

Burden of cystic fibrosis in children <12 years of age prior to the introduction of CFTR modulator therapies

Kathryn Bresnick,¹ Emilio Arteaga-Solis,² Stefanie J Millar,³ Glen Laird,⁴ Cecile LeCamus²

To cite: Bresnick K, Arteaga-Solis E, Millar SJ, *et al.* Burden of cystic fibrosis in children <12 years of age prior to the introduction of CFTR modulator therapies. *BMJ Open Res* 2021;**8**:e000998. doi:10.1136/bmjresp-2021-000998

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjresp-2021-000998>).

Received 24 May 2021
Accepted 19 October 2021



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¹Real World Evidence, Vertex Pharmaceuticals Incorporated, Boston, Massachusetts, USA

²Global Medical Affairs, Vertex Pharmaceuticals Incorporated, Boston, Massachusetts, USA

³Biostatistics & Medical Writing, ICON PLC, North Wales, Pennsylvania, USA

⁴Biostatistics, Vertex Pharmaceuticals Incorporated, Boston, Massachusetts, USA

Correspondence to

Dr Kathryn Bresnick;
katie_bresnick@vrtx.com

ABSTRACT

Background Cystic fibrosis (CF) is a genetic, multisystemic, progressive and life-shortening disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. Different genotypes have been linked to variations in disease progression among people with CF. The burden of illness (BOI) in children with CF is incompletely characterised, particularly as it relates to *CFTR* genotypes prior to the availability of the first CFTR modulators. This retrospective, cross-sectional, descriptive study evaluated the BOI in US children with CF <12 years of age prior to the first approval of CFTR modulators.

Methods Data from the US Cystic Fibrosis Foundation Patient Registry from 2011 were used to summarise key patient and disease characteristics using descriptive statistics, overall and grouped by age (0 to <2 years, 2 to <6 years and 6 to <12 years) and genotype (*F508del*/*F508del*, *F508del*/minimal function (MF), MF/MF, gating mutation on ≥1 allele, residual function mutation on ≥1 allele and *R117H* on ≥1 allele) group.

Results The analysis included 9185 children. Among 6-year-olds to <12-year-olds, mean (SD) per cent predicted FEV₁ in 1 s was 92.6% (17.5%). Among all children <12 years of age, the mean (SD) all-cause hospitalisation and pulmonary exacerbation rates in 2011 were 0.4 (1.0) and 0.3 (0.8), respectively. Most (93.6%) had ≥1 positive lung microbiology culture. CF-related medication and nutritional supplementation use was common across all ages and genotypes. More than half (54.7%) had ≥1 CF-related complication. Evidence of disease burden was observed across the age and genotype groups studied.

Conclusions Prior to the approval of the first CFTR modulator therapies in children <12 years of age, CF was associated with substantial BOI from an early age—including respiratory infections, hospitalisations/pulmonary exacerbations, need for supplemental nutrition and pharmacological treatments—irrespective of genotype.

INTRODUCTION

Cystic fibrosis (CF) is a genetic, multisystemic, progressive and life-shortening disease caused by a loss of CF transmembrane conductance regulator (*CFTR*) function resulting from mutations in the *CFTR* gene.¹ People with CF have mutations in both copies of the

Key messages

- What was the burden of illness of cystic fibrosis (CF) in US children <12 years of age prior to the first approval of CF transmembrane conductance regulator (*CFTR*) modulators?
- Prior to CFTR modulator therapies, CF was associated with substantial burden of illness from an early age—including respiratory infections, hospitalisations, pulmonary exacerbations, need for supplemental nutrition and pharmacological treatments—irrespective of genotype.
- The results of this retrospective, cross-sectional, descriptive analysis are consistent with the progressive nature of CF from infancy across childhood and demonstrate the substantial disease burden for children with CF, irrespective of genotype.

CFTR gene, which affects the activity of the *CFTR* protein. The deficiency in *CFTR* leads to manifestations that present as early as in utero and progress throughout life.^{1,2} Prenatally, abnormalities in the digestive, pancreatic and (in males) reproductive systems are observed.^{1,3} Between infancy and childhood, abnormalities of the pancreas, intestine, liver and airways result in malnutrition, poor growth and lung infections and inflammation.^{1,2} These manifestations require aggressive symptomatic therapies from an early age.^{4,5} Symptomatic therapies are essential to preserving lung function and maintaining adequate nutrition and growth.^{6,7} Inhaled agents, such as dornase alfa and hypertonic saline, and chest physiotherapy are used to improve airway clearance.^{6,7} Systemic and/or inhaled antibiotics and anti-inflammatory agents are used to treat lung infections.⁶ Pancreatic enzyme replacement therapy (PERT) and nutritional supplementation are used to maintain adequate nutrition and growth.⁶ With symptomatic therapies alone, the median predicted survival for people with CF in the USA was 36.8 (95% CI 34.7 to 40.3) years in 2011.⁸ This increased to 46.2 (95% CI

45.2 to 47.6) years in 2019 with advances in CF care that include the introduction of CFTR modulator therapies, which treat the underlying cause of disease.^{9 10}

More than 2000 *CFTR* gene mutations have been identified to date.¹¹ The classification of mutations is evolving from a system based on molecular mechanism¹² to one based on a combination of molecular mechanism and therapeutic approach/response.^{7 13} More than 80% of people with CF have at least one *F508del-CFTR* mutation, and genotypes can be classified based on presence of this common mutation.⁹ Minimal function mutations are a group of mutations that have no biologic plausibility of translated CFTR protein as predicted by the genetic sequence or for which in vitro testing supports lack of response to tezacaftor, ivacaftor or tezacaftor/ivacaftor and there is evidence of clinical severity on a population basis.¹⁴ Gating mutations are defined by a defect in the function of the chloride channel opening and closing, which results in significantly reduced chloride transport.^{11 12} Residual function mutations are characterised by the presence of chloride transport at the cell surface, although at a reduced level compared with normal.^{15 16} *CFTR* genotypes have been linked to variations in the progression of CF,¹⁷ and the burden of illness (BOI) in children with CF, particularly as it relates to *CFTR* genotype groups, is not fully characterised.

The objective of this study was to evaluate the BOI in children <12 years of age with CF in the USA prior to the first approval of CFTR modulators using retrospective, cross-sectional, descriptive analyses.

METHODS

The US Cystic Fibrosis Foundation Patient Registry (CFFPR) is an ongoing patient registry first established in the 1960s to collect information about the disease course of CF.¹⁸ The registry has excellent coverage of US patients with CF (approximately 84%) and captures patient demographic and clinical characteristics with high accuracy.¹⁸ CFFPR data from 2011 were used to describe key patient and disease characteristics in children with CF prior to the first approval of CFTR modulator therapies. In 2011, 27 111 individuals with CF were included in the US CFFPR.⁸ For inclusion into this study, individuals must have had a CF diagnosis with ≥1 physician visit at an accredited CF centre in 2011 and been <12 years of age as of 1 January 2011. All disease characteristics were reported directly by staff at accredited CF centres through an online data entry system. Disease characteristics queried for this study included pulmonary function and exacerbations, hospitalisations, lung microbiology, CF-related complications and use of nutritional supplementation and CF-related medications.

In children 6 to <12 years of age, lung function was characterised by per cent predicted FEV₁ (ppFEV₁). Spirometry is not routinely performed in children <6 years of age, and these data are not reported by the US CFFPR.⁸ The ppFEV₁ was calculated using Global Lung

Function Initiative 2012 equations,¹⁹ which are the current standard and were retroactively applied to 2011 data from CFFPR. The annual ppFEV₁ measure for each child was calculated as the average of the child's single-best measurement from each available quarter. The population mean was calculated as the average of the annual measures.

Mean number of hospitalisations and pulmonary exacerbations (PEX) per child were calculated as the total number of events during 2011 divided by the total number of children. A PEX was defined as a care episode with a 'pulmonary exacerbation' reported by the child's physician.

The percentage of children with positive lung microbiology was calculated as the proportion of children with ≥1 positive culture reported by the centre during 2011. Microorganisms included *Staphylococcus aureus*, methicillin-resistant (MRSA) and methicillin-sensitive *S. aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Burkholderia cepacia*, *Aspergillus* (any species) and nontuberculous mycobacteria.

The percentage of children using CF-related medications was calculated as the proportion of children with a center-reported CF-related prescription during 2011. CF-related medications included antibiotics, antifungals, mucolytics, nonsteroidal anti-inflammatories, hypertonic saline, bronchodilators, corticosteroids, pancreatic enzymes, acid blockers and ursodiol.

Use of nutritional supplementation was calculated as the percentage of children with any centre-reported use during 2011. Types of supplemental feeding mechanisms studied included oral, nasogastric, gastrostomy and jejunal tubes and total parenteral nutritional supplementation.

Centre-reported complications of CF during 2011 were collected through check-all-that-apply fields and included pancreatic, hepatobiliary, pulmonary, gastrointestinal and psychological conditions.

Results were summarised overall and by age and genotype groups using descriptive statistics. Counts and percentages were reported for discrete measures and means, and SDs were reported for continuous measures. Age groups were 0 to <2 years, 2 to <6 years and 6 to <12 years. Genotype groups studied were *F508del/F508del*, *F508del*/minimal function (MF), gating mutation on ≥1 allele, residual function (RF) mutation on ≥1 allele, MF/MF and *R117H* on ≥1 allele. Mutations included in each group are listed in online supplemental table S1. *R117H* was treated as a separate RF group because the registry had incomplete information on the associated poly-T and TG-tract mutations, which impact the clinical phenotype of these children. These common genotype groups do not encompass all patients with CF and are not all mutually exclusive; thus, the total number of patients included in the genotype analyses does not equal the total patient population in 2011.

Missing data varied by disease characteristic and were not imputed. The number of evaluable patients with

non-missing data is detailed for each characteristic and patient group.

Data availability statement

Data sharing is not applicable to this article as no data sets were generated or analysed by the coauthors in the present study. The US CFFPR collects and manages its own data and maintains processes for researchers to request summarised data (<https://www.cff.org/Research/Researcher-Resources/Tools-and-Resources/Patient-Registry-Data-Requests/>).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

RESULTS

Study population

A total of 9185 children met the inclusion criteria in 2011, including 4398 (47.9%) children with the *F508del/F508del* genotype, 1887 (20.5%) with *F508del/MF* genotypes, 439 (4.8%) with a gating mutation on ≥ 1 allele, 438 (4.8%) with an RF mutation on ≥ 1 allele, 336 (3.7%) with MF/MF genotypes and 262 (2.9%) with *R117H* on ≥ 1 allele. Sex was balanced overall and in all genotype groups; 49.9% of included children were female. The majority of children were identified as White (92.6%); however, the percentage ranged from 79.5% among MF/MF children to 96.5% among *F508del/F508del* children (table 1).

Pulmonary function, hospitalisations and pulmonary exacerbations

Among all children 6 to <12 years of age, the annual mean (SD) ppFEV₁ was 92.6% (17.5%) (table 2), and an estimated 15.8% of children had ppFEV₁ <75%. The mean (SD) ppFEV₁ was 92.2% (17.5%) among children with the *F508del/F508del* genotype, 92.1% (17.5%) among children with *F508del/MF* genotypes, 95.0% (16.6%) among children with a gating mutation on ≥ 1 allele, 98.3% (16.4%) among children with an RF mutation on ≥ 1 allele, 87.4% (19.1%) among children with MF/MF genotypes and 97.9% (11.8%) among children with *R117H* on ≥ 1 allele (table 2).

Among all children <12 years of age, the mean (SD) all-cause hospitalisation rate in 2011 was 0.4 (1.0). Annual hospitalisation rates by genotype and age groups are shown in figure 1A. In most genotype groups, the highest hospitalisation rate was seen among children 6 to <12 years of age compared with younger children. Across all age groups, the lowest overall rate of hospitalisation was seen in children with an *R117H* mutation on ≥ 1 allele and the highest among children with MF/MF genotypes.

Among all children <12 years of age, the mean (SD) annual rate of PEx was 0.3 (0.8). Annual PEx rates by genotype and age groups are shown in figure 1B. Overall and in most genotype groups, children 6 to <12 years of

age had a higher mean number of PEx compared with younger children in 2011. The lowest annual PEx rates were observed among children with RF or *R117H* mutations on ≥ 1 allele, and the highest were observed among children with *F508del/F508del*, *F508del/MF*, MF/MF genotypes or gating mutations on ≥ 1 allele.

Lung microbiology

Most (93.6%) children <12 years of age had ≥ 1 positive lung microbiology culture in 2011. A high proportion of positive microbiology cultures was observed across all age and genotype groups (>80%) (figure 2). In most genotype groups, a higher proportion of positive cultures was observed among children 6 to <12 years compared with children <6 years. This trend was also seen when examining the studied organisms individually, except for *H. influenzae*, which was less common among the oldest age group. The greatest variation across genotypes in the proportion of positive microbiology was seen in children 6 to <12 years of age for *P. aeruginosa* (12.2% [*R117H* on ≥ 1 allele] to 47.3% [MF/MF]) and MRSA (9.5% [*R117H* on ≥ 1 allele] to 33.2% [*F508del/MF*]; online supplemental figure S1).

Medication use

Use of CF-related medications was common across all age and genotype groups, and use increased across the increasing age groups. The most-used medications among children <12 years of age were inhaled bronchodilators (89.7%), followed by pancreatic enzyme replacement therapy (PERT) (89.3%), dornase alfa (74.0%) and hypertonic saline (41.6%) (online supplemental table S2).

Prevalence of use of inhaled airway clearance medications overall and by age group was similar among children with *F508del/F508del*, *F508del/MF*, MF/MF genotypes and gating mutation on ≥ 1 allele and was lower among children with *R117H* or RF mutations on ≥ 1 allele. Similarly, use of PERT varied by genotype group; the vast majority of children with *F508del/F508del* (99.6%), *F508del/MF* (98.1%) and MF/MF (97.3%) genotypes or a gating mutation on ≥ 1 allele (93.6%) used PERT from infancy, while fewer than half of the children with RF mutations (37.2%) or *R117H* (19.3%) on ≥ 1 allele used PERT (online supplemental table S2).

Nutritional supplementation

The majority (59%) of children received oral nutritional supplementation. While no difference in the prevalence of oral nutritional supplementation was clearly evident across age groups, differences were observed across genotype groups: oral nutritional supplementation was more common among *F508del/F508del*, *F508del/MF* and MF/MF genotype groups and among children with a gating mutation on ≥ 1 allele,

Table 1 Demographics by genotype group*

	Overall (0 to <12 years of age)	0 to <2 years of age	2 to <6 years of age	6 to <12 years of age
Overall, n†	9185	1593	2979	4613
Age, mean (SD)	6.0 (3.5)	1.0 (0.6)	4.0 (1.2)	9.1 (1.7)
Female, n (%)	4586 (49.9)	773 (48.5)	1456 (48.9)	2357 (51.1)
White, n (%)	8505 (92.6)	1449 (91.0)	2726 (91.5)	4330 (93.9)
<i>F508del/F508del</i> , n†	4398	708	1382	2308
Age, mean (SD)	6.2 (3.5)	1.0 (0.6)	4.0 (1.2)	9.1 (1.7)
Female, n (%)	2183 (49.6)	339 (47.9)	682 (49.3)	1162 (50.3)
White, n (%)	4242 (96.5)	680 (96.0)	1324 (95.8)	2238 (97.0)
<i>F508del/MF</i> , n†	1887	304	586	997
Age, mean (SD)	6.2 (3.5)	1.0 (0.6)	4.0 (1.1)	9.0 (1.7)
Female, n (%)	972 (51.5)	156 (51.3)	299 (51.0)	517 (51.9)
White, n (%)	1739 (92.2)	277 (91.1)	537 (91.6)	925 (92.8)
Gating mutation on ≥1 allele, n†	439	82	137	220
Age, mean (SD)	6.0 (3.6)	1.0 (0.5)	4.0 (1.1)	9.1 (1.7)
Female, n (%)	220 (50.1)	35 (42.7)	64 (46.7)	121 (55.0)
White, n (%)	410 (93.4)	76 (92.7)	127 (92.7)	207 (94.1)
RF on ≥1 allele, n†	438	113	151	174
Age, mean (SD)	5.0 (3.4)	1.1 (0.5)	3.7 (1.1)	8.7 (1.8)
Female, n (%)	216 (49.3)	59 (52.2)	70 (46.4)	87 (50.0)
White, n (%)	400 (91.3)	102 (90.3)	136 (90.1)	162 (93.1)
<i>MF/MF</i> , n†‡	336	51	116	169
Age, mean (SD)	6.2 (3.5)	1.0 (0.6)	4.0 (1.1)	9.2 (1.7)
Female, n (%)	175 (52.1)	25 (49.0)	53 (45.7)	97 (57.4)
White, n (%)	267 (79.5)	38 (74.5)	96 (82.8)	133 (78.7)
<i>R117H</i> on ≥1 allele, n†	262	52	109	101
Age, mean (SD)	5.2 (3.4)	1.0 (0.6)	3.8 (1.1)	8.9 (1.7)
Female, n (%)	120 (45.8)	25 (48.1)	41 (37.6)	54 (53.5)
White, n (%)	255 (97.3)	49 (94.2)	105 (96.3)	101 (100)

*The genotype groups displayed are not exhaustive; therefore, subgroups do not sum to 9185.

†n indicates the number of children with non-missing data.

‡Online supplemental table S1 provides a full list of qualifying MF mutations.

MF, minimal function; RF, residual function.

and it was less common among children with RF mutations or *R117H* on ≥1 allele (online supplemental figure S2A).

Supplemental feeding via a gastronomy tube was received by 13.5% of all children (online supplemental figure S2B). Overall, the observed proportion of children receiving such supplemental feeding was 15.9% among children 6 to <12 years of age, 12.3% among children 2 to <6 years of age and 8.7% among children 0 to <2 years of age. The numerical differences between age groups were driven by the *F508del/F508del* and *F508del/MF* groups; other groups did not show obvious differences by age group.

Complications of CF

More than half (54.7%) of all children with CF <12 years of age had ≥1 complication of CF as of 2011. Overall, and within each genotype group, the proportions of children with any complication increased in older age groups (figure 3). Not all complications of CF, however, followed this pattern. Gastro-oesophageal reflux disease (GORD), which was the most common CF-related complication (occurring in 25.7% of all children), was reported among 28.3% of children 0 to <2 years of age, 26.1% of children 2 to <6 years of age and 24.5% of children 6 to <12 years of age. This decrease in the rate of GORD in older age groups was only seen in the *F508del/F508del* and *F508del/*

Table 2 ppFEV₁ by genotype group in children 6 to <12 years of age*

	Evaluable children, n†	ppFEV ₁ , mean (SD), percentage points
Overall	4481	92.6 (17.5)
<i>F508del/F508del</i>	2251	92.2 (17.5)
<i>F508del/MF</i>	968	92.1 (17.5)
Gating mutation on ≥1 allele	218	95.0 (16.6)
RF on ≥1 allele	170	98.3 (16.4)
MF/MF	163	87.4 (19.1)
<i>R117H</i> on ≥1 allele	96	97.9 (11.8)

*ppFEV₁ is not routinely measured in children <6 years of age.

†n indicates the number of children with non-missing data.

MF, minimal function; ppFEV₁, per cent predicted forced expiratory volume in 1 s; RF, residual function.

MF groups (online supplemental table S3). The second and third most common complications of CF, asthma (22.2% of all children) and sinus disease (15.8% of all children), were reported in higher proportions of children in older age groups, both overall and within the genotype groups (online supplemental table S3). All

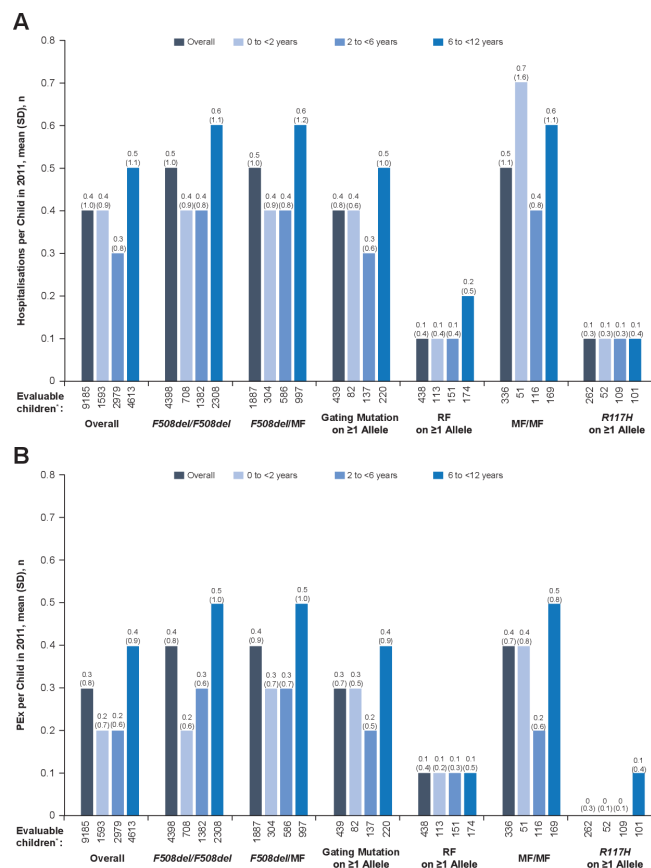


Figure 1 (A) Hospitalisation and (B) PEx rates according to age and genotype group. **'Evaluable children' includes all children with non-missing data. MF, minimal function; PEx, pulmonary exacerbation; RF, residual function.

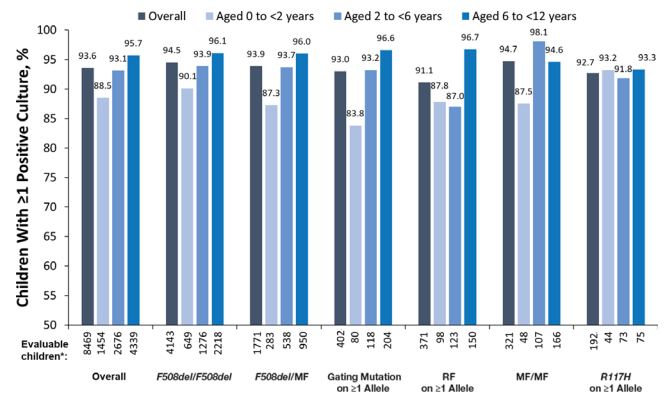


Figure 2 Positive lung microbiology rates by age and genotype groups for any positive microbiology. **'Evaluable children' includes all children with non-missing data. MF, minimal function; RF, residual function.

other complications of CF studied (pancreatic, hepatobiliary, psychological, and additional pulmonary or gastrointestinal) were reported in <15% of the children.

DISCUSSION

The results from this analysis illustrate the substantial burden of CF from infancy through childhood and across genotypes prior to the first approval of CFTR modulator therapies. Overall and within most genotype groups, PEx, complications of CF, respiratory infections and need for symptomatic treatments increased as patients aged. More importantly, BOI starts early, as substantiated by the use of symptomatic treatments and supplemental nutrition and by the proportion of children experiencing respiratory infections and complications of CF. These findings highlight the considerable burden of CF from infancy. Lung disease was an important contributor to the burden of CF from an early age and prior to routine assessment of lung function starting at 6 years of age. This was illustrated by the high use of pulmonary-related symptomatic therapies and the high rate of positive lung microbiology cultures, including *P. aeruginosa*, which is associated with

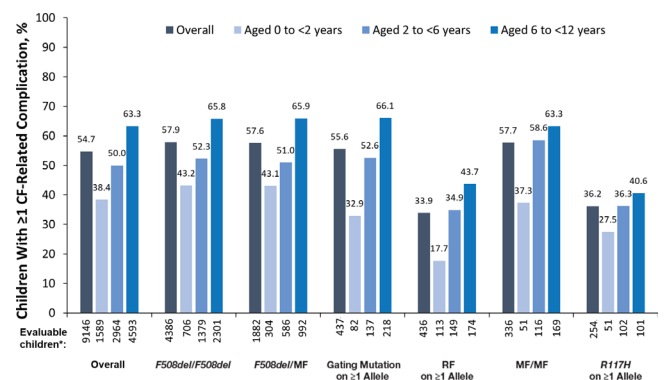


Figure 3 CF-related complications according to age and genotype group. **'Evaluable children' includes all children with non-missing data. CF, cystic fibrosis; MF, minimal function; RF, residual function.

a worse prognosis^{20 21} despite the use of symptomatic therapies. Of note, the decline with age in the rates of *H. influenzae* is consistent with the recommended vaccination schedule in the USA.²² Further burden resulted from PEx, which are severe life events associated with high morbidity that can lead to an increased rate of lung function decline, worse long-term prognosis and death.^{23–29} While reduced lung function, as measured by spirometry (ie, ppFEV₁), was observed among children 6 to <12 years of age, the impact of CF on lung function in children <6 years of age is not generally assessed as spirometry is an effort-dependent manoeuvre and may be unreliable or infeasible in this population. Importantly, spirometry is known to have limited sensitivity in evaluating early lung disease; other modalities, such as multiple breath washout (ie, lung clearance index), have demonstrated functional lung disease in those with normal ppFEV₁.^{8 30} These observations underscore the need for more sensitive and age-appropriate methods to assess lung disease in children.³¹

Additional burden was observed as a result of the multi-systemic nature of the disease. The majority (59%) of children received oral nutritional supplementation, with 13.5% requiring gastrostomy tube feeding. The impact of impaired exocrine pancreatic function was illustrated by the high prevalence of PERT use starting in infancy (86.3%). The observation that most children required nutritional supplementation, PERT and other symptomatic therapies suggests that substantial and progressive disease burden persisted and highlights the need for novel therapies that treat the underlying cause of CF.^{11 32} Early treatment with such therapies provides the potential to slow disease progression and ameliorate the increasing symptomatic treatment and disease burden on patients and their caregivers.^{11 32}

This registry-based descriptive study has inherent limitations. Data were collected by CF centres and submitted to the US CFFPR; thus, reported data may be incomplete or reflect individual centre practices or interpretations. An evaluation of 2012 US CFFPR data suggested that 95% of clinic visits and 90% of hospitalisations were entered into the registry, and an audit of select data fields found high concordance between the medical records and the registry, ranging from 82.6% (aztreonam, tobramycin use) to 99.9% (patient sex).¹⁸ Furthermore, this study only included children in the USA, and results may not be generalisable to children with CF outside the USA. Finally, stratification by both age and genotype group led to small numbers for certain subgroups, limiting interpretation.

This study demonstrated that, prior to the first approval of CFTR modulator therapies, CF was associated with substantial BOI from an early age—including respiratory infections, hospitalisations and PEx; need for supplemental nutrition; and high treatment utilisation—irrespective of genotype.

Acknowledgements The authors gratefully acknowledge the patients with CF, families and physicians who participated in the Cystic Fibrosis Foundation Patient Registry (CFFPR) and the CFFPR for supplying the data that made this analysis possible. The authors are also grateful to Kelli Edwards-Malone, PharmD (who was an employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company), and Francesca Francois, PharmD, MPH (who is an employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company), for their coordination and support, along with the medical writing and editorial support by Karen Kaluza Smith, PhD, of ArticulateScience LLC, which received funding from Vertex.

Contributors KB was involved in data collection. KB, EA-S, SJM, GL and CLC contributed to interpretation of the data, drafted and critically revised the manuscript and approved the manuscript for publication. KB accepts full responsibility for the finished work as the guarantor; KB had access to the aggregated data and controlled the decision to publish.

Funding This study was supported by Vertex Pharmaceuticals Incorporated, Boston, MA, USA.

Competing interests KB, EA-S, GL and CLC are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. SJM is an employee of ICON Clinical Research, which received funding from Vertex Pharmaceuticals Incorporated for analytic consulting services for this study and which receives funding from various pharmaceutical, biotechnology and device companies for providing clinical research services.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable to this article as no data sets were generated or analysed by the coauthors in the present study. The US CFFPR collects and manages its own data and maintains processes for researchers to request summarised data (<https://www.cff.org/Research/Researcher-Resources/Tools-and-Resources/Patient-Registry-Data-Requests/>).

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SUPPLEMENTAL MATERIAL

Table S1. Qualifying Minimal Function Mutations Per Protocol of NCT03525444[1]

Minimal Function Mutation Category		Mutation				
Class I mutations (absence of CFTR protein production)	Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
		S4X	Q220X	G542X	E822X	W1145X
		W19X	Y275X	G550X	W882X	R1158X
		G27X	C276X	Q552X	W846X	R1162X
		Q39X	Q290X	R553X	Y849X	S1196X
		W57X	G330X	E585X	R851X	W1204X
		E60X	W401X	G673X	Q890X	L1254X
		R75X	Q414X	Q685X	S912X	S1255X
		L88X	S434X	R709X	Y913X	W1282X
		E92X	S466X	K710X	Q1042X	Q1313X
		Q98X	S489X	Q715X	W1089X	Q1330X
		Y122X	Q493X	L732X	Y1092X	E1371X
		E193X	W496X	R764X	W1098X	Q1382X
		W216X	C524X	R785X	R1102X	Q1411X

	Canonical splice mutations	185+1G→T 296+1G→A 296+1G→T 405+1G→A 405+3A→C 406-1G→A 621+1G→T 711+1G→T	711+5G→A 712-1G→T 1248+1G→A 1249-1G→A 1341+1G→A 1525-2A→G 1525-1G→A 1898+1G→C	1717-8G→A 1717-1G→A 1811+1G→C 1811+1.6kbA→G 1811+1643G→T 1812-1G→A 1898+1G→A	2622+1G→A 2790-1G→C 3040G→C (G970R) 3850-1G→A 3120G→A 3120+1G→A 3121-2A→G	3121-1G→A 3500-2A→G 3600+2insT 4005+1G→A 4374+1G→T
	Small (≤3 nucleotide) ins/del frameshift mutations	182delT 306insA 306delTAGA 365-366insT 394delTT 442delA 444delA 457TAT→G 541delC 574delA 663delT 849delG	1078delT 1119delA 1138insG 1154insTC 1161delC 1213delT 1259insA 1288insTA 1343delG 1471delA 1497delGG 1548delG	1677delTA 1782delA 1824delA 1833delT 2043delG 2143delT 2183AA→G ^a 2184delA 2184insA 2307insA 2347delG 2585delT	2711delT 2732insA 2869insG 2896insAG 2942insT 2957delT 3007delG 3028delA 3171delC 3171insC 3271delGG 3349insT	3737delA 3791delC 3821delT 3876delA 3878delG 3905insT 4016insT 4021dupT 4022insT 4040delA 4279insA 4326delTC

		935delA	1609del CA	2594delGT	3659delC
	Non-small (>3 nucleotide) ins/del frameshift mutations	CFTRdele1 CFTRdele2 CFTRdele2,3 CFTRdele2-4 CFTRdele3-10,14b-16 CFTRdele4-7 CFTRdele4-11 CFTR50kbdel CFTRdup6b-10 CFTRdele11 CFTRdele13,14a CFTRdele14b-17b	CFTRdele16-17b CFTRdele17a,17b CFTRdele17a-18 CFTRdele19 CFTRdele19-21 CFTRdele21 CFTRdele22-24 CFTRdele22,23 124del23bp 602del14 852del22 991del5	1461ins4 1924del7 2055del9→A 2105-2117del13insAGAAA 2372del8 2721del11 2991del32 3121-977_3499+248del2515 3667ins4 4010del4 4209TGTT→AA	
Missense and in-frame deletion mutations	Missense mutations that are not responsive in vitro to tezacaftor, ivacaftor, or tezacaftor/ivacaftor and	A46D ^b G85E R347P L467P ^b I507del	V520F A559T ^b R560T R560S A561E	Y569D ^b L1065P R1066C L1077P ^b M1101K	N1303K

	%PI >50% and sweat chloride >86 mmol/L ^c	
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%PI, percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient;[2] CFTR, cystic fibrosis transmembrane conductance regulator; ins/del, insertion/deletion.

^a Also known as *2183delAA→G*.

^b Unpublished data.

^c Mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry.[2]

Table S2. CF Medication Use According to Age and Genotype Group

	Overall (0 to <12 years of age)	0 to <2 years of age	2 to <6 years of age	6 to <12 years of age
Overall, n ^a	9,146	1,589	2,964	4,593
Inhaled bronchodilators, %	89.7	84.4	88.2	92.5
PERT, %	89.3	86.3	88.5	90.8
Dornase alfa, %	74.0	47.4	70.4	85.5
Hypertonic saline, %	41.6	23.1	34.0	53.0
Inhaled corticosteroids, %	34.2	23.3	33.6	38.4
Chronic oral macrolides, %	25.0	4.9	13.0	39.7
<i>F508del/F508del</i> , n ^a	4,386	706	1,379	2,301
Inhaled bronchodilators, %	90.4	84.3	89.1	93.2
PERT, %	99.6	99.7	99.8	99.4
Dornase alfa, %	79.2	53.5	75.6	89.3
Hypertonic saline, %	44.9	25.2	35.6	56.5
Inhaled corticosteroids, %	35.6	26.6	33.4	39.6
Chronic oral macrolides, %	28.7	6.4	14.5	44.0
<i>F508del/MF</i> , n ^a	1,882	304	586	992
Inhaled bronchodilators, %	91.7	89.8	90.6	92.9
PERT, %	98.1	97.7	98.8	97.8
Dornase alfa, %	78.1	51.3	76.3	87.3
Hypertonic saline, %	43.8	25.3	38.9	52.4
Inhaled corticosteroids, %	34.8	24.7	33.8	38.4
Chronic oral macrolides, %	24.9	3.3	13.7	38.1
Gating mutation on ≥1 allele, n ^a	437	82	137	218
Inhaled bronchodilators, %	91.5	85.4	88.3	95.9
PERT, %	93.6	87.8	95.6	94.5

Dornase alfa, %	76.0	47.6	69.3	90.8
Hypertonic saline, %	42.6	23.2	38.7	52.3
Inhaled corticosteroids, %	36.4	24.4	35.0	41.7
Chronic oral macrolides, %	25.9	0	15.3	42.2
RF on ≥ 1 allele, n ^a	436	113	149	174
Inhaled bronchodilators, %	83.5	77.9	83.2	87.4
PERT, %	37.2	43.4	36.2	33.9
Dornase alfa, %	52.8	31.0	51.0	68.4
Hypertonic saline, %	25.7	14.2	20.8	37.4
Inhaled corticosteroids, %	23.6	14.2	27.5	26.4
Chronic oral macrolides, %	11.9	3.5	5.4	23.0
MF/MF, n ^a	336	51	116	169
Inhaled bronchodilators, %	93.8	92.2	93.1	94.7
PERT, %	97.3	94.1	97.4	98.2
Dornase alfa, %	80.4	54.9	77.6	89.9
Hypertonic saline, %	45.8	19.6	38.8	58.6
Inhaled corticosteroids, %	36.3	19.6	40.5	38.5
Chronic oral macrolides, %	30.7	2.0	14.7	50.3
R117H on ≥ 1 allele, n ^a	254	51	102	101
Inhaled bronchodilators, %	77.2	78.4	74.5	79.2
PERT, %	19.3	15.7	23.5	16.8
Dornase alfa, %	39.0	23.5	38.2	47.5
Hypertonic saline, %	16.9	7.8	16.7	21.8
Inhaled corticosteroids, %	22.0	11.8	20.6	28.7
Chronic oral macrolides, %	8.7	3.9	4.9	14.9

CF, cystic fibrosis; MF, minimal function; PERT, pancreatic enzyme replacement therapy; RF, residual function.

^a n indicates the number of children with non-missing data.

Table S3. Complications of CF Occurring in ≥15% of Children Overall

	Overall (0 to <12 years)	0 to <2 years	2 to <6 years	6 to <12 years
Overall, n ^a	9,146	1,589	2,964	4,593
GERD, %	25.7	28.3	26.1	24.5
Asthma, %	22.2	9.1	18.0	29.4
Sinus disease, %	15.8	2.8	13.3	22.0
<i>F508del/F508del</i> , n ^a	4,386	706	1,379	2,301
GERD, %	28.1	32.3	28.7	26.4
Asthma, %	23.7	10.5	17.8	31.3
Sinus disease, %	17.2	3.1	14.4	23.3
<i>F508del/MF</i> , n ^a	1,882	304	586	992
GERD, %	28.3	32.6	28.2	27.0
Asthma, %	22.7	10.9	18.3	28.9
Sinus disease, %	16.3	3.3	12.6	22.4
Gating mutation on ≥1 allele, n ^a	437	82	137	218
GERD, %	21.7	28.0	19.0	21.1
Asthma, %	26.5	7.3	24.8	34.9
Sinus disease, %	15.1	1.2	14.6	20.6
RF on ≥1 allele, n ^a	436	113	149	174
GERD, %	14.9	13.3	20.1	11.5
Asthma, %	13.8	1.8	12.1	23.0
Sinus disease, %	11.0	1.8	9.4	18.4
MF/MF, n ^a	336	51	116	169
GERD, %	28.3	19.6	33.6	27.2
Asthma, %	22.3	5.9	19.0	29.6
Sinus disease, %	17.0	5.9	13.8	22.5
<i>R117H</i> on ≥1 allele, n ^a	254	51	102	101
GERD, %	15.7	15.7	17.6	13.9

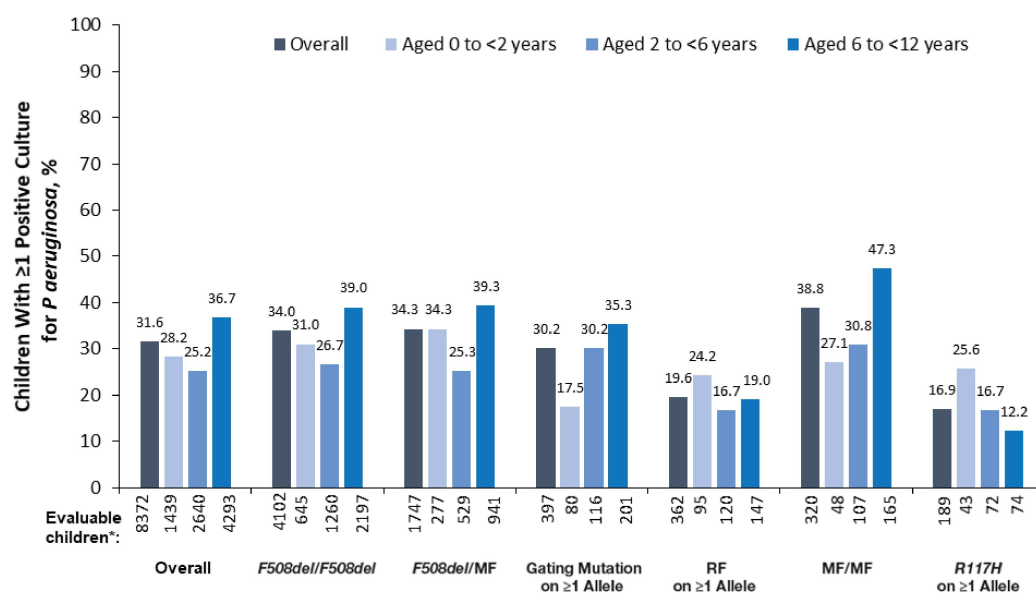
Asthma, %	15.4	9.8	13.7	19.8
Sinus disease, %	11.0	3.9	12.7	12.9

CF, cystic fibrosis; GERD, gastroesophageal reflux disease; MF, minimal function; RF, residual function.

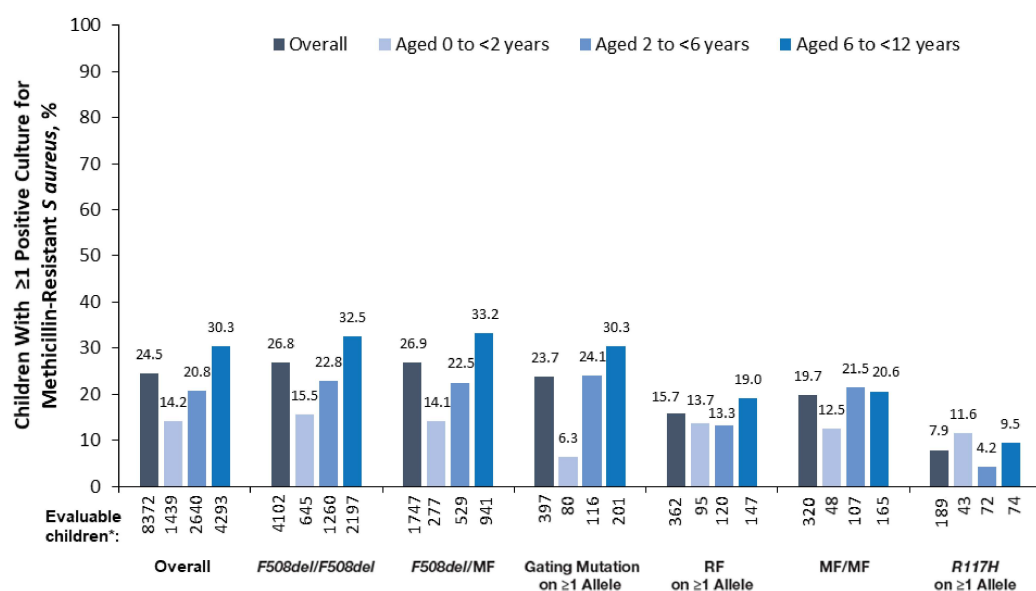
^a n indicates the number of children with non-missing data.

Figure S1. Positive lung microbiology rates according to the age and genotype group for (A) *Pseudomonas aeruginosa*, (B) methicillin-resistant *Staphylococcus aureus*, (C) methicillin-sensitive *S aureus*, (D) *S aureus*, (E) *Haemophilus influenzae*, (F) *Burkholderia cepacia*, (G) *Aspergillus*, and (H) nontuberculous mycobacteria.

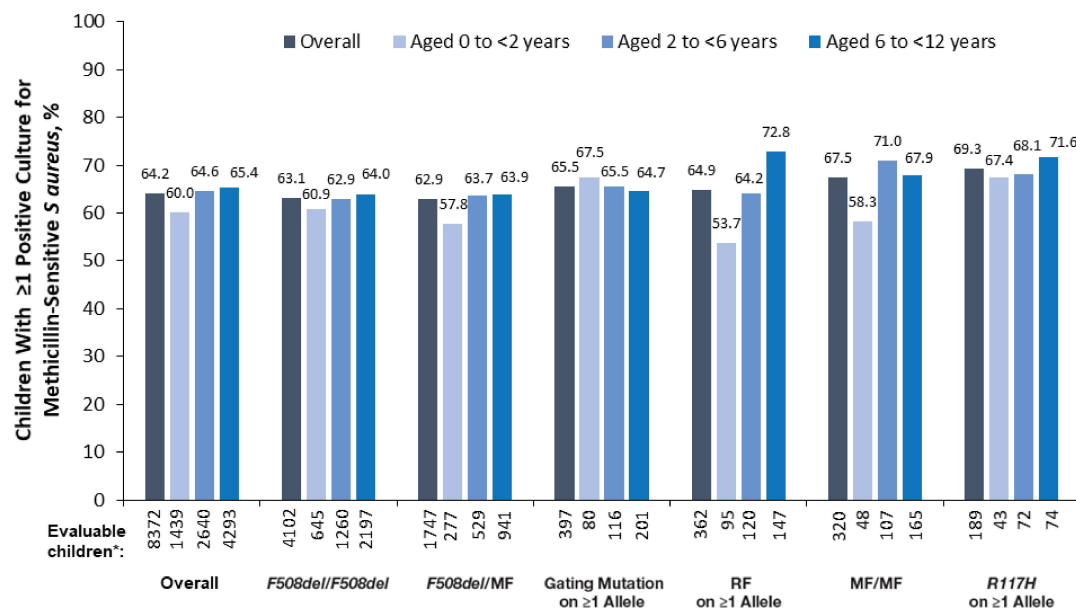
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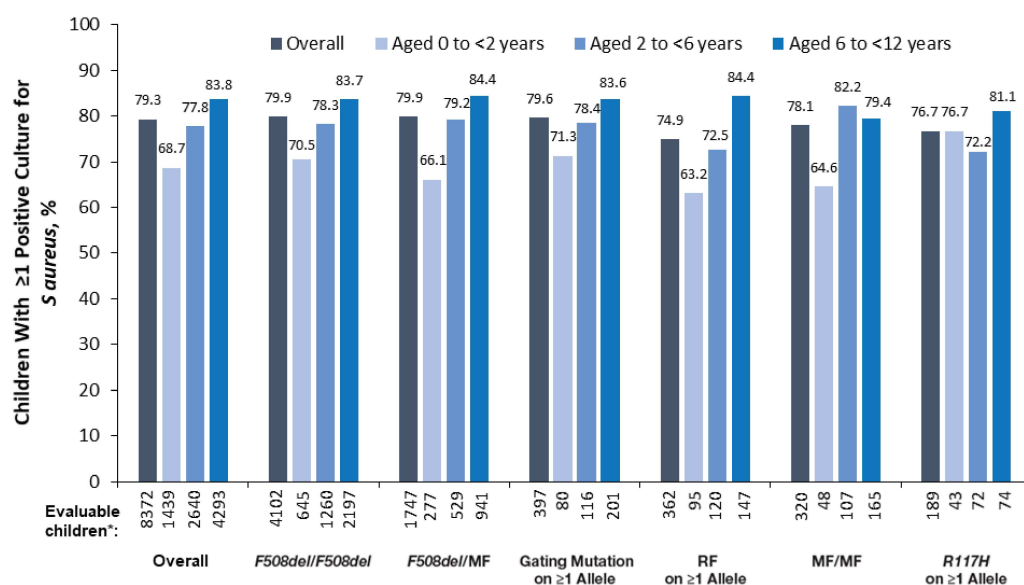
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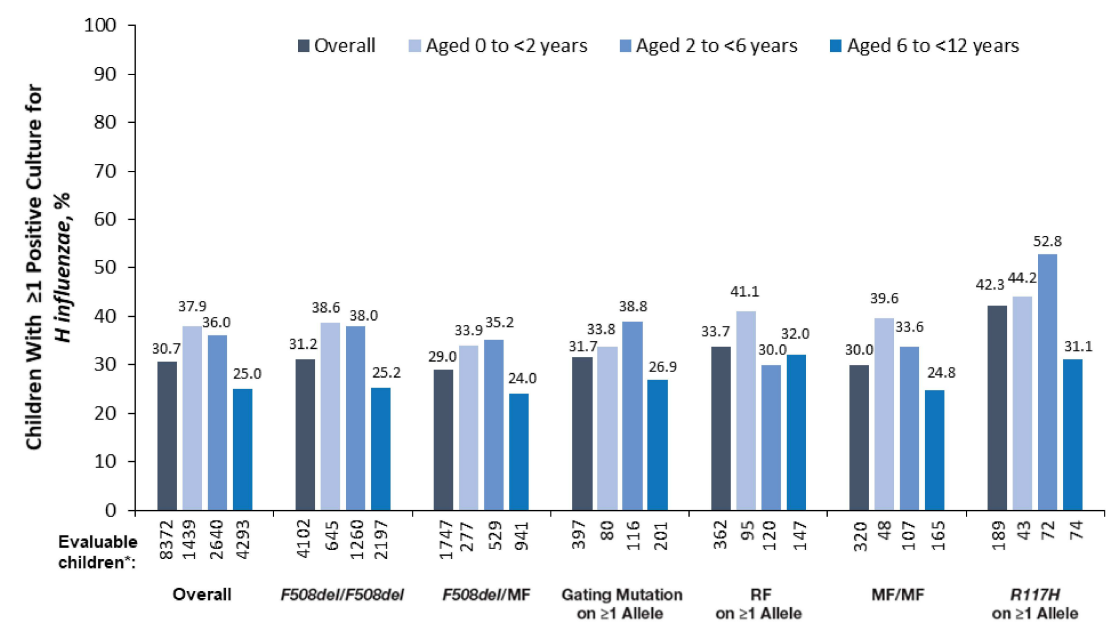
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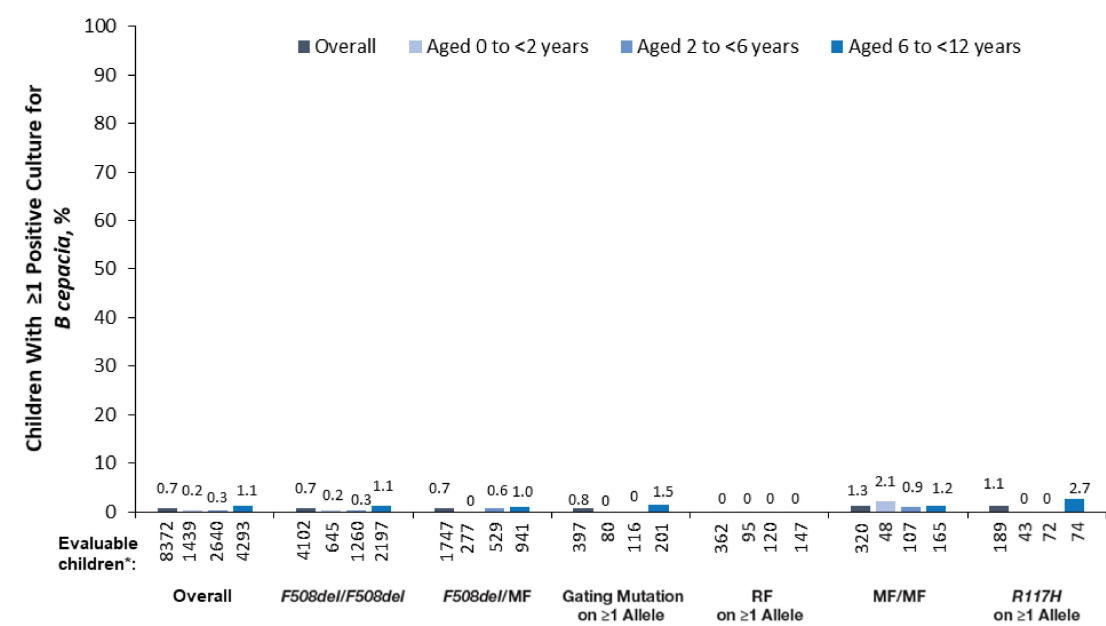
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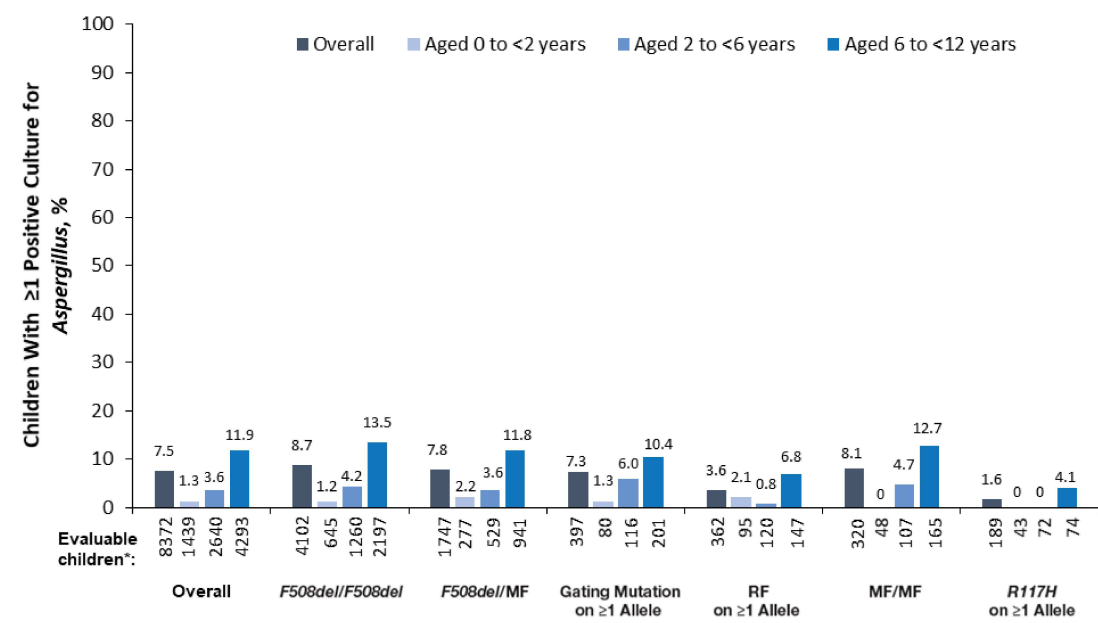
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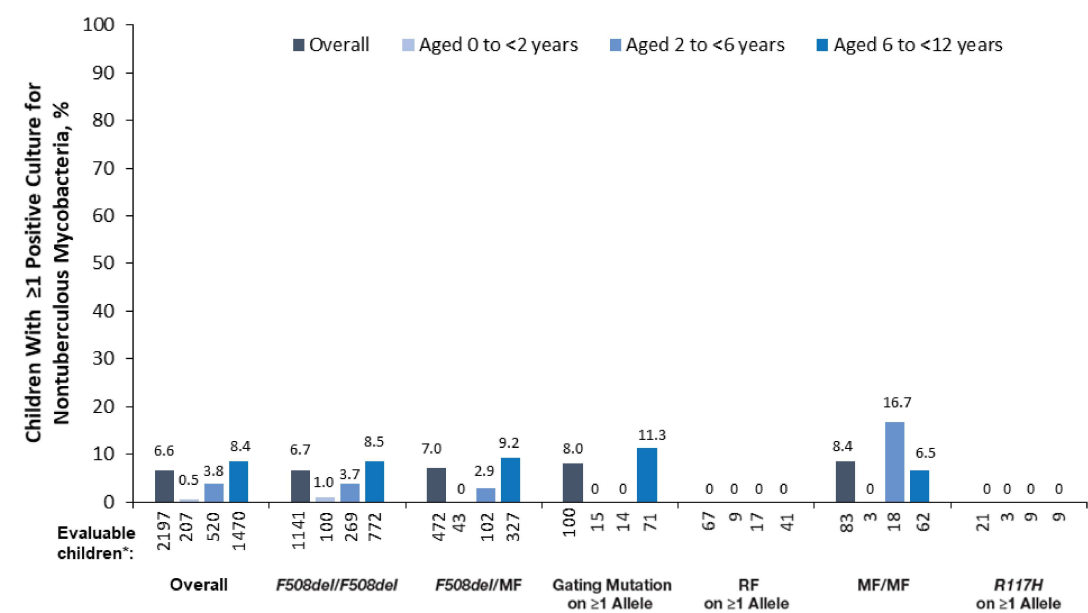
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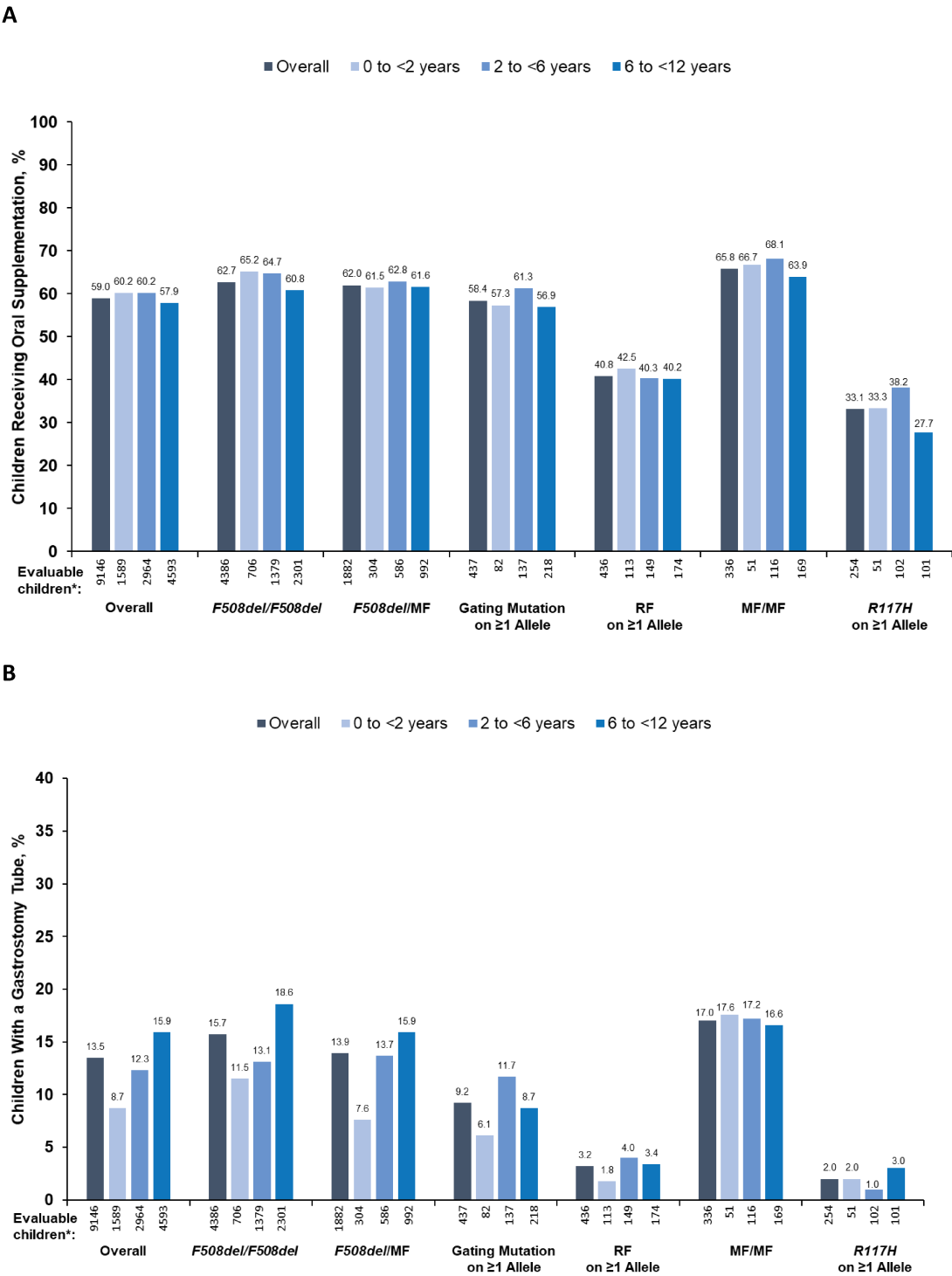
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MF, minimal function; RF, residual function.

* “Evaluable children” includes all children with non-missing data.

Figure S2. Oral supplementation and gastrostomy tube use according to age and genotype.



MF, minimal function; RF, residual function.

* “Evaluable children” includes all children with non-missing data.

SUPPLEMENTAL REFERENCES

- 1 Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;**381**(19):1809–19. doi: 10.1056/NEJMoa1908639
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