ELSEVIER

Journal of Cystic Fibrosis xx (2016) xxx – xxx

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

The benefits of newborn screening for cystic fibrosis: The Canadian experience

D.Y.F. Mak [a], J. Sykes [b,c], A.L. Stephenson [b,c,1], L.C. Lands [d,e,*]

[a] *Cystic Fibrosis Canada, 2323 Yonge Street Suite 800, Toronto, M4P 2C9, Canada*
[b] *Department of Respirology, St. Michael's Hospital, 30 Bond Street, Toronto, M5B 1W8, Canada*
[c] *Keenan Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, 209 Victoria Street, Toronto, Ontario, M5B 1T8, Canada*
[d] *Meakins-Christie Laboratories, Research Institute of McGill University Health Centre, Montreal, Canada*
[e] *Montreal Children's Hospital-McGill University Health Centre, Respiratory Division, Montreal, Canada*

Received 7 December 2015; revised 29 March 2016; accepted 5 April 2016
Available online xxxx

Abstract

Background: The impact of newborn screening (NBS) for cystic fibrosis (CF) on early indicators of long-term health was evaluated in the context of government-sponsored healthcare and access to current therapies.
Methods: Using data from the Canadian CF Registry between 2008 and 2013, we compared the rates of respiratory infections and markers of nutritional status in those diagnosed through NBS to those who were diagnosed clinically within the same time period using Mann–Whitney and Fischer's exact test as appropriate.
Results: The study included 303 subjects, 201 in the NBS group and 102 in the non-NBS group. NBS patients were diagnosed earlier and had their first clinic visit at a younger age. Pancreatic insufficiency was less common in NBS patients. The incidence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* were lower in NBS patients. After adjusting for age at clinic visit, gender, pancreatic status, and *Pseudomonas aeruginosa* infection status, mean *z*-scores for weight-for-age and height-for-age were higher in NBS patients, with no differences in BMI-for-age.
Conclusions: NBS programs for CF lead to improved long-term health outcomes for the CF population.

Keywords: Newborn screening; Hospitalization; Nutritional status; Growth; Infection

1. Introduction

There is overwhelming evidence that supports the establishment of newborn screening (NBS) programs for cystic fibrosis (CF) to improve the overall survival, long-term growth and health outcomes of people living with CF [1–3]. NBS programs for CF have been widely adopted in several European countries, Australia, New Zealand and the majority of North America — with the exception of Quebec (QC) and Mexico [4–7]. NBS most often consists of a two-step screening test using immunoreactive trypsinogen (IRT) from a blood spot procured during the first few days of life that is followed by a search for common mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, although other approaches exist. A positive CF screen results in a referral to a CF clinic to confirm the diagnosis through additional blood and sweat testing. Babies with a high risk of having CF are identified and once the diagnosis is confirmed, education and treatment is initiated, typically in the first 4 to 6 weeks of life.

* Corresponding author at: Division of Pediatric Respiratory Medicine, Meakins-Christie Laboratories, Research Institute-McGill University Health Centre, 1001 boul Décarie, Room EM3.2220, Montreal, Quebec, H4A 3J1, Canada. Tel.: +1 514 412 4400x23015; fax: +1 514 412 4364.
E-mail addresses: dmak@cysticfibrosis.ca (D.Y.F. Mak), SykesJ@smh.ca (J. Sykes), StephensonA@smh.ca (A.L. Stephenson), larry.lands@mcgill.ca (L.C. Lands).
[1] Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, Toronto, Ontario, Canada M5 T 3 M6.

http://dx.doi.org/10.1016/j.jcf.2016.04.001
1569-1993/

The benefits of NBS for CF have been studied in other parts of the world and reported in 2005 [3,8]. In the US, between 1988 and 2013, there have been major improvements in both nutritional status and lung function in young children [9]. This may be due to a combination of early diagnosis through NBS and intervention, including mucolytic therapy, aggressive treatment of infection with *Pseudomonas aeruginosa* (*P. aeruginosa*), and aggressive nutritional supplementation to prevent malnutrition. Recognition of the need for early intervention in regards to treatments such as nutritional support, early eradication of *P. aeruginosa*, and airway clearance has resulted in improvements in clinical factors in young CF patients, such as lung function and nutritional status [10]. It is currently unknown if these interventions could mitigate the consequences of later diagnosis and diminish the benefits of newborn screening.

In Canada, NBS for CF was first introduced in the province of Alberta (AB) in April 2007, followed by Ontario (ON) a year later in April 2008. The screening algorithms differ slightly between AB and ON [11]. In AB, the IRT cutoff is >60 μg/L or 98th percentile and in ON, it is the 96th percentile. In both cases, this is followed by genetic testing using the TM Biosciences Tag-It 39+3 mutation kit. The diagnosis of CF is typically confirmed when two disease causing mutations are identified along with a sweat chloride value >60 mmol/L. QC is the last province in Canada that has not committed to adding CF testing to their NBS program. The objective of this study is to compare health outcomes in the first 6 years of life in children diagnosed through NBS in AB and ON, with children born in QC who did not have access to NBS. This comparison will allow us to evaluate the potential effects of NBS on early clinical outcomes specifically within the Canadian context where non-screened children would have the benefit of government-sponsored access to healthcare and medications. To our knowledge, this is the first study conducted to evaluate the impact of NBS programs for CF in Canada.

2. Materials and methods

2.1. Data source

There are 42 accredited Canadian CF clinics found in all provinces with the exception of Prince Edward Island and the three territories. All CF clinics receive annual incentive grants from Cystic Fibrosis Canada (CFC) to support and enhance their clinical services that are contingent on submitting patient data to the Canadian CF Registry (CCFR). The CCFR is a patient registry and has been in existence since the early 1970s and currently contains over 110,000 annual records on more than 7100 unique individuals with CF who have attended a CF clinic in Canada. It is estimated that the majority of the Canadian CF population is represented within the CCFR, giving a comprehensive picture of the CF population in Canada.

The CCFR data undergo routine validation checks to ensure that they are free of errors. Discrepancies are resolved by directly contacting the reporting CF clinic so that the raw data can be reviewed and unusual data can be confirmed or revised. All individuals within the CCFR have provided informed consent for having their data collected and used for research purposes. This study was approved by the Research Ethics Board of Montreal Children's Hospital and the CCFR oversight committee.

Patient data from the CCFR collected between January 1, 2008 and December 31, 2013 were used in this study. During this time period, the CCFR only captured data on patients with a confirmed diagnosis of CF based on current guidelines [12]. Longitudinal clinical measurements such as height and weight, were recorded from the first stable visit of the year while other variables such as microbiology, pancreatic status, genotype, number of hospitalizations, length of hospital stay, and other CF-complications reflect events that occurred within the calendar year. Lung function is typically measured reliably at 6 years of age and older; therefore, lung function measurements were not included as an outcome for this study.

2.2. Study cohort

The study included two groups of patients followed from 2008 to 2013: (1) infants diagnosed through NBS in AB and ON identified as the *NBS group*; and (2) the *non-NBS group* comprised of children diagnosed with CF in QC. Subjects were followed for a maximum of 6 years to reflect the starting date of the NBS program for CF in both AB and ON. In the CCFR, the upper limit of 6 years for diagnosis covers more than 80% of Canadian CF patients, and those diagnosed after 6 years of age are more likely to have milder forms and thus may not benefit from NBS. Children in QC diagnosed prenatally, due to an affected sibling, or presenting with meconium ileus were excluded, as these circumstances would increase the likelihood of an early diagnosis and they would be unlikely to benefit from an NBS program. With respect to microbiology, once a subject was found to have a positive respiratory sample for a bacteria, they were categorized as positive for all subsequent years in the analysis. Subjects who never had a specimen culture taken were removed to avoid misrepresenting their infection status. We categorized patients into three genotype classifications: homozygous for F508del, heterozygous for F508del and other.

We examined multiple health outcomes of early clinical factors that have been well-established as key indicators of long-term health outcomes in CF [13]. The primary outcomes of this study were markers of nutritional status, specifically weight-for-age, height-for-age and BMI-for-age measurements. World Health Organization (WHO) growth charts were used for all calculations [14,15]. Secondary outcomes included the incidence rate of infection with *P. aeruginosa* and *S. aureus*; the number of hospitalizations; and length of hospital stay.

2.3. Statistical analysis

Demographic and baseline characteristics between the NBS and non-NBS groups were compared using the Mann–Whitney test for continuous variables and the Fisher's exact test for categorical variables. We used generalized estimating equations (GEE) model and generalized linear mixed models (GLMM) to evaluate differences in health outcomes over time between the

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001

two study groups, as these models account for the correlated longitudinal nature of the data. In order to account for over-dispersion of hospitalization data, we used a negative binomial distribution to model this outcome. Additional covariates included in the models were: age at the time of the clinic visit; gender; pancreatic status; *P. aeruginosa* and *S. aureus* infection status; CF clinic location; and genotype.

In order to rationalize our decision to combine the populations from AB and ON, a sensitivity analysis was conducted to investigate potential effects between the three provinces. The same regression models comparing outcomes used in the main analysis were done across three subgroups (AB vs. ON, AB vs. QC and ON vs. QC) instead of by NBS status.

For all analyses, $p < 0.05$ (two-tailed) was used as the criterion for statistical significance. Statistical analysis was performed using R software (version 3.1.2) with the following packages: geepack (version 1.2.0) and glmmADMB (version 0.8.0). Asymptotic 95% confidence intervals were calculated and added to the figures where appropriate.

3. Results

The study included 303 subjects: 201 in the NBS group (66 from AB and 135 from ON) and 102 in the non-NBS group (QC). There were no deaths reported in our study cohort and none have had a transplant.

There was no evidence of a statistical difference between NBS and non-NBS patients in terms of age ($p = 0.10$) and gender ($p = 0.12$). Children in the NBS group were diagnosed earlier with CF ($p < 0.001$) and had their first clinic visit recorded at a younger age ($p < 0.001$). Three children in the NBS group were diagnosed after the age of 1 year as their initial screens were positive but classified as categories B and C (high IRT levels detected but only one or no CF mutations found) [16,17]. Positive sweat tests appeared in subsequent follow-up testing resulting in a delayed diagnosis date. Non-NBS patients were also more likely to be pancreatic insufficient ($p < 0.001$) and attended fewer clinics ($p < 0.001$) (Table 1).

When first diagnosed, those in the NBS group were taller and more likely to have a healthy weight as measured by their first *z*-scores for height-for-age and BMI-for-age ($p < 0.001$). The NBS group showed significantly better overall growth in height and weight as seen with their most recent *z*-scores for weight-for-age and height-for-age ($p < 0.001$) (Table 2).

The NBS group had fewer and shorter hospitalizations ($p < 0.001$) due to pulmonary exacerbations (Fig. 1). Patients in the non-NBS group had a higher rate of *P. aeruginosa* than the NBS group ($p < 0.001$) and less than 30% of the NBS group had evidence of *P. aeruginosa* infection compared to more than 60% of the non-NBS group ($p < 0.001$) (Fig. 2). However, the prevalence of *S. aureus* is slightly higher in the non-NBS group compared to the NBS group (77.5% vs. 63.2% respectively, $p = 0.013$).

Across the 6-year time period, we found higher growth rates in weight and height in the NBS group and a trend towards fewer hospitalizations and lower infection rates of *P. aeruginosa* (Table 3, Figs. 3 and 4). We also found that clinic location, genotype and the infection status of *S. aureus* had no effect on the health outcomes tested. Similar results can be found using only the homozygous F508del cohort (data not shown).

Table 1
Baseline statistics of the NBS and non-NBS groups. All comparisons were calculated using the Fisher's exact test, except † which used the Mann–Whitney test.

	NBS group $N = 201$ children Number (%)	Non-NBS group $N = 102$ children Number (%)	*p*
Current age as of December 31, 2013 (months)			
Median	37.4	45.9	0.10†
Range	[1.1, 70.3]	[1.8, 70.3]	
Age at diagnosis (months)			
All	179 (89.1%)	101 (99.0%)	
Median	0.7	4.9	**<0.001**†
Range	[0.03, 60.5]	[0.03, 52.4]	
Age at first clinic visit (months)			
Median	0.9	6.5	**<0.001**†
Range	[0.1, 61.9]	[0.7, 54.4]	
Gender %			
Female	112 (55.7%)	47 (46.1%)	0.12
Male	89 (44.3%)	55 (53.9%)	
Pancreatic insufficiency %			
All	147 (73.1%)	89 (87.3%)	**0.005**
F508del/F508del	84 (92.3%)	48 (98.0%)	0.26
F508del/Other	50 (54.9%)	30 (81.1%)	**0.008**
Other/Other	10 (62.5%)	8 (61.5%)	1
Genotype breakdown %			
All	198 (98.5%)	99 (97.1%)	
F508del/F508del	91 (45.3%)	49 (48.0%)	0.22
F508del/Other	91 (45.3%)	37 (36.3%)	
Other/Other	16 (8.0%)	13 (12.8%)	
Number of hospital days			
Median	0.0	5.5	**< 0.001**†
Range	[0.0, 117.0]	[0.0, 109.0]	
Number of hospitalizations			
Median	0.0	1.0	**< 0.001**†
Range	[0.0, 4.0]	[0.0, 5.0]	
Prevalence of *P. aeruginosa*	57 (28.4%)	63 (61.8%)	**< 0.001**
Prevalence of *S. aureus*	127 (63.2%)	79 (77.5%)	**< 0.001**

Table 2
The median and range of the *z*-scores for the health outcomes for the first and most recent visit (*N*th) per subject. All comparisons were calculated using the Mann–Whitney test.

Health outcome (*z*-scores)	Visit	NBS group	Non-NBS group	*p*
Weight-for-age				
Median	1st	−0.86	−1.07	0.04
Range	1st	[−4.01, 3.24]	[−5.17, 1.49]	
Median	*N*th	0.04	−0.28	0.002
Range	*N*th	[−2.55, 3.18]	[−3.12, 2.57]	
Height-for-age				
Median	1st	−0.64	−1.58	<0.001
Range	1st	[−8.89, 7.44]	[−5.28, 1.43]	
Median	*N*th	−0.50	−0.97	<0.001
Range	*N*th	[−5.84, 2.86]	[−4.69, 1.72]	
BMI-for-age				
Median	1st	−0.92	−0.36	0.005
Range	1st	[−3.64, 4.81]	[−3.37, 1.95]	
Median	*N*th	0.38	0.39	0.53
Range	*N*th	[−2.54, 3.47]	[−2.52, 2.92]	

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001

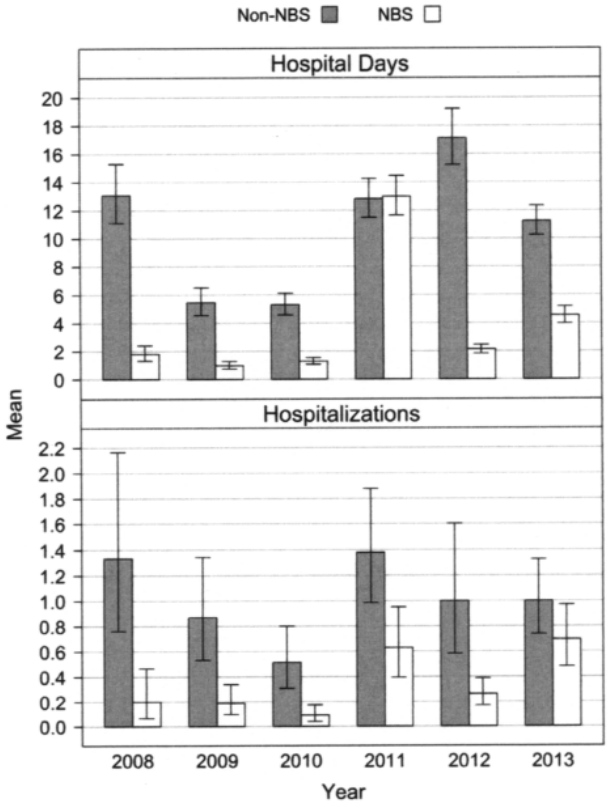

Fig. 1. Mean number of hospital days (top) and hospitalizations (bottom) by reporting year for the NBS and non-NBS groups with 95% confidence interval bars.

Table 3
Results comparing the health outcome over time between the NBS and non-NBS groups using the statistical model specified. All visits per subject were included in the calculations. The estimate describes the average difference between the groups. CI: confidence interval. All comparisons were calculated using the GEE model, except † which used GLMM.

Health outcome	Estimate	95% CI	*p*
Weight-for-age	0.45	[0.24, 0.65]	<0.001
Height-for-age	0.75	[0.50, 1.00]	<0.001
BMI-for-age	−0.05	[−0.24, 0.15]	0.64
Prevalence of *P. aeruginosa*	−1.21	[−1.74, −0.68]	<0.001
Prevalence of *S. aureus*	−0.53	[−1.08, 0.03]	0.06
Hospitalizations	−1.13	[−1.48, −0.77]	<0.001†
Length of hospital stay	−2.31	[−3.06, −1.56]	<0.001†

We found no significant differences in our sensitivity analysis comparing health outcomes between AB vs. ON which validates our use of combining the two datasets (data not shown).

4. Discussion

Our data demonstrate that NBS resulted in better nutritional parameters, lower prevalence of infection with *P. aeruginosa* and *S. aureus*, and fewer hospitalizations in Canadian CF patients. Our results show that children diagnosed through the presence of symptoms are at an important disadvantage, compared to those diagnosed through NBS. The higher incidences of smaller stature and increased hospitalizations are likely to have long-term consequences in terms of need for more therapies and

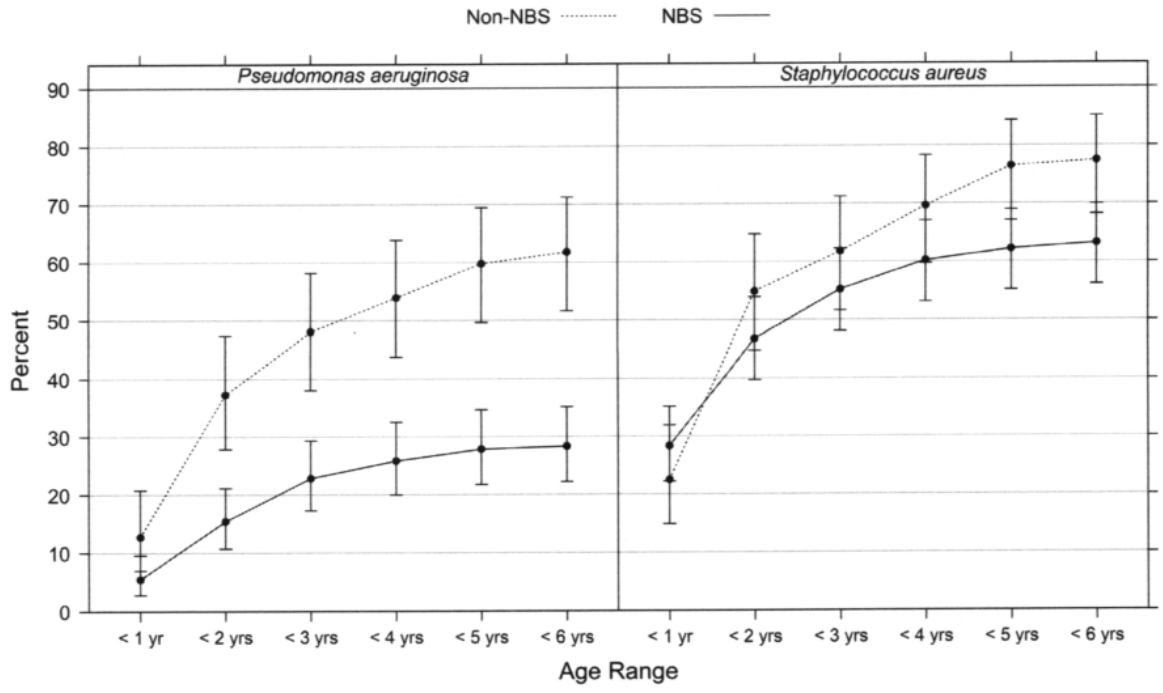

Fig. 2. Percentage of the first occurrence of colonization of *P. aeruginosa* and *S. aureus* with 95% confidence interval bars between the NBS and non-NBS groups for increasing age ranges.

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001

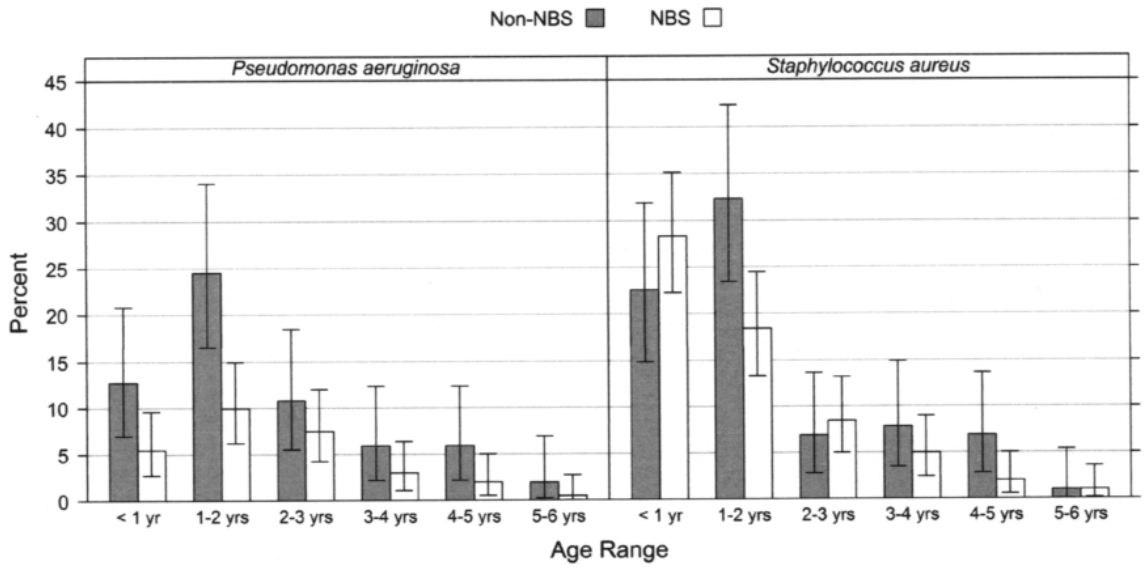

Fig. 3. Cumulative percentage with 95% confidence interval bars of the first occurrence of colonization of *P. aeruginosa* and *S. aureus* between the NBS and non-NBS groups for increasing age ranges.

earlier recourse to lung transplantation [18,19]. Lung infections [20–22] are aggressively treated as they can cause irreversible lung damage and our results indicate that those in the non-NBS group have higher incidences of *P. aeruginosa* suggesting that timely diagnosis and treatment may play a pivotal role in the long-term health outlook of people living with CF. While *S. aureus* is common in CF [21], in Canada it is not routinely treated, unless symptomatic, so prevalence may be high, even in the screened population.

Recent therapeutic approaches have resulted in improved life expectancy for CF patients [23]. Much of the improvements in lung function and nutritional status, two critical clinical factors associated with survival [24], have come during early childhood [10]. These early improvements translate into better long-term health outcomes [19,25], and thus patients who are diagnosed later, end up missing out on the possibility of early intervention to prevent lung damage and improve prognosis [13]. This is important, as novel therapies aimed at correcting the fundamental genetic defect in CF, while demonstrating remarkable improvements in health outcomes, may not reverse pre-existing lung damage [26]. Thus, symptomatically diagnosed patients may not gain optimal benefit from such treatments.

While there have been several prospective and retrospective studies evaluating the potential benefits of newborn screening

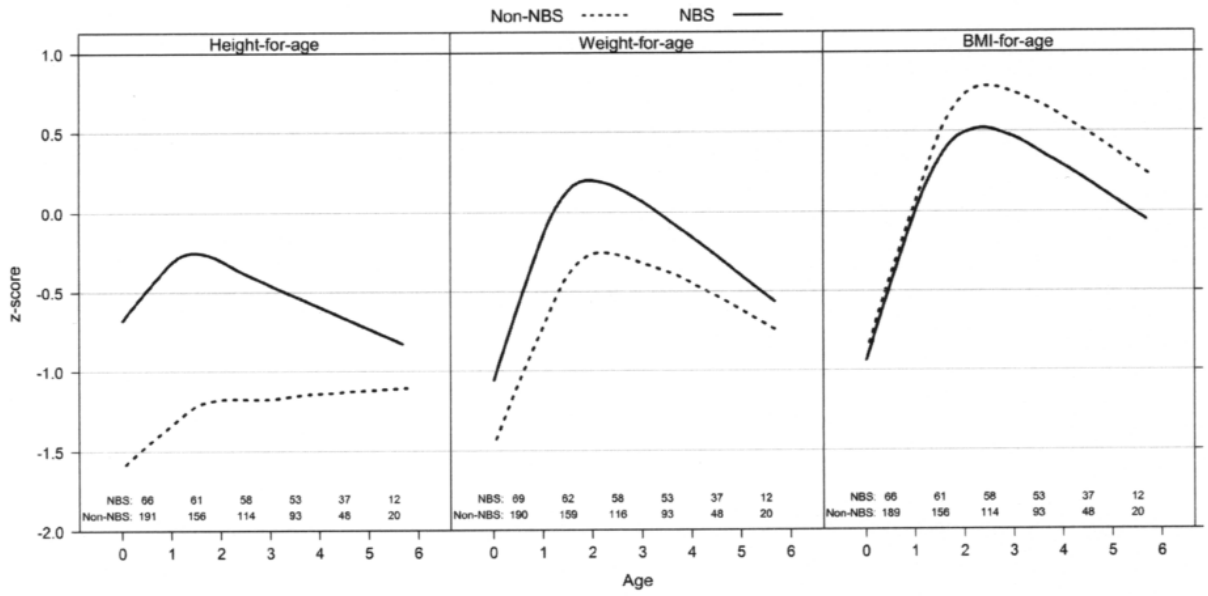

Fig. 4. Regression curves (LOESS) for weight-for-age, height-for-age and BMI-for-age *z*-scores between the NBS and non-NBS groups. The NBS and non-NBS numbers at the bottom of the graph represent the sample sizes for each group for the age range indicated between the age markers along the *x*-axis.

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001

[1,27,28], these were mostly done prior to the widespread availability of therapies for young children, including mucolytics (human recombinant DNase, hypertonic saline), aggressive approaches to the eradication and treatment of *P. aeruginosa* (inhaled aminoglycosides and other antimicrobials), and a better appreciation of the importance of aggressive nutritional support. It could be argued that such interventions could mitigate the effects of making symptom-based diagnosis, and thus diminish the benefits of newborn screening. In the present study, where there is access to mucolytic therapy and a focus on *P. aeruginosa* eradications, NBS had significant positive impact by reducing hospitalizations, prevalence of pathogenic bacteria, and improving nutritional status. In other words, current management strategies do not correct for the lack of NBS.

It should be emphasized that the NBS program was introduced 6 years ago in certain provinces within Canada and as a result, the data reflect many children of differing ages and that there are few children in the data who are over 5 years of age. This attrition of our dataset limits the ability to investigate the long-term impact of the NBS program and future studies are needed. Previous literature has demonstrated that non-screened patients had weight catch-up but not height catch-up in the first 6 years of life [29]. It is likely that those who were not screened profited from catch-up growth following diagnosis and treatment, but that such growth was more successful in adding weight compared to height, leaving the non-screened patients stunted, resulting in a relatively normal BMI. Another possible limitation is that pancreatic insufficiency is determined clinically by the treating physician and entered as a yes/no in the CCFR. We recognize that this may lead to an overestimation of pancreatic insufficiency status due to misclassification [30].

The strengths of our study include the longitudinal nature of our dataset and the fact that CCFR data captures essentially the entire Canadian CF population with similar access to care in the current context of recommended practice. Such use of registry data is currently viewed as highly valuable for healthcare planning [31]. Although we included important clinical outcomes in our study, we did not have access to information on illnesses and patterns of healthcare use prior to the diagnosis of CF which is a limitation of the dataset.

In conclusion, patients diagnosed through NBS in Canada demonstrate better nutritional status, fewer hospitalizations, and less carriage of *P. aeruginosa* in the 5 years following diagnosis, compared to those patients diagnosed clinically. This is despite all children having access to current recognized management strategies to optimize these outcomes. These therapies cannot make up for the absence of NBS.

Conflict of interest statement

No authors have any conflicts of interest to declare in relation to this manuscript.

Acknowledgments

We would like to thank the CF healthcare community for their work with the CCFR. We also wish to extend our deepest gratitude and appreciation to Canadian CF patients for allowing their data to be collected. This study would not have been possible without their support and participation. We would also like to thank CF Canada for their in-kind support.

References

[1] McKay K, Wilcken B. Newborn screening for cystic fibrosis offers an advantage over symptomatic diagnosis for the long term benefit of patients: the motion for. Paediatr Respir Rev 2008;9(4):290–4. http://dx.doi.org/10.1016/j.prrv.2008.09.004.

[2] Grosse SD, Boyle C a, Botkin JR, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. Morb Mortal Wkly Rep 2004;53(RR-13):1–36 [http://www.ncbi.nlm.nih.gov/pubmed/15483524].

[3] Farrell PM, Lai HJ, Li Z, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough! J Pediatr 2005;147(3 Suppl):S30–6. http://dx.doi.org/10.1016/j.jpeds.2005.08.012.

[4] Southern KW, Munck A, Pollitt R, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros 2007;6(1):57–65. http://dx.doi.org/10.1016/j.jcf.2006.05.008.

[5] Massie J, Clements B. The Australian Paediatric Respiratory Group. Diagnosis of cystic fibrosis after newborn screening: the Australasian experience—twenty years and five million babies later: a consensus statement from the Australasian Paediatric Respiratory Group. Pediatr Pulmonol 2005;39(5):440–6. http://dx.doi.org/10.1002/ppul.20191.

[6] Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic fibrosis foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155(6 Suppl):S73–93. http://dx.doi.org/10.1016/j.jpeds.2009.09.001.

[7] Canadian Organization for Rare Disorders. Newborn screening in Canada Status Report. https://www.raredisorders.ca/content/uploads/Canada-NBS-status-updated-Sept.-3-2015.pdf; 2015.

[8] Dankert-Roelse JE, Mérelle ME. Review of outcomes of neonatal screening for cystic fibrosis versus non-screening in Europe. J Pediatr 2005;147(3 Suppl):S15–20. http://dx.doi.org/10.1016/j.jpeds.2005.08.009.

[9] CFF: Patient Registry Annual Data Report. https://www.cff.org/2013_CFF_Patient_Registry_Annual_Data_Report.pdf; 2013. [Accessed February 9, 2016].

[10] VanDevanter DR, Pasta DJ, Konstan MW. Improvements in lung function and height among cohorts of 6-year-olds with cystic fibrosis from 1994 to 2012. J Pediatr 2014;165(6):1091–7. http://dx.doi.org/10.1016/j.jpeds.2014.06.061 [e2].

[11] Canadian College of Medical Geneticists. Newborn screening for cystic fibrosis; 2010 8.

[12] Farrell PMP, Rosenstein BJB, White TTB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153(2):S4–S14. http://dx.doi.org/10.1016/j.jpeds.2008.05.005.Guidelines.

[13] Konstan MW, Butler SM, Wohl MEB, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. J Pediatr 2003;142(6):624–30. http://dx.doi.org/10.1067/mpd.2003.152.

[14] De Onis M, Garza C, Onyango AW, Rolland-Cachera M-F. WHO growth standards for infants and young children. Arch Pediatr 2009;16(1):47–53. http://dx.doi.org/10.1016/j.arcped.2008.10.010.

[15] De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85(9):660–7 [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2636412&tool=pmcentrez&rendertype=abstract. Accessed August 16, 2015].

[16] Newborn Screening Ontario. For health care providers: a discussion guide to help counsel parents about a positive newborn screen for cystic fibrosis; 2014 1.

[17] Lilley M, Christian S, Hume S, et al. Newborn screening for cystic fibrosis in Alberta: two years of experience. Paediatr Child Health 2010;15(9):590–4

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001

[http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3009566&tool=pmcentrez&rendertype=abstract. Accessed March 24, 2016].

[18] Cogen J, Emerson J, Sanders DB, et al. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. Pediatr Pulmonol 2015;50(April):763–70. http://dx.doi.org/10.1002/ppul.23217.

[19] Simmonds NJ, MacNeill SJ, Cullinan P, Hodson ME. Cystic fibrosis and survival to 40 years: a case–control study. Eur Respir J 2010;36(6):1277–83. http://dx.doi.org/10.1183/09031936.00001710.

[20] Goss CH, Muhlebach MS. Review: *Staphylococcus aureus* and MRSA in cystic fibrosis. J Cyst Fibros 2011;10(5):298–306. http://dx.doi.org/10.1016/j.jcf.2011.06.002.

[21] Kahl BC. Impact of *Staphylococcus aureus* on the pathogenesis of chronic cystic fibrosis lung disease. Int J Med Microbiol 2010;300(8):514–9. http://dx.doi.org/10.1016/j.ijmm.2010.08.002.

[22] Davies JC. *Pseudomonas aeruginosa* in cystic fibrosis: pathogenesis and persistence. Paediatr Respir Rev 2002;3(2):128–34 [http://www.ncbi.nlm.nih.gov/pubmed/12297059. Accessed June 13, 2015].

[23] Cystic Fibrosis Canada. The Canadian Cystic Fibrosis Registry: 2013 annual report; 2013.

[24] Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax 2002;57(7):596–601 [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1746376&tool=pmcentrez&rendertype=abstract. Accessed July 20, 2015].

[25] Tluczek A, Laxova A, Grieve A, et al. Long-term follow-up of cystic fibrosis newborn screening: psychosocial functioning of adolescents and young adults. J Cyst Fibros 2014;13(2):227–34. http://dx.doi.org/10.1016/j.jcf.2013.10.001.

[26] Sheikh SI, Long FR, McCoy KS, Johnson T, Ryan-Wenger, N a, Hayes D. Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation. J Cyst Fibros 2015;14(1):84–9. http://dx.doi.org/10.1016/j.jcf.2014.06.011.

[27] Dijk FN, Fitzgerald DA. The impact of newborn screening and earlier intervention on the clinical course of cystic fibrosis. Paediatr Respir Rev 2012;13(4):220–5. http://dx.doi.org/10.1016/j.prrv.2012.05.003.

[28] Grosse SD, Rosenfeld M, Devine OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. J Pediatr 2006;149(3):362–6. http://dx.doi.org/10.1016/j.jpeds.2006.04.059.

[29] Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Pediatrics 2001;107(1):1–13. http://dx.doi.org/10.1542/peds.107.1.1.

[30] Borowitz D, Baker SS, Duffy L, et al. Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis. J Pediatr 2004;145(3):322–6. http://dx.doi.org/10.1016/j.jpeds.2004.04.049.

[31] Viviani L, Zolin A, Mehta A, Olesen HV. The European Cystic Fibrosis Society Patient Registry: valuable lessons learned on how to sustain a disease registry. Orphanet J Rare Dis 2014;9:81. http://dx.doi.org/10.1186/1750-1172-9-81.

Please cite this article as: Mak DYF, et al, The benefits of newborn screening for cystic fibrosis: The Canadian experience, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.04.001