Journal of Cystic Fibrosis 16 (2017) 207–213

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe

Jürg Barben [a,*], Carlo Castellani [b], Jeannette Dankert-Roelse [c], Silvia Gartner [d], Nataliya Kashirskaya [e], Barry Linnane [f], Sarah Mayell [g], Anne Munck [h], Dorota Sands [i], Olaf Sommerburg [j,k], Simon Pybus [l], Victoria Winters [l], Kevin W Southern [l]

[a] *Cystic Fibrosis Centre, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland*
[b] *Cystic Fibrosis Centre, Azienda Ospedaliera Verona, Verona, Italy*
[c] *Atrium Medical Centre, Department of Pediatrics, Heerlen, The Netherlands*
[d] *Cystic Fibrosis Centre, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[e] *Department of Cystic Fibrosis, Research Centre for Medical Genetics, Moscow, Russia*
[f] *Mid-Western Regional Hospital, Dooradoyle, Limerick, Ireland*
[g] *Alder Hey Children's NHS Foundation Trust, Liverpool, UK*
[h] *AFDPHE & Hôpital Robert Debré, Paris, France*
[i] *Cystic Fibrosis Centre, Institute of Mother and Child, Warsaw, Poland*
[j] *Division of Pediatric Pulmonology & Allergy, Department of Pediatrics III, University of Heidelberg, Heidelberg, Germany*
[k] *Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany*
[l] *Institute in the Park, Alder Hey Children's Hospital, University of Liverpool, UK*

Received 17 September 2016; revised 10 December 2016; accepted 12 December 2016
Available online 30 December 2016

Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) is a well-established public health strategy with international standards. The aim of this study was to provide an update on NBS for CF in Europe and assess performance against the standards.
Methods: Questionnaires were sent to key workers in each European country.
Results: In 2016, there were 17 national programmes, 4 countries with regional programmes and 25 countries not screening in Europe. All national programmes employed different protocols, with IRT-DNA the most common strategy. Five countries were not using DNA analysis. In addition, the processing and structure of programmes varied considerably. Most programmes were achieving the ECFS standards with respect to timeliness, but were less successful with respect to sensitivity and specificity.
Conclusions: There has been a steady increase in national CF NBS programmes across Europe with variable strategies and outcomes that reflect the different approaches.

Keywords: Cystic fibrosis; Newborn bloodspot screening; IRT; PAP; CFSPID; Carriers

1. Introduction

Over the last 50 years, European countries have introduced newborn bloodspot screening (NBS) programmes for a range of inherited diseases as an important public health programme [1,2]. Increasingly, cystic fibrosis (CF) has become a core component of these programmes. The rationale for NBS for CF is well established and there is a robust evidence base to support this strategy, however the challenges of this public health initiative are well documented [3].

In 2004, the European CF Society (ECFS) established the Neonatal Screening Working Group (NSWG) to track current

* Corresponding author at: Paediatric Pulmonology & CF Centre, Children's Hospital of Eastern Switzerland, CH-9006 St. Gallen, Switzerland.
E-mail address: juerg.barben@kispisg.ch (J. Barben).

http://dx.doi.org/10.1016/j.jcf.2016.12.012
1569-1993/

practices in NBS, support implementation of NBS and establish consensus on issues arising in NBS. The first survey of the NSWG was performed in 2004/2005 and identified a wide variety of CF NBS programmes across Europe [4]. Of 26 programmes reported in this publication, two were nationally co-ordinated (France and Austria). In 2008, the NSWG published guidelines for CF NBS and recognised the wide variance in protocols. They suggested that given the geographic, ethnic, and health economic variations between countries, complete harmonisation of protocols was not appropriate, and every country had to evaluate and optimise their approach to CF NBS in light of the health structure and population screened [5].

In this study, we aim to provide 1) an update on CF NBS programmes in Europe, 2) describe and discuss differences between protocols, 3) identify barriers to establishing national NBS programmes, and (4) compare the performance with the recently published *ECFS Standards of Care Best Practice Guideline* [6].

2. Methods

An important early task of the ECFS NSWG was to identify a key worker in each country to provide information and act as a local co-ordinator. This was achieved and enabled complete coverage for the purpose of this exercise. The Core Committee of the NSWG developed three distinct questionnaires; for countries with national NBS programmes, regional NBS programmes, and without NBS (Appendix). The questionnaire for the national programmes was divided into 3 sections: (A) questions about the screening protocol, (B) the performance of the protocol in the year 2014, and (C) the structure of NBS in the country. The first section (A) included questions regarding the screening protocol with description of the specific algorithm, proportion of the screened population, sample collection (collection day), details of immune-reactive trypsinogen (IRT) measurement, second tier used including details of DNA analysis and/or pancreatitis-associated protein (PAP), procedure for one mutation and safety net strategy. The second section (B) included questions about the performance of the protocol in the year 2014 (if available), including the number of population screened, percentage above cut-off, percentage of referrals for clinical assessment (sweat test), CF diagnosis, inconclusive diagnosis, carrier detection, safety net, average and median age for diagnosis, first appointment in a CF centre, and number of false negatives and false positives. The third section (C) included questions regarding the processing of results including number of NBS laboratories in the country and details of informed consent. The questionnaires were sent to the key worker in each country in summer 2015. In some cases, they were not able to complete the survey and were encouraged to forward the survey to an appropriate colleague.

2.1. Data analysis

Performance of national programmes was assessed through data obtained from the 2014 survey and subsequent follow-up questionnaires to determine sensitivity by accurately reporting false negative cases. Data from our 2016 survey were also included to provide a more accurate assessment of practice in 2016, but not an assessment of performance of those programmes.

The data were presented graphically. Positive predictive value (PPV) was calculated as the number of true positive cases as a proportion of all positive NBS results (presented as a percentage). A positive NBS result was defined as an infant referred for clinical and diagnostic assessment (sweat testing). We also collected data about children screened positive for CF but their further clinical and diagnostic assessment was inconclusive, and these children were labelled as having an "inconclusive" diagnosis [7]. These infants are designated as CF Screen Positive, Inconclusive Diagnosis (CFSPID) in Europe [8]. We have included PPV calculations with and without CFSPID infants.

Programmes were asked to report the number of affected but not detected infants (false negatives) born in the year 2014. These numbers were used to calculate the sensitivity of the protocol in that year (the number of infants diagnosed with CF as a proportion of all infants with CF born in 2014). Infants who presented clinically (meconium ileus) but had a false negative NBS result were not included in the sensitivity calculation as this presentation does not delay diagnosis. We re-approached the 13 national programmes in 2016 to enquire if any additional false negative NBS results had been reported from 2014.

3. Results

3.1. Description of the current status of NBS for CF across Europe

A total of 31 countries provided data for 2014–2015 (16 returns from national programmes, 4 from regional programmes and 11 from countries not screening). Fifteen countries did not provide a full data reply, but confirmed that the situation had not changed (no plans for NBS). Overall, this represents a considerable increase in NBS programmes over a sixteen-year period, in particular national programmes (Fig. 1). In 2007, the Working Group reported two national programmes in Austria and France, although programmes in Northern Ireland and Wales described as regional at that time should now be considered national, as those countries have become devolved authorities within the UK. At end of 2015, there were 17 national programmes in Europe, including the most recent, Denmark (2015 data were not available for this country). Four countries (Spain, Italy, Germany and Serbia) report regional programmes. In Spain, there is complete coverage of the population, but each region uses a distinct NBS protocol. Germany has announced to start the national programme in September 2016. Twenty-five countries have no current programme. Ten were considering and planning for NBS programmes for CF. The most frequently reported barrier to implementation was a lack of financial support (4/11 countries). Other barriers included ethical concerns, a preference for antenatal screening and methodological arguments. In 2016, NBS for CF is undertaken in 21 countries in Europe. For the 13 national programmes that provided complete 2014 datasets, this corresponds to 2.7 million screened babies per year, compared to 1.6 million who were being screened annually ten years ago [4]. Bearing in mind that 2014 data do not include