1	21	2				24
R560 T/K			12	1		1		14
1717–1 G–>A			10		2			12
621+1, G–>T			9					9
G542X			8	2				10
N1303K			3					3
R352Q			1					1
R553X				1				1
3849+10KbC–>T			3					3
E60X			3					3
IVS1–5842_IVS4+401del			1	2				3
Other			16	1	2	0	5	24
Total	**38**	**1**	**584**	**14**	**8**	**2**	**7**	**654**

Table 7: Breakdown of 'Other' mutations from Table 6 (n=24)

"Other" Table								
	Allele 1							
Allele 2	ΔF508	G551D	R117H	1154 insTC	1471 delA	1525–1 G–>A	P574H	TOTAL
V520F	2							2
1471delA					2			2
2622+1G–>A	1		1					2
3849+4G–>A			1					1
A209s	1							1
c.2052delA	1							1
c.262_263del TT	1							1
L1335P	1							1
M1105R	1							1
Q493X	1							1
R1162x	1							1
1154insTC				1				1
1461ins4	1							1
1525–1 G–>A						1		1
2184delA	1							1
2623–2A–>G							1	1
3120 G–>A	1							1
3272–26A–>G	1							1
3659delC		1						1
G85E	1							1
Other	1							1
TOTAL	**16**	**1**	**2**	**1**	**2**	**1**	**1**	**24**

Hospitalisations and Complications

In order to assist planning of hospital services, it is useful to gather information on the number of hospitalisations and the types of complications that PWCF display. For this exercise we divide the CFRI population into those who are less than 18 years of age (Paediatric) and those who are 18 years of age and over (Adults). This is guided by the division of paediatric or adult CF centres.

The data used for this exercise was taken from three hundred eighty-nine annual assessments carried out during both 2005 and 2006 and are all from different individuals. There were almost twice as many paediatric as adult assessments. A comparison was made between the two age groups by taking the rate of occurrence in the Adult group and dividing it by the rate of occurrence in the Paediatric group to yield the "Ratio of Episode rate Adult to Paed" (right hand column, Table 8).

Table 8 shows that there were more 'hospitalisations', 'respiratory exacerbations', 'other exacerbations', and 'complications' in the adult group as the paediatric group. This is to be expected and in keeping with data from studies in other countries.

Table 8: Hospitalisations and complications, paediatric vs. adult

2005 & 2006 Annual Assessments					
Age Total no. in group Ave age of group in yrs	< 18 249 10		≥18 140 25		Ratio of Episode rate Adult to Paed
	No.	Per PWCF	No.	Per PWCF	
Hospitalisations	109	0.44	110	0.79	1.79 : 1
Respiratory Exacerbations	128	0.51	205	1.46	2.85 : 1
Other Exacerbations	59	0.24	52	0.37	1.57 : 1
Complications	577	2.32	535	3.82	1.65 : 1

Note the numbers in the right-hand column of Table 8; the higher the number, the more the adult population is affected, compared with the paediatric population. There were nearly twice (1.79) as many hospitalisations in those over 18 years of age and there were nearly three times (2.85) as many respiratory exacerbations. The category, 'other exacerbations' excludes respiratory problems while including problems in other systems; an example would be DIOS (distal intestinal obstructive syndrome). Again, these occur with greater frequency in the adult group. Complications occur with greater frequency and variety in the adult group. The data in the table can be shown in chart form as in Figure 23. This picture is consistent with the data presented in previous years. As more data accumulates, we would hope to break the data down on a regional basis or according to genotype; but, the dataset is too small for such comparisons at present.

There is an extensive section for recording the presence of complications on each annual assessment. The most frequently occurring complications are shown in Table 9 and chart

form (Figure 24), followed by the separate detail of each system, shown only in chart form. The ratio of adult to paediatric complications is also shown in the table. Again, the adult to paediatric ratio shows a strong emphasis on the adult PWCF. They have more complications in all categories, while displaying a much lower proportion of people with "no complications". The PWCF who have "no complications" is very low in both groups, being less than 3 per 100 [9 paeds; 2 adults].

Figure 23: Rate of hospitalisations & exacerbations, paediatric vs. adult

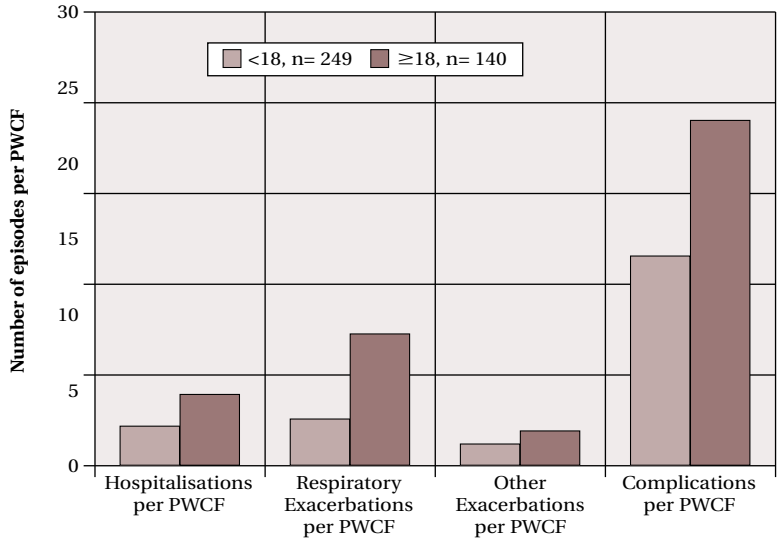


Table 9: Complication rates, paediatric vs. adult

Complication Rates per PWCF, Major Categories					
Age Total no. in group Ave age of group in yrs	< 18 270 9		≥18 119 25		Ratio of Episode rate Adult to Paed
Type of Complication	Total number	Rate per person	Total number	Rate per person	
Had No Complication	9	0.03	2	0.02	0.5 : 1
Cardio/Pulmonary	247	0.91	154	1.29	1.4 : 1
Gastrointestinal	282	1.04	146	1.23	1.2 : 1
Miscellaneous	117	0.43	142	1.19	2.8 : 1

Figure 24 charts the most frequently occurring complications from all systems and shows a higher proportion of adults than paediatric PWCF for all common complications, with the exception of 'chronic staphylococcus'. Over 80% of both groups feature 'pancreatic insufficiency' and this is no doubt related to genotype. There is a higher frequency of 'osteoporosis', 'clubbing', 'diabetes requiring insulin' and 'chronic pseudomonas' which are all related to age. Of note is a similar rate of infection with MRSA in both groups which is slightly less than 10%.

Other complications are shown in detail in charts for the "Cardio/pulmonary" category (Figure 25) and the "Gastrointestinal" category (Figure 26) [N.B.: the most frequently occurring complications in these categories have been included in Figure 24]. Note that the scale is from 0% to 20% in these two charts and that no complication surpasses the 10% mark in either group with the exception of DIOS in the adults. The percentage of PWCF who had "no complications" is shown on all charts for comparison.

Those complications that appear in Table 9 listed as 'Miscellaneous' are shown in detail in Figure 24: 'clubbing', 'diabetes requiring insulin', and 'osteopenia/osteoporosis'.

Figure 24: Frequently occurring complications, paediatric vs. adult

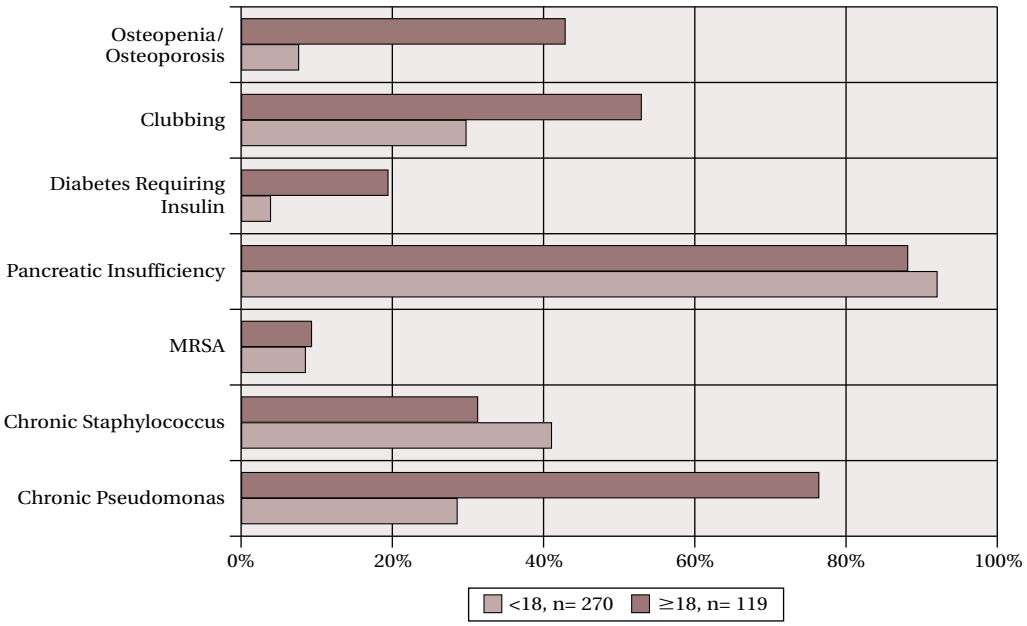


Figure 25: Cardio/pulmonary complications, paediatric vs. adult

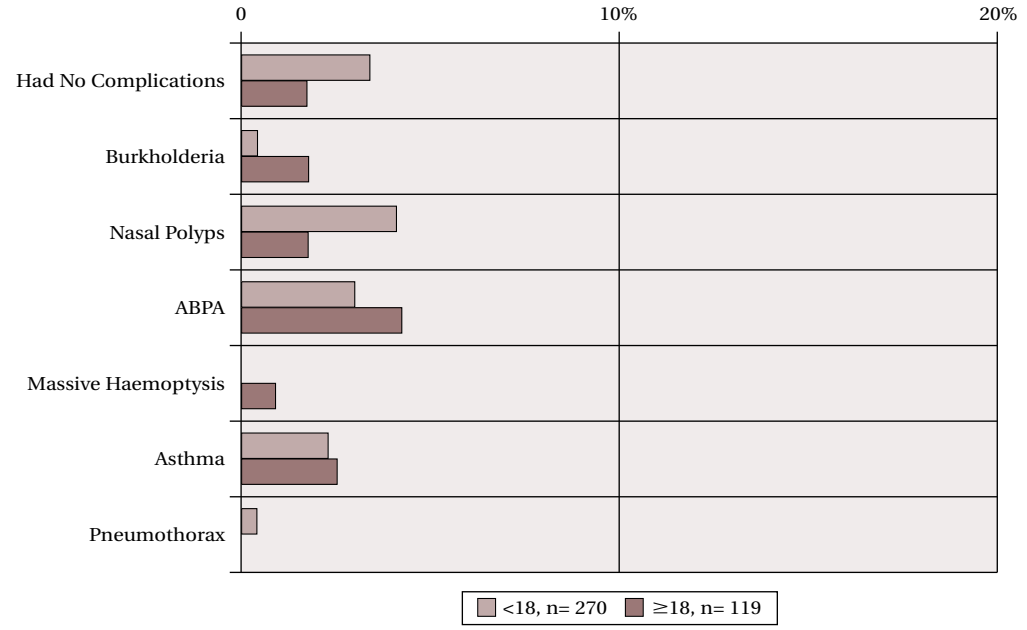
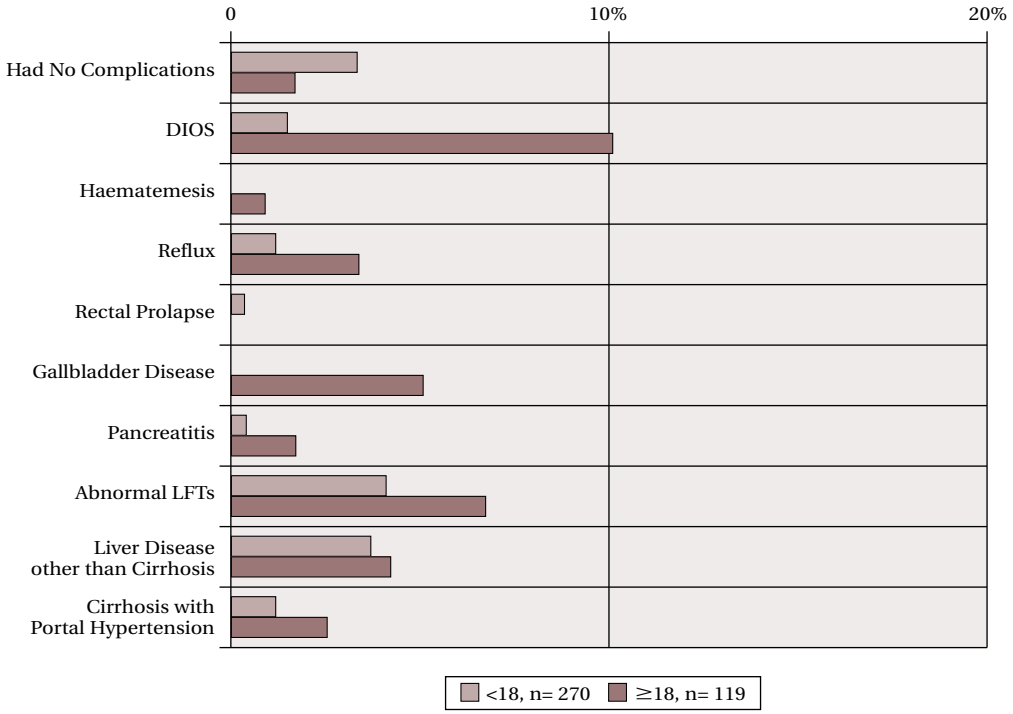


Figure 26: Gastrointestinal complications, paediatric vs. adult



Cultures

From the microbiological data come the type of culture samples taken and the type of specimen detected. Each microbiological sample may yield more than one positive result; so, the number of 'samples' in Table 10 are not necessarily discrete, individual investigations, but rather the

Table 10: Culture types, paediatric vs. adult

2005 & 2006 Annual Assessments				
Age	< 18		≥18	
Total no. in group	270		119	
Ave age of group in yrs	9		25	
Type	**No.**	**rate**	**No.**	**rate**
Sputum samples	1212	4.5	910	7.6
Cough Swab samples	695	2.6	33	0.3
Throat Swab samples	188	0.7	7	0.1
Nasal Swab samples	37	0.1	4	0.03
BAL samples	11	0.04	4	0.03

total number of positive results. What is intended to show is the relative frequency of microbiological results and where they come from. Also, Table 10 reveals the relative frequencies of the type of sample within each age group. The rate of sputum samples in the

adult PWCF is considerably higher than in the paediatric group, while the rate of cough swabs in the paediatric group is far higher than in the adult group. For both, the rate of BAL samples is very low. Annual Assessments from 2005 and 2006 have been combined.

If all of the sputum results are counted according to culture type, there were over 2000 positive specimens taken from 389 PWCF in this sample of annual assessments; or over 5 positive cultures per person. The proportion of the twelve most frequently occurring results are shown in Table 11, and the proportions of each type of culture are shown in Figure 27. These are in line with what one would expect in this population.

Figure 27:
Proportion of 12 most frequently occurring cultures

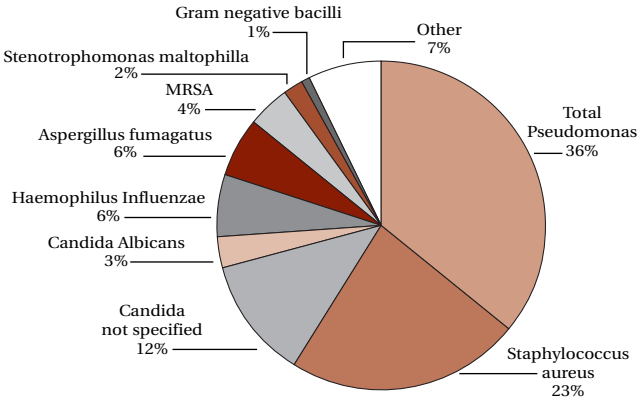


Table 11: Twelve most frequent positive cultures

	Culture Name	% of total number of cultures
1	Pseudomonas aeruginosa (Mucoid status not reported)	26%
2	Staphylococcus aureus	23%
3	Candida not specified	12%
4	Pseudomonas aeruginosa (Mucoid)	7%
5	Haemophilus influenzae	6%
6	Aspergillus fumagatus	6%
7	MRSA	4%
8	Candida: Albicans	3%
9	Stenotrophomonas maltophilia	2%
10	Pseudomonas aeruginosa (Non-mucoid)	2%
11	Gram negative bacilli	1%
12	Pseudomonas fluorescens	1%
	Total	**93%**

If we turn to the PWCF and summarise their culture results, we can calculate the number of cultures produced by a given set of PWCF. Table 12 shows the total number of cultures for each microbe, represented by the number of PWCF in each age group, paediatrics and adults. The following points may be made:

- There appears to be a higher occurrence of Haemophilus influenzae in the paediatric group (36%) than the adult group (11%);
- There is also a higher occurrence of Staphylococcus aureus in the paediatric group (58%) and this has been shown in other studies;

- The occurrence of Pseudomonas aeruginosa (all varieties) is far higher in the adult group; with the exception of Pseudomonas alcaligen and Pseudomonas fluorescens which occur with the same frequency in both groups;
- The paediatric group has a far higher rate of 'other' types of cultures (outside of the 12 cultures of greatest interest).

It is heartening to note that there were only 6 positive cultures for Burkholderia Cepacia Complex from the entire group of 389 annual assessments for both 2005 and 2006.

Table 12: Pathogens of interest, paediatric vs. adult

PWCF with at least one positive culture in 2005 & 2006						
2005 & 2006 Annual Assessments						
Age	< 18			≥18		
Total no. in group	270			119		
Ave age of group in yrs	9			25		
Culture Type	**No. of PWCF***	**Total no. Cultures**	**% age of group**	**No. of PWCF***	**Total no. Cultures**	**% age of group**
Aspergillus Fumagatus	30	63	11%	18	62	15%
Burkholderia Cepacia Complex: All Genomovars	2	2	0.7%	2	4	1.7%
Haemophilus Influenza	97	215	36%	13	17	11%
MRSA	25	82	9%	11	36	9%
Pseudomonas aeruginosa Mucoid status not reported	95	263	35%	69	302	58%
Pseudomonas aeruginosa Mucoid	27	47	10%	39	107	33%
Pseudomonas aeruginosa Non Mucoid	8	8	3%	14	24	12%
Pseudomonas fluorescens	9	10	3%	3	6	3%
Pseudomonas alcaligen	3	5	1%	1	4	0.8%
Staphylococcus aureus	157	510	58%	42	132	35%
Stenotrophomonas maltophilia	15	29	6%	7	17	6%
Streptococcus pneumoniae	16	18	6%	0	0	–
TOTAL "Pathogens of Interest" Other Cultures	**202**	**910**	**75%**	**64**	**245**	**54%**

* = Number of PWCF with at least one positive culture in 2005/06

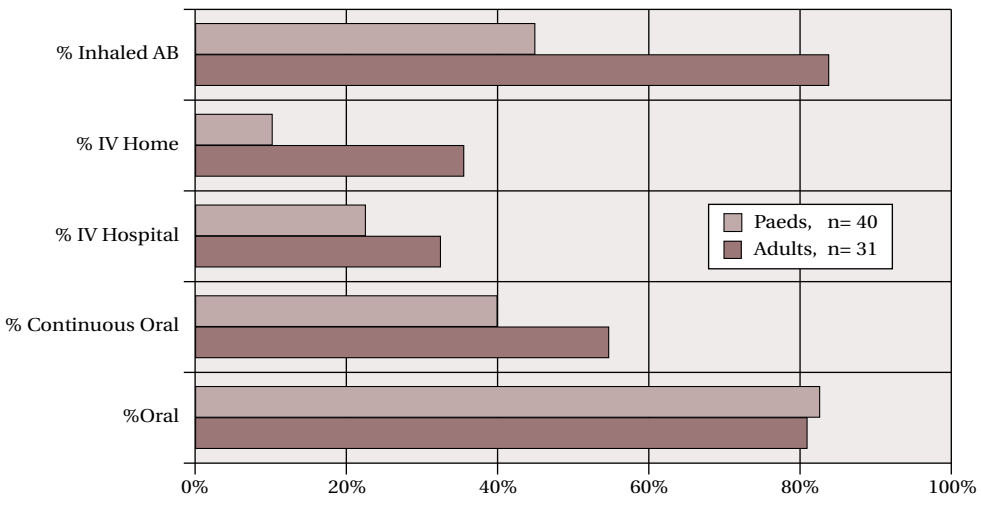
Antibiotics

Antibiotic (AB) data is collected annually, but it is retrospective from the Annual Assessment date. So, if a person has their annual assessment on January 1st, antibiotic data will be transcribed for the previous 12 months; that is, the year just up to the annual assessment date. In contrast, if a person has an annual assessment on December 31st of a given year, antibiotic data will be collected for the present year. In order to obtain an 'annual' picture of antibiotic consumption, we have taken all those PWCF who had 2006 Annual Assessments, and have extracted their complete 2005 antibiotic data in order to get a full 12-month set of data. Because of these restrictions there are smaller numbers of PWCF in the two groups, paediatric (40) and adult (31); but they are roughly similar in size. Table 13 shows the three separate presentations and some of the differences in antibiotic consumption between the two groups.

Table 13: Antibiotics by route of administration; paediatric vs. adult

2005 Antibiotic Usage (retrospective from 06 AA's)				
Age	**<18 yrs**		**≥18 yrs**	
n	**40**		**31**	
Mean age	10 years		26 years	
Median age	10 years		24 years	
ORAL	n	%	n	%
Continuous Oral	16	40%	17	55%
Non-continuous Oral	17	43%	8	26%
Total Oral	33	83%	25	81%
INHALED	18	45%	26	84%
IV				
No. PWCF IV Hosp	9	23%	10	32%
No. PWCF IV Home	4	10%	11	35%
IV Hosp days per PWCF	9		20	
IV Home days per PWCF	6		25	
Total IV days per PWCF	**14.5**		**45.7**	

Figure 28: Antibiotic route of administration; paediatric vs. adult



In summary:

- There are no discernible differences in the two groups with respect to oral antibiotics, although the adult group has a slightly higher proportion on continuous oral antibiotics and the paediatric group has a higher proportion taking non-continuous oral antibiotics.
- The percentage of adults on continuously inhaled antibiotic is roughly twice the percentage of paediatric PWCF.
- The major differences between the two groups are in the two intravenous antibiotic categories.
- There are a higher proportion of adults who take IV antibiotics both at home and in hospital; and the number of days per person annually is notably higher in the adult group.

The data in Table 13 is represented in a bar chart in Figure 28 and show the larger differences.

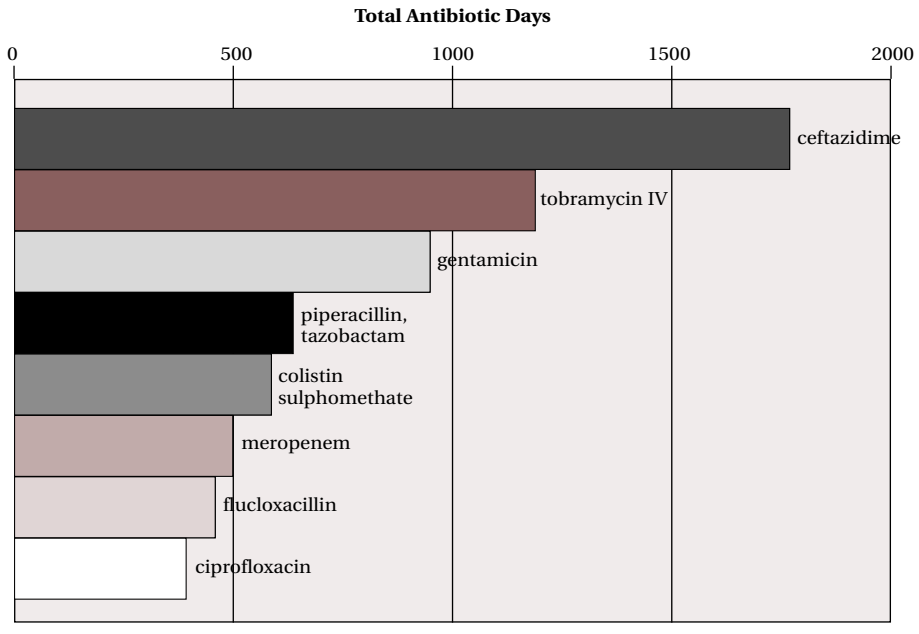
These observations are to be expected especially if one takes into consideration the percentage of each group that display positive Pseudomonas cultures. Unfortunately the numbers of PWCF in these groups is too small to conduct statistical testing. In future years, as data accumulates we will be able to test these observations to see if the differences prove significant.

Most Frequently Prescribed IV Antibiotics

It is useful to examine the prescribing trends in terms of the eight most frequently prescribed intravenous antibiotics. Again, we are selecting only the annual records from those who have complete yearly totals for 2005. We can calculate all of the days for each of the antibiotics prescribed and show them in rank order (Figure 29).

This pattern is not surprising given the nature of the cultures, as these antibiotics are primarily administered to treat pseudomonas infection.

Figure 29: Rank order of IV antibiotics



If we then look at the number of days prescribed and split this into whether the antibiotic was given at hospital, or at home; the difference favours hospital administration (Figure 30).

Figure 30: IV antibiotic administration; IV Hospital vs. IV Home

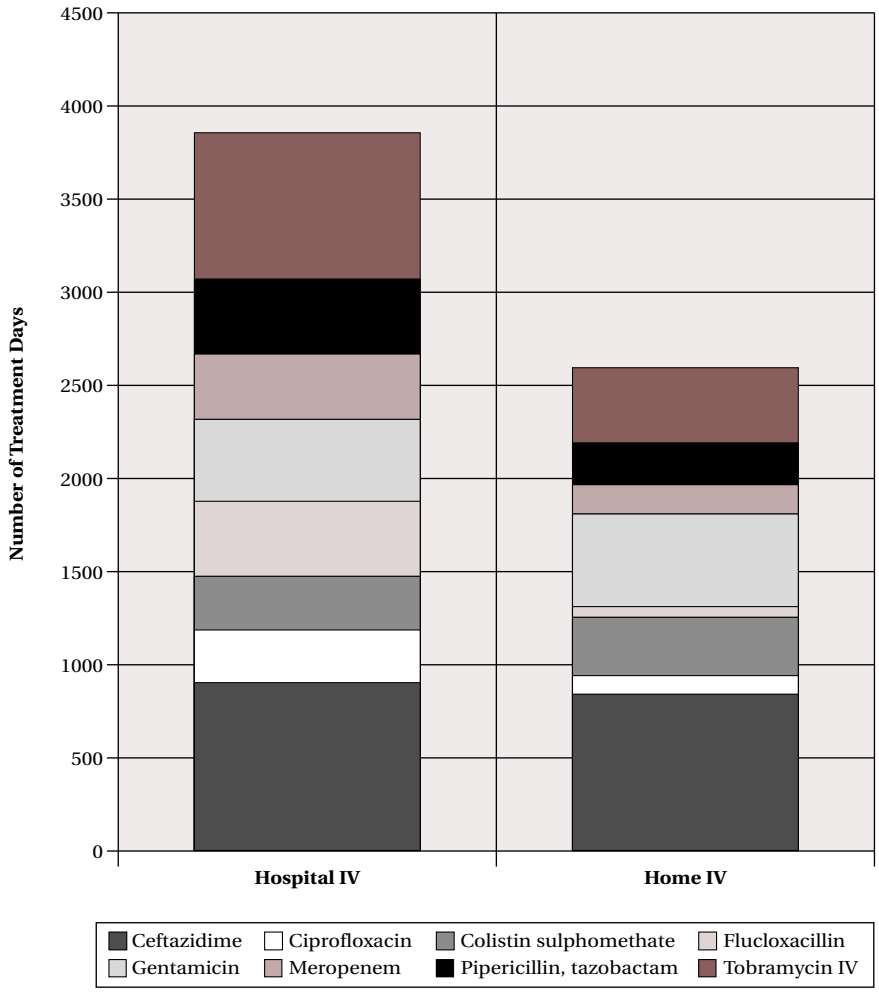


Table 14: Proportion of IV days treatment; paediatric vs. adult

Proportion of treatment days		
Age Group	<18	≥18
Hospital IV	64%	57%
Home IV	36%	43%

Finally, we can compare the paediatric age group with the adult age group (Table 14). Here we find that the differences are small, but of the under-18 group, 64% of their IV treatment is in hospital, versus 57% of the IV treatment of the ≥18's.

Overall, we found that the average number of days for each of the selected antibiotics for each prescribed course is 14 days in IV Hospital courses, and 16 days in IV Home courses.

Pulmonary Function and BMI

As we are interested in analysing possible gender differences and age differences, we have combined two years data for summary: 2005 and 2006. The data from annual assessments are all taken from separate PWCF.

PFT and BMI explained

Pulmonary function test (PFT) and height/weight (from which you can calculate Body Mass Index, or BMI) are generally measured at the same time. Many studies have shown that pulmonary function and body mass index are positively associated.

The pulmonary function tests recorded are 'Forced Expiratory Volume in 1 second' (FEV_1) and 'Forced Vital Capacity' (FVC). Both these tests are an indication of the condition of lung functioning. These results are usually compared with other people in the same are group who are of the same sex, weight and height. These values are than calculated as a 'percent of the predicted' result for the normal population of the same age, sex height and weight. If a value is over 80% (for either FVC–% predicted) this is considered within the normal range. [Pulmonary function tests are not normally carried out in children under 4/5 years old.]

The BMI is an indication of the relationship between height and weight of a person. The height and weight are generally taken every time pulmonary function tests are performed, so the BMI can be calculated alongside the PTF's. BMI is an important figure to track over time, as it will give an indication of nutritional status and growth.

In our data, we have separated the groups by sex and then taken an average of all of the people within an age group (band).

Table 15: Pulmonary function test summary 2005 & 2006

		Males			Females	
		Mean FEV_1 %-Predicted	Mean FVC %-Predicted		Mean FEV_1 %-Predicted	Mean FVC %-Predicted
Age Bands	**N**	**Males**	**Males**	**N**	**Females**	**Females**
5–<10	47	92	91.9	36	85	86.7
10–<15	40	71	79.8	35	74	80.6
15–<20	34	72	82.7	34	71	81.5
20–<25	31	60	73.2	19	57	72.2
25–<30	10	55	74.3	11	55	78.6
30–<40	3	55	74.3	9	47	60.1
≥40	2	32	62	3	49	70.7
Total analysed	**167**			**147**		

Table 15 displays results from 167 males and 147 females ranging in age from 5 years to over 40 years. Two figures (Figures 31 and 32) represent the data shown in Table 15. The figures show negligible differences between the sexes over all of the age bands. However, in both FEV1-% predicted and in FVC-% predicted the mean value for females in the lowest age band is slightly lower than in males. This may be relevant and related to 'age at diagnosis', or it may merely be an artefact. But, it is an observation that occurred in the same data in the 2005 Annual Report and so it merits further study. As with most of the data in this and previous reports, we must wait for greater data accumulation before we can delve too deeply into analysis.

Figure 31: FEV_1 – % predicted Males vs Females in age bands

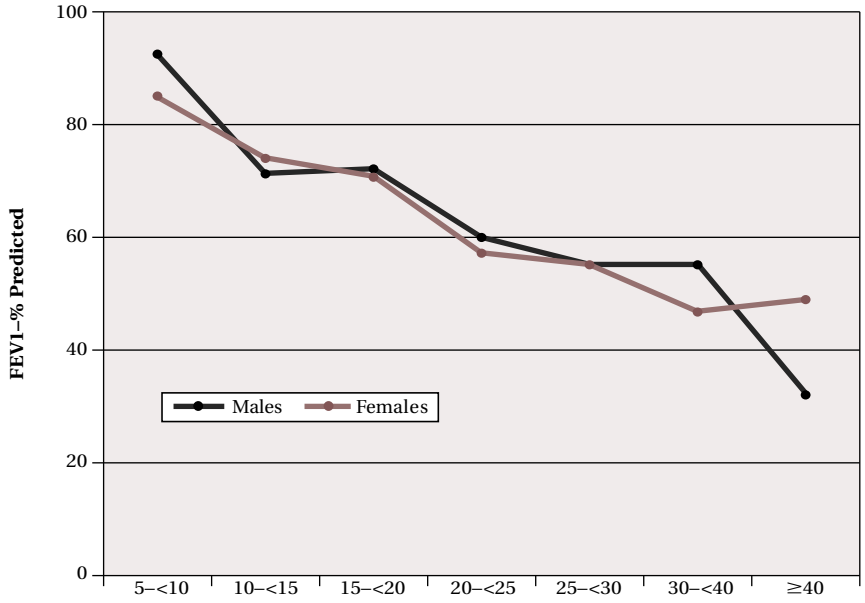
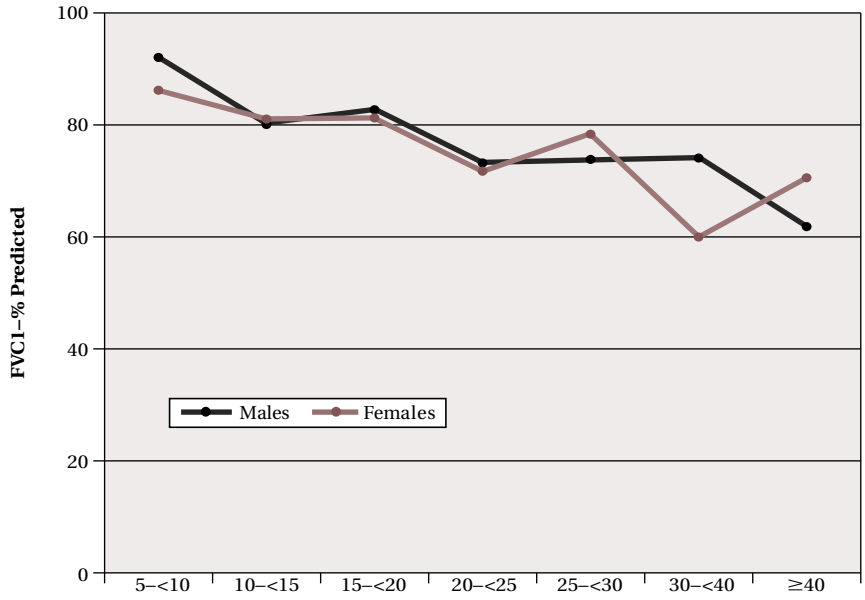


Figure 32: FVC – % predicted, males vs females in age bands



Some simple observations can be made, however:

- Both sexes in both sets of PFT data already show deterioration by the age of five.
- This is accompanied by a further deterioration in function in the 10–<15 age group, followed by a plateau until the 15–<20 age group. Interestingly, the "plateau" occurs during normal growth spurts.
- Later, a further deterioration occurs after age 20, which again plateaus during the late 20's.
- Because the numbers are so small in the later age bands, it is probably invalid to draw any conclusions beyond the age of 30.

It is interesting to see similar curves in both sexes throughout the age bands. The apparent differences, in the very young and in the over-30 age groups, merit further attention and study to see if they persist as more data accumulates into the future.

Table 16: BMI Summary; 2005 & 2006 combined

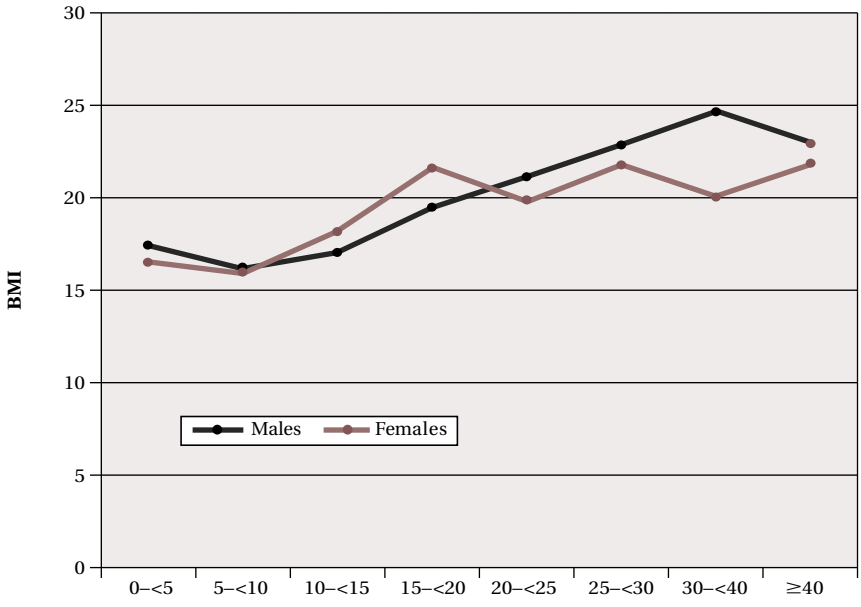
Age Bands	N	MALES	N	FEMALES	Total in set
0–<5	17	17.4	15	16.4	32
5–<10	47	16.1	36	15.9	83
10–<15	40	17	35	18	75
15–<20	34	19.4	34	21.5	68
20–<25	31	21.1	19	19.8	50
25–<30	10	22.8	11	21.7	21
30–<40	3	24.7	9	20	12
≥40	2	22.9	3	21.8	5
Total analysed	184		162		346
BMI NOT done	0		0		
Total AA's in set	184		162		346

Table 16 shows a summary of the Body Mass Index (BMI) across age bands. We do not have large data numbers yet, but in time we should be able to compare our data on a percentile basis. That is, once the group data is large enough, we will be able to compare our groups and individuals against a "standard BMI" for the age group.

The data from Table 16 is depicted in chart form in Figure 33. Again, we do not see any striking differences between the sexes, but the male group shows a steady incline throughout the age bands, while the female group displays a plateau pattern after the age of 20 years. (Note that the numbers in both groups are small after age 25.) Both patterns may be typical. For many people growth continues throughout the twenties, but we do not yet know how to predict growth in the PWCF population.

It is important to track an individual's BMI over time. Changes, especially declines in BMI should be noted and corrected. Also, if a person does not achieve a minimum expected value for their sex or age group, they should be kept under close surveillance. The CFRI produces individual charts for each PWCF and we can superimpose these onto standard charts. This would show, in graphic form, declines over time which would indicate further treatment assessment.

Figure 33: BMI Comparison males vs. females in age bands



Nutrition

An annual visit to the CF Dietician is extremely important. This is when growth and weight maintenance can be checked and strategies for improvements are initiated. From the CFRI records we can see that very few PWCF miss that annual appointment. To get an overall representation of the number and percentage of PWCF who take various forms of feeds and supplements, we have combined 2005 and 2006 annual assessment data (Table 17).

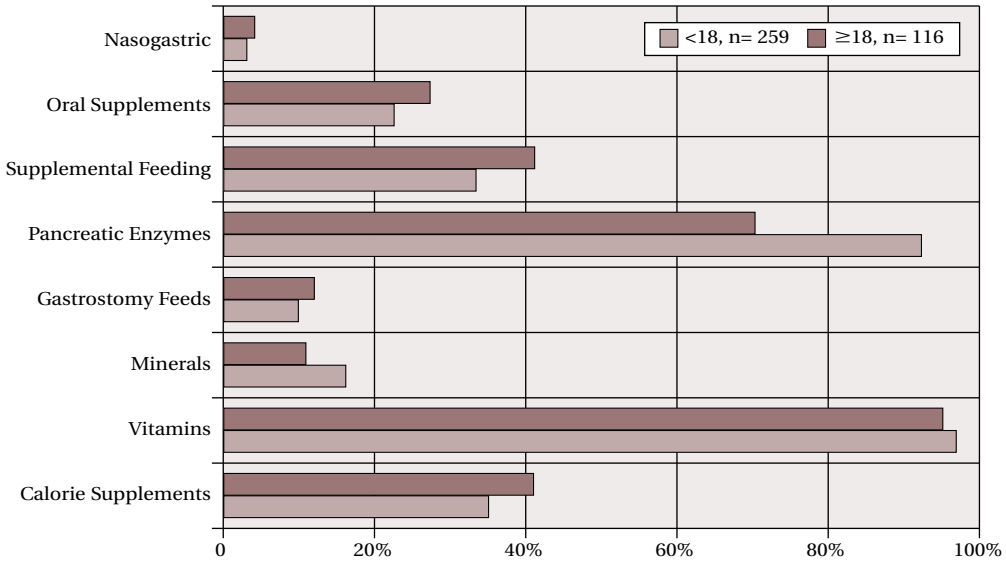
Table 17: Nutrition summary 2005 & 2006

	< 18		≥18	
Total no. in group	259		116	
Ave age of group in yrs	9		25	
Type	**No.**	**% of group**	**No.**	**% of group**
Calorie Supplements	91	35%	48	41%
Vitamins	252	97%	111	96%
Minerals	42	16%	13	11%
Gastrostomy Feeds	26	10%	14	12%
Pan Enzymes	240	93%	82	71%
Supplemental Feeding	87	34%	48	41%
Oral Supplements	59	23%	32	28%
Nasogastric	8	3%	5	4%
Parenteral Feeds	0	0%	0	0%
Other Supplement Feeds	0	0%	0	0%

Nutrition and dietary care often remain fairly standard and we see similar proportions of each group taking nutritional products.

Figure 34 shows the similarity in percentages of each age group who consistently take appropriate supplements. Of note is the fact that neither age group recorded either 'parenteral feeds' or 'other supplement feeds' during 2005 or 2006. This data supports the data in previous sections which shows the proportions of PWCF who are pancreatic insufficient: over 70% of both groups take pancreatic enzymes. It may also be used in the future to correlate body mass index with the type of nutritional supplement consumed.

Figure 34: Nutrition summary 2005 & 2006



Physiotherapy

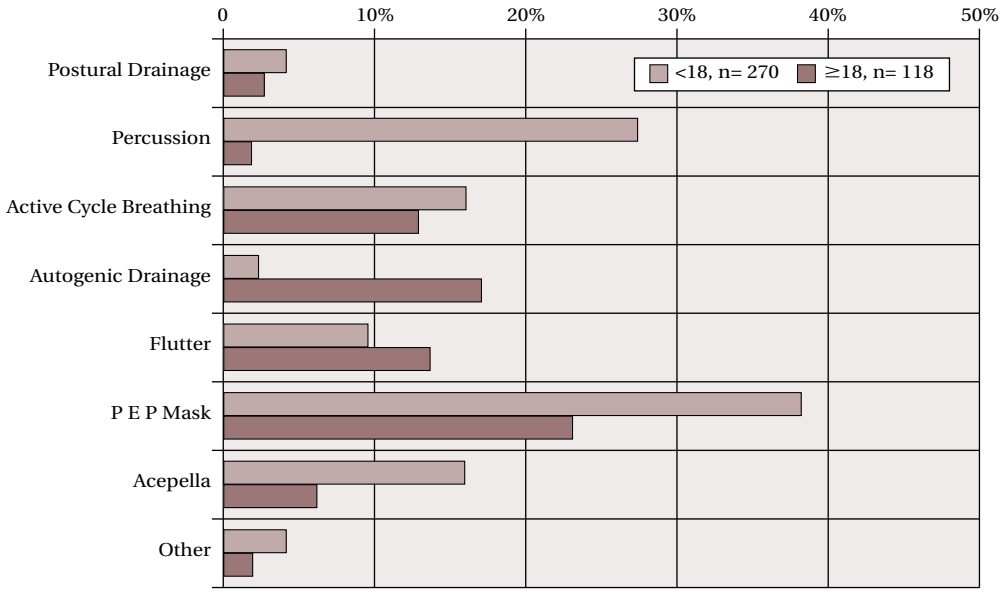
Table 18: Physiotherapy summary, 2005 & 2006

	< 18	% seen by physiotherapist	≥18	% seen by physiotherapist
Total no. in group	270		118	
Total Seen by Physio at AA	246	91%	98	83%
Ave age of group in yrs	9		25	
Type	**No.**	**% of group**	**No.**	**% of group**
Postural Drainage	11	4%	3	3%
Percussion	74	27%	2	2%
Active Cycle Breathing	43	16%	15	13%
Autogenic Drainage	6	2%	20	17%
Flutter	26	10%	16	14%
Positive Expiratory Pressure Mask	103	38%	27	23%
Acapella	43	16%	7	6%
Other	11	4%	2	2%
Regular Exercise	270	100%	118	100%

We have combined both 2005 and 2006 annual assessment records for this summary. Consistent, quality physiotherapy is essential to PWCF. Approximately 20% of adults and 40% of paediatric PWCF practice more than one modality of physiotherapy on a regular/daily basis. And all PWCF from both groups take regular exercise (Table 18). There are some other notable differences between practices in the two groups. The 'PEP Mask', 'Percussion', and 'Acapella' are practiced by a larger proportion of PWCF in the under 18 year age group; while 'Autogenic Drainage' is found in a higher proportion in the adult group.

This can be seen in Figure 35. Although the CFRI data indicates that not everyone is seen on the annual assessment date, this should be verified by cross-referencing to the physiotherapy department records.

Figure 35: Physiotherapy summary 2005 & 06



Long Term Medications

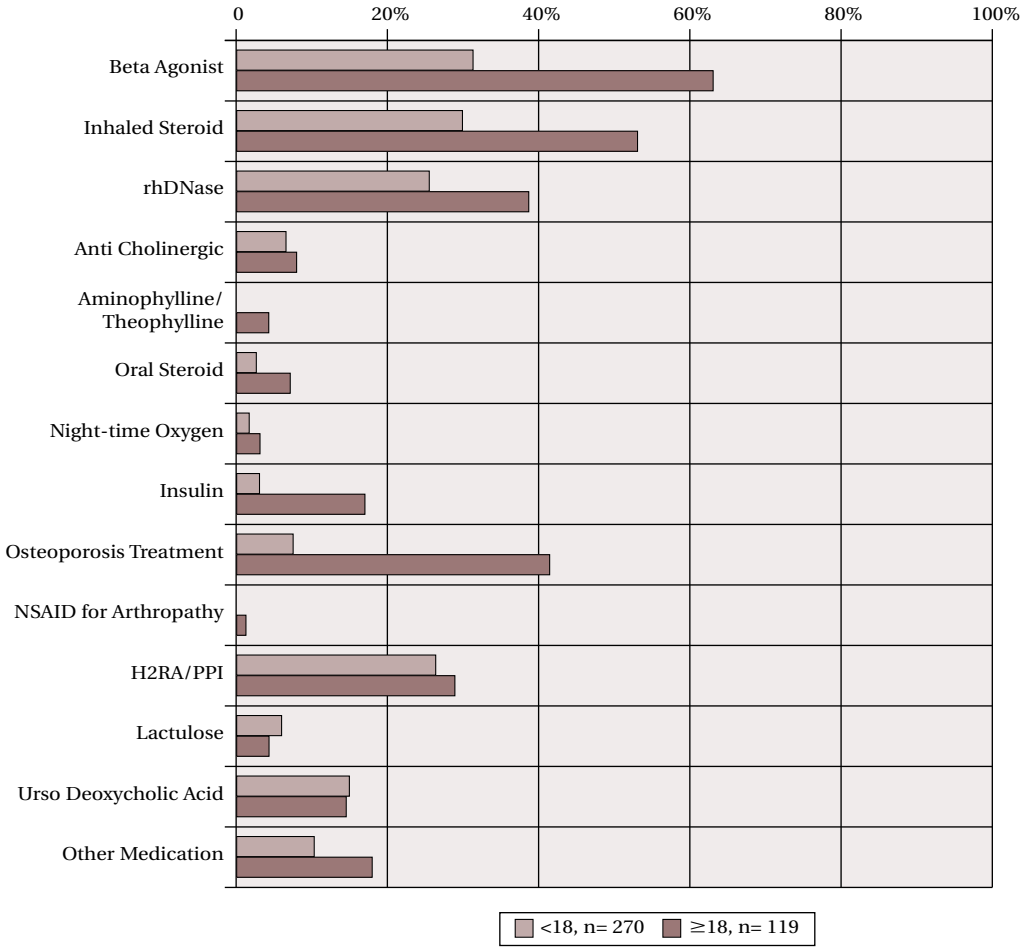
Table 19: Long term medications summary, 2005 & 06

	< 18		≥18		Ratio Adult percentage to Paediatric percentage
Total no. in group	270		119		
Ave age of group in yrs	9		25		
Type	**No.**	**% of group**	**No.**	**% of group**	
Beta Agonist	84	31%	75	63%	2.0
Inhaled Steroid	81	30%	63	53%	1.8
rhDNase	69	26%	46	39%	1.5
Anti Cholinergic	17	6%	9	8%	1.2
Aminophylline /Theophylline	0	0%	5	4%	n/a
Oral Steroid	6	2%	8	7%	3.0
Night-time Oxygen	3	1%	3	3%	2.3
Insulin	7	3%	20	17%	6.5
Osteoporosis Treatment	20	7%	49	41%	5.6
NSAID for Arthropathy	0	0%	1	1%	n/a
H2RA/PPI	70	26%	34	29%	1.1
Lactulose	15	6%	5	4%	0.8
Urso Deoxycholic Acid	39	14%	17	14%	1.0
Other Medication	27	10%	21	18%	1.8

Long term medications describe those that are taken every day, often to treat underlying conditions that have developed with age. These include insulin-dependent diabetes and osteoporosis. In order to illustrate this age-related attribute, we have calculated a ratio of Adult PWCF to Paediatric PWCF using the percentages in each group (Table 19). By examining the ratio, we can see that insulin is prescribed 6.5 times more in adult PWCF, than in paediatric PWCF; and osteoporosis treatment is 5.6 times more likely to be prescribed in the adult PWCF. Other long-term medications that reflect the progression of the condition are the use of beta agonists, inhaled and oral steroids, and rhDNase. Figure 36 shows these relative differences. Forty-one per cent of adults take osteoporosis treatment, and this correlates with the 'complications' figure of 40%; 17% of adults are taking daily insulin and 20% of adult PWCF report 'diabetes' as a complication. Some of the medications are related to gastrointestinal/liver problems, and there are similar proportions in each age group reliant on these medications. The proportional use of these products reflects the presence of liver involvement in a person's CF. The use of night-time oxygen remains very low at less than 3% in both groups.

This data is useful as validation evidence to confirm the proportions of complications within each group. Also, since these medications are taken every day, this information can be used in resource assessment analysis when one wishes to predict the costs of treatment.

Figure 36: Long term medications summary, 2006 & 2006



Social Data

This year we have chosen to examine just one centre's social data (over both years, 2005 and 2006) as it has returned the most complete social information in the registry. There are similar numbers in the two groups, paediatric and adult, and the total is 85 PWCF. This represents approximately 13% of the total Irish CF population. Some interesting points may be made from this sample:

- Of the adult group, 36% are living independently of their family home.
- Four (3 females and one male) are married (10% of the adult group).
- 62% are working full-time or part-time.

'Time off' school or work is a reliable indicator of well-being. Among the adult group, 63% had either "no days off" or "less than 2 weeks off" work or school. This figure was even greater in the paediatric group which reported 89% who had either "no days off" or "less than 2 weeks off" work or school. Only 3 (5%) PWCF (one <18; and 2 adults) reported "more than 8 weeks off" in a twelve month period.

Table 20: Social data summary, 2005 & 2006

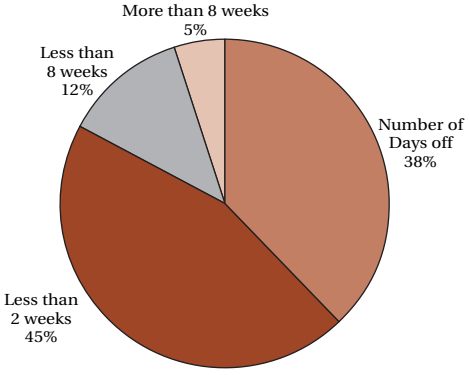
One Centre with Data for 2005 & 2006				
	<18, n=46	**%**	**≥18, n=39**	**%**
Age Range	3–17		18–46	
Mean age	10 years		25 years	
Median age	11 years		23 years	
	Number	**%**	**Number**	**%**
Independent living	n/a		14	36%
Married	n/a		4	10%
Working Full time	n/a		14	36%
Working Part time	1	2%	10	26%
Total working	1	2%	24	62%
Total who have gone to 3rd level education	n/a		16	41%
Time OFF School or Work				
No days off	16	43%	6	25%
Less than 2 weeks	17	46%	9	38%
Less than 8 weeks	3	8%	4	17%
More than 8 weeks	1	3%	2	8%
No data for Time OFF	9		15	
Number in Work or School group	37		24	
Leisure Time				
Number who holidayed in Ireland?	9	20%	7	18%
Number who holidayed abroad?	14	30%	15	38%
Number of alcohol active?	2	–	29	74%

Holidays were reported by 50% of the paediatric group and 56% of the adult group, and twice as many adults holidayed abroad as in Ireland.

This type of social data is very important to have as it can be used to verify other findings, such as hospitalisations.

It is very heartening to see that only 5% of the whole group had 'more than 8 weeks off' from either school or work. CF can be a weakening condition but it is by no means incapacitating.

Figure 37:
Time-off work or school, 2005-06



Financial

The financial summary (Table 21) lists the expenses for the CFRI in 2005.

The following points should be noted:

- The only source of income for the CFRI is the Department of Health & Children, through the Health Service Executive which has been an annual grant of €132,000 beginning in 2003.
- Development costs were kept lower than previous years, in an attempt to remain within the confines of the budget.
- There is a deficit which increases each year because the present grant level is insufficient to cover the essential expenses of the CFRI. It is hoped that this will be addressed in 2007.

The accounts were prepared and audited by Farrell Grant Sparks, Chartered Accountants, Molyneux House, Bride Street, Dublin 8.

Table 21: Financial Summary, 2005

Financial Summary 2005	
	€
INCOME (Grant)	132,000
SYSTEM SPECIFICATION Hosting Fee, Domain maintenance, Security Certificate	12,419
DEVELOPMENT COSTS Database Application, programming	10,929
HARDWARE Laptop, printer, software	n/a
TRAVELLING EXPENSES	7,962
ADMINISTRATION COSTS Telephone, heat, electricity, printing, office supplies, insurance	7,336
ANNUAL REPORT Design, printing	5,261
DEPRECIATION	2,072
WAGES and SALARIES PAYE, PRSI, Employers PRSI	99,727
TOTAL COSTS	145,706
DEFICIT	13,706

Acknowledgements

The Registry Management Committee of the CF Registry has always given its full support to all activities and is gratefully acknowledged for that support. We are about to move through a change process and they will continue to form the backbone of the new organisation which will provide much needed continuity in the new circumstances.

The Health Service Executive has been supporting the CFRI with an annual grant since 2001, and this is most appreciated.

Since 2005, the School of Public Health and Population Science at UCD has provided the CFRI with office space and other infrastructural services. As the CFRI moves towards generating research outputs, this relationship will continue to strengthen.

Much of the care of PWCF is carried out selflessly by the CF Nurses Specialists. They are key to the coordination of the CF Specialty teams and provide the CFRI with continuous support and assistance.

Each brings us closer to the creation of a European CF Registry. Colleagues in other countries continue to provide advice and assistance and I thank them for this. Not only are there Euro colleagues, but there are several new Irish CF consultants who are enthusiastic and keen to make suggestions for improvement and this contributes to a dynamic atmosphere for the CFRI.

There are many PWCF who do not complete another year. It is my hope that the CFRI will contribute to a reduction in this number. I would like to dedicate this Annual Report to all PWCF in Ireland.

Publications from CFRI, 2006

L Foley, Y Bimpeh, S Zhou, C Kelleher The gender gap in cystic fibrosis: how early does it emerge? Faculty of Public Health Medicine Summer Scientific Meeting 30-31 May 2006. Poster. CF Registry of Ireland, School of Public Health and Population Sciences, University College Dublin

"The national Cystic Fibrosis Registry of Ireland will endeavour to collect and analyse information relating to cystic fibrosis in order to improve the quality of care for all of the people with cystic fibrosis in the Republic of Ireland."

Mission Statement of the Cystic Fibrosis Registry of Ireland

Cystic Fibrosis is an inherited condition that affects many body functions such as breathing, digestion, and reproduction. This lifelong condition usually becomes more severe with age and affects both males and females in equal proportions. The symptoms and severity of cystic fibrosis vary from person to person. The majority of people have both respiratory and digestive problems. There is no cure for cystic fibrosis. Life expectancy has increased steadily over the past 20 years, and today cystic fibrosis is no longer exclusive to childhood.

Better treatment strategies help to improve the length and quality of life of people with CF by controlling their symptoms. Improved treatments can be developed using patient registries. Cystic fibrosis registries gather information on all aspects of a patient's condition. They act as information storehouses for infection and treatment statistics. Detailed analysis of this information can yield significant findings about the most effective treatments for CF. It is through these analyses that better management of CF may be achieved.

Cystic Fibrosis Registry of Ireland
School of Public Health and Population Science
Woodview House
University College Dublin
Belfield, Dublin 4
Ireland

www.cfairegistry.org

CFRI
The Cystic Fibrosis Registry of Ireland