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Diagnosis of cystic fibrosis in London and South East England before and after the introduction of newborn screening

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ABSTRACT

Introduction Newborn screening (NBS) for cystic fibrosis (CF) was introduced to London and South East England in 2007. We wished to assess the details of missed cases, and to compare the age at diagnosis and other clinical parameters, prescreening and postscreening.

Methods Retrospective and prospective case notes and database review of all newly diagnosed CF patients in our 7 CF centres, for 18 months before and 4 years after NBS started.

Results 347 patients were diagnosed with CF. 126 patients were not screened (born before or abroad), and had a median age at diagnosis of 2.4 years, excluding those with meconium ileus (MI). Their median time to diagnosis from initial symptoms was 1 year, and in 10% it was >6 years. After NBS started, 170 were diagnosed by NBS (48% were already symptomatic); 7 moved into the region after NBS elsewhere; 34 presented with MI (6 were negative on NBS); and 10 screened children were missed (false negative cases). Median age of diagnosis was 3 weeks. Prevalence was 1 in 3991 live births. By 2 years of age (with data on 104 patients), 49 children (47%) had their first isolation of *Pseudomonas aeruginosa*, while 37 (36%) had their first growth of *Staphylococcus aureus* from respiratory cultures.

Conclusions NBS has significantly reduced the age of diagnosis, although many were symptomatic even at 3 weeks of age. A small number of patients with CF can still be missed by the screening programme, and the diagnosis should be considered even with a negative screen result.

What is already known on this topic

- Newborn screening for cystic fibrosis (CF) was introduced to London and South East England in July 2007.
- There are certain unique aspects to this protocol—high cut-off for 1st immunoreactive trypsinogen (IRT); limited initial panel of four gene mutations; 2nd IRT measured for infants with one mutation; the 'safety net' for infants with no mutations but a very high 1st IRT.
- Screening is not infallible, and cases may be missed.

What this study adds

- The prevalence of CF in London and South East England is 1 in 3991 live births, which is lower than the overall figure for the UK (1 in 2400) due to greater ethnic diversity.
- In the first 4 years, 10 cases were missed out of approximately 920 000 screened babies.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder, caused by a genetic defect on the CF transmembrane conductance regulator (CFTR) gene. There are currently more than 1900 variations identified on the CFTR gene, although not all are pathogenic; the commonest one is p.Phe508del (ΔF508) (see http://www.cftr2.org). Diagnosis is confirmed by the presence of two disease-causing mutations and/or raised sweat chloride. Early diagnosis is possible through newborn screening (NBS) and its advantages are generally accepted.[1]

Screening was introduced to London and South East England (Bedfordshire, Essex, Hertfordshire, Kent, Surrey, and Sussex) in July 2007. The English CF Screening Protocol uses the day 5–8 Guthrie card dried blood spot to measure immunoreactive trypsinogen (IRT) using the PerkinElmer AutoDELFIA Neonatal IRT kit. If the IRT is elevated >99.5th centile (which is a high cut-off), DNA analysis for only 4 CFTR mutations is measured, and in certain circumstances a 2nd IRT measurement is made on day 21 (this is known as the IRT-DNA-IRT protocol—see figure 1).[2] Additionally a 30–32 gene mutation panel is employed if only one mutation is detected initially. Another unique feature of the programme is the 'safety net' for infants with no mutations detected but a very high 1st IRT (>99.9th centile).[2] This approach was chosen to reduce false positives, improve the positive predictive value of screening, and to reduce the number of carriers detected.[3–6] The 2nd IRT measurement also increases the chances of detecting CF in ethnic minorities (particularly important in the multicultural population of London), as the 31 mutation panel has a pick-up rate of 65% in minorities compared to 95% in Caucasians.[7]

With the introduction of NBS to our region, we wished to assess the extent of cases missed through NBS but subsequently diagnosed symptomatically; and secondarily to compare the age at diagnosis,

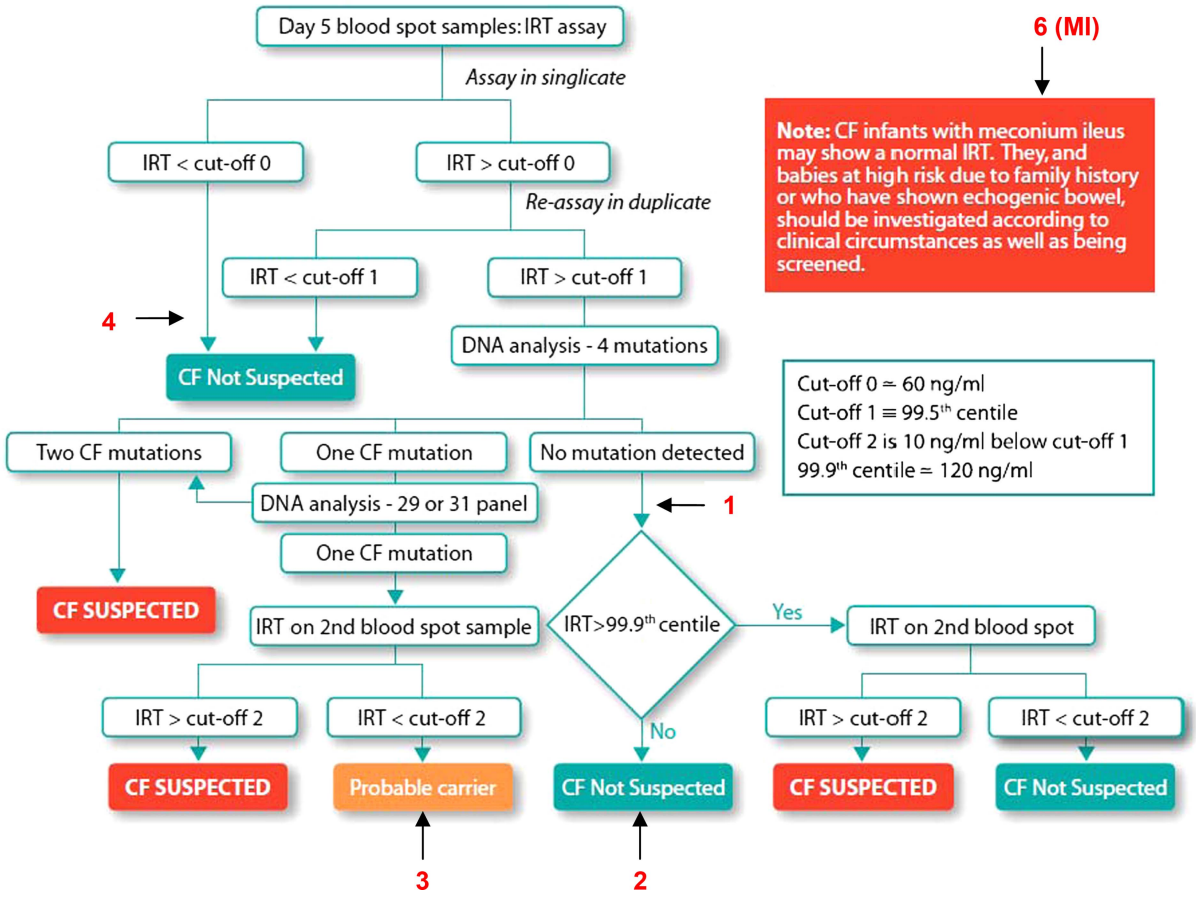

Figure 1 Algorithm for UK Newborn Screening Programme.[2] Added red numbers refer to the number of false negative patients, adjacent to the relevant stage in the screening algorithm.

mode of presentation and other clinical parameters, before and after the start of NBS.

METHODS

This study was a case notes and database review of all newly diagnosed CF patients in the London and South East England. All patients were under the care of one of the 7 CF specialist centres in the region (some also having shared care with a district general hospital as part of a CF network). Retrospective data was collected for those diagnosed in the 18 months prior to the introduction of NBS (1.1.06–30.6.07) and prospective data collected for those diagnosed in the following 4 years (1.7.07–30.6.11). The inclusion criterion for a patient was having a standard diagnosis of CF confirmed by either a raised sweat chloride (≥30 mmol/L), presence of two disease-causing CFTR gene mutations, or abnormal nasal potential difference. Ethics approval was obtained from the UK National Research Ethics Committee (REC reference number 07/MRE09/56). Research and Development approval was obtained at each centre involved in the study. Parental consent was not required for this service review, and data was pooled anonymously.

RESULTS

Over the 5.5-year study period, 347 patients were newly diagnosed with CF (figure 2). Two hundred and twenty-one patients underwent NBS, including seven born outside the region and subsequently referred to one of our centres. One hundred and twenty-six patients did not undergo NBS because they were either born before the implementation of the screening programme, or in two cases, born abroad. Comparison of number of new patients per year in London and South East England and whole of UK (latter data from UK CF Registry) is shown in table 1. Available data from the 2009–2010 and 2010–2011 (1 April–31 March) national NBS reports show that the number of babies screened in our region by the three screening laboratories (Great Ormond Street Hospital, South East Thames and South West Thames) was 233 208 and 229 777/year respectively.[8] This represents 34% and 33% of all screened babies in England for those 2 years. In that period, there were 116 newly diagnosed babies (screening and meconium ileus—MI) in our region making our prevalence 1 in 3991 live births. For the UK as a whole, in those 2 years, 0.06% and 0.07% parents declined the screening test, but figures are not available for London and South East England specifically.

Demographics

As expected, the median age at diagnosis has fallen with NBS to 19–22 days in the 4 years since implementation, prior to that it was 16.8 months in 2006, and 4.9 months in 2007 when NBS took place from July onwards (table 1, see online supplementary figure S1). In terms of ethnicity, 292 (84%) patients were Caucasian, 23 (7%) were Asian (from the Indian subcontinent), 20 (6%) were of mixed background, 5 (1.5%) were of Black Caribbean/African ethnicity, and the remaining 7 (2%) were from other backgrounds (see online supplementary table S1). A detailed breakdown of the officially classified ethnic groupings

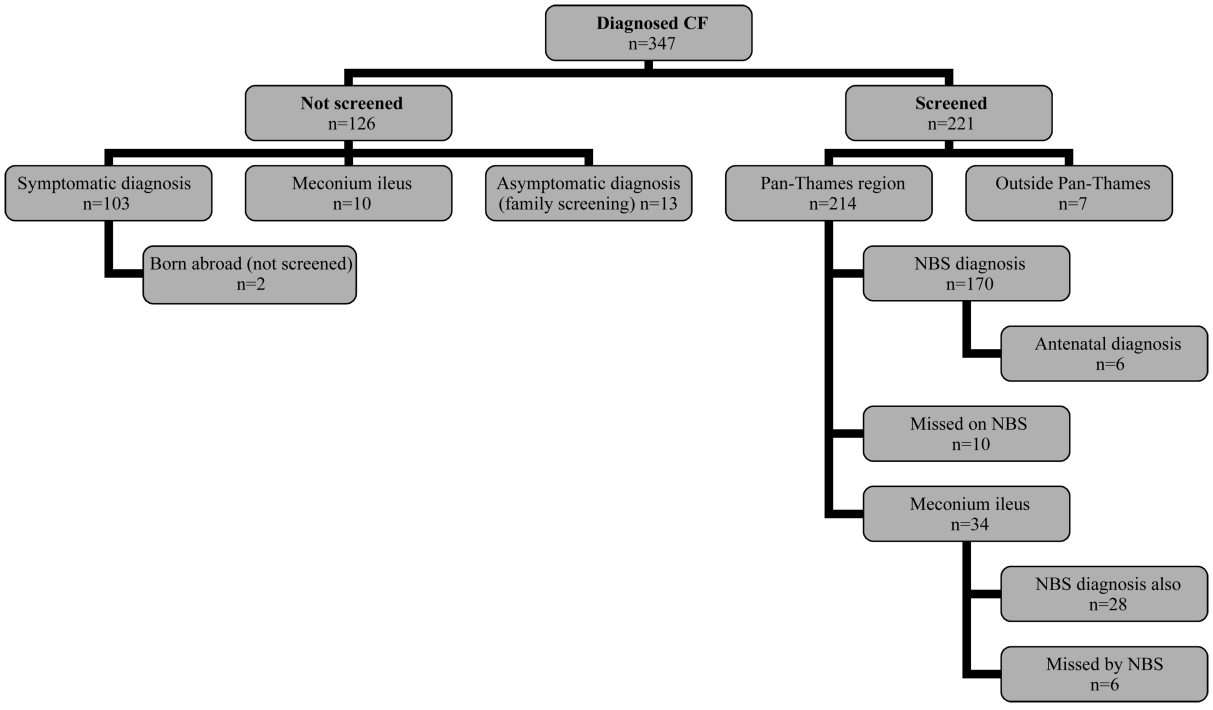

Figure 2 Mode of cystic fibrosis (CF) diagnosis in the 347 children presenting to the 7 CF centres in London and South East England for the 18 months before screening was instituted and the 4 years afterwards. Boxes also include figures for those already diagnosed antenatally.

is given in online supplementary table S2. The frequency of common genotypes in the 347 London and South East England patients were similar to the figures given for the 8294 UK patients in the 2011 UK CF registry,[9] namely 50% vs 52% homozygous for the p.Phe508del; and 36% versus 39% heterozygous for p.Phe508del and one other mutation (see online supplementary table S1). The frequency of gene mutations was also similar in the 214 babies screened in London and South East England compared to the UK (table 2). Regarding the four genotypes tested in the initial four-mutation panel of the English CF Screening Protocol, only 123/214 (57%) children had two of them identified, but 193/214 (90%) children had at least one of the four mutations.

Presentation of patients who were not screened

Of the 126 patients who did not undergo NBS, 103 presented with typical symptoms of CF (excluding MI)—see online supplementary table S3; 10 presented with MI (including three with abnormal antenatal ultrasound scans); and 13 were diagnosed before any symptoms appeared (12 following cascade screening due to affected family members, and one with the diagnosis confirmed on chorionic villus sampling). The median age at diagnosis for those diagnosed symptomatically (excluding MI) was 2.4 years (range 3 weeks–16 years). 79 patients (77%) had at least three visits to their general practitioner, 44 (43%) had at least two visits to a paediatric clinic, and 61 (59%) had at least one hospital admission before the diagnosis of CF was made. The median time to diagnose CF from the 1st presentation of CF-related symptoms to a health professional was 1.0-year (range 0 to 16.1 years, IQR 0.2–2.5 years). In 10 patients (10%), the diagnosis was delayed more than 6 years after the initial presentation of symptoms, all of which were classic for CF (see online supplementary table S4).

Table 1 Comparison of number of newly diagnosed patients per year and median age at diagnosis in London and South East England and whole of UK (latter data from UK CF Registry, available at http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/, and based on CF Registry data available March 2013)

Year	New paediatric patients in UK	New paediatric patients in our region	Median age of diagnosis in paediatric patients in the UK	Median age of diagnosis in paediatric patients in our region
2006	No data	44	No data	16.8 months
2007	338	69 (20% UK cases)	33 days	4.9 months*
2008	325	71 (22% UK cases)	24 days	22 days
2009	289 (151 NBS—52%)	63 (22% UK cases)	24 days	21 days
2010	314 (189 NBS—62%)	76 (24% UK cases)	23 days	19 days
2011	232 (155 NBS—67%)	24†	23 days	20 days

This includes those diagnosed by screening, with meconium ileus and late diagnoses born in earlier years.
*Newborn screening (NBS) in place 2nd 6 months only.
†1st 6 months data only.
CF, cystic fibrosis.

Table 2 Frequency of CF mutations present in the 214 children screened in London and South East England, compared to UK CF Registry for 2011.[9]

Mutation	NBS patients in London & South East England n=214*	London & South East England %	UK CF Registry 2011 n=8294%
p.Phe508del (ΔF508)	187	87.4	90.6
p.Gly551Asp (G551D)	7	3.3	5.6
p.Gly542X (G542X)	9	4.2	3.6
c.489+1G>T (621 +1G>T)	3	1.4	2.3
p.Arg117His (R117H)	10†	4.7	4.1
p.Asn1303Lys (N1303K)	4	1.9	1.4
c.1585-1G>A (1717-1G>A)	5	2.3	1.3
c.2988+1G>A (3120 +1G>A)	3	1.4	0.1
c.3140-26A>G (3272-26A>G)	3	1.4	Not given
p.Gly85Glu (G85E)	3	1.4	0.7

Shaded cells represent genotypes tested in the initial four-mutation panel of the English CF Screening Protocol.
*193/214 (90%) children had at least one of the four mutations in the initial panel. 109 were homozygous for the p.Phe508del gene mutation; six were heterozygous for p.Phe508del and p.Gly551Asp; four were heterozygous for p.Phe508del & p.Gly542X; three were heterozygous for p.Phe508del & c.489+1G>T; and one was homozygous for p.Gly542X.
†For the 10 with p.Arg117His, 8 were associated with 7 T and 2 with the 5 T variants of the poly T tract on intron 8 of the CF trans-membrane conductance regulator gene.
CF, cystic fibrosis; NBS, newborn screening.

Presentation of screened patients

Of the 214 patients with CF screened in our region, 170 had a positive diagnosis of CF from the screening (figure 2). Six of the 170 had already been diagnosed antenatally (four following suspicious ultrasound scans and two with a family history). One patient had the diagnosis confirmed at almost 2 years of age due to persistent non-attendance for further investigations following a raised IRT level. At the first medical review of the 170 children, the most common symptoms were loose stools (in 32% patients), poor weight gain (21%), and recurrent cough (4%). Only 89 children (52%) were symptom free at the time of diagnosis, although four of them had been diagnosed antenatally. Seven other patients did not have symptoms from CF, but had comorbidities, including three who were preterm.

Most importantly, in the 4 years, 10 patients had false negative results from NBS but were subsequently diagnosed with CF (details in table 3). Three of them were still asymptomatic, but had further testing at parental requests; six presented with classic symptoms of CF and were diagnosed aged 6 weeks–2 years. Since 4 years is the maximum length of follow-up after screening in our study, there may well be further patients who have not yet been diagnosed having been screen-negative.

Out of the 180 babies with CF who had been screened in our region (includes 170 diagnosed and 10 missed, but excludes the 34 with MI), the 1st IRT had a median level of 162 mcg/L (IQR 117–216, range 43–410). Second blood spots were collected in 36/180 babies at a median age of 27 days (range 21–39 days). In these 36, the 2nd IRT median was 131 mcg/L (IQR 98–163, range 29–376). Despite the national protocol, 26% did not have a sweat test performed, with their diagnosis made on genetic testing alone (presumably the majority with the result taken from the screening blood test). Of the 134 sweat tests, 4 (3%) were normal (chlorides of 16, 19, 22 and 29 mmol/L), 12 (9%) abnormal with chloride 30–60 mmol/L, and 118 (88%) abnormal with chloride ≥60 mmol/L. Overall, the median sweat chloride was 95 mmol/L (IQR 86–101, range 16–164); genotypes and other details of those with normal or intermediate sweat chloride results are in table 4). Stool elastase was measured in 175/180 children and was abnormal in 141 (81%); 5/34 children with normal elastase levels subsequently became abnormal, so overall, 83% were pancreatic insufficient. Growth parameters are shown in online supplementary table S1, but even at diagnosis at 3 weeks of age, median Z score for weight was −1.2 (IQR −2.0 to −0.6), and for height −0.6 (IQR −1.6 to 0.04).

In total, 28/34 patients with MI were also screened positive for CF (in two cases, the diagnosis had been made on amniocentesis or chorionic villus sampling done for echogenic bowel). Five patients had low IRT levels (ie, negative screening), and in one patient, an IRT sample was invalid as it was collected too soon after a blood transfusion. Overall, the 1st IRT had a median level of 104 mcg/L (IQR 85–135, range 20–259). This was significantly lower than the IRT in the 180 non-MI CF babies (Mann Whitney test—$p<0.0001$). Nevertheless, these six patients all had a genetic confirmation of their CF, and all were pancreatic insufficient.

Microbiology of respiratory samples in the screened cases

Results of the first respiratory microbiology sample (cough swab or bronchoalveolar lavage) were obtained from 179 out of the 180 CF children screened (excluding MI). A positive culture was found in 35/179 (20%) children who were sampled, mostly with *Staphylococcus aureus* (31/35), but even at this early stage, three were positive for *Pseudomonas aeruginosa* (see online supplementary table S1); 158/170 (93%) of these first samples were taken within 6 weeks of age, and 97% within 12 weeks. However, this compares favourably to the non-screened children, in whom 51/103 (50%) had a positive culture at the time of diagnosis ($p<0.0001$ screened vs non-screened), 31% with *S aureus* ($p<0.001$ screened vs non-screened) and 19% with *P aeruginosa* ($p<0.0001$ screened vs non-screened). Two-year follow-up microbiology data was available for 104/211 patients. By 2 years of age, 49 children (47%) had their first isolation of *P aeruginosa*, while 37 (36%) had their first growth of *S aureus*. Three-year follow-up data were available in 60 patients; by 3 years of age, 38 patients (63%) had isolated *P aeruginosa* and 30 (50%) isolated *S aureus*. Median age of first isolation of *P aeruginosa* was 1.0 year and *S aureus* 2.9 months (see online supplementary table S1).

DISCUSSION

We present 4 years of screening data from 920 000 screened babies in London and South East England, which is one-third of all those screened for CF in England. This is the first detailed report of the current NBS protocol in England. As expected, the median age of diagnosis (excluding those with MI) has been significantly reduced with NBS, from 2.4 years to 3 weeks of age. It was striking that of the 103 children diagnosed symptomatically in the 18 months prior to screening, 10 of them (10%) had a delay of over 6 years from presentation to diagnosis despite classic CF symptoms. The introduction of this screening programme confirms that undue delay in a CF diagnosis will be rare.

It has been shown in the USA that screening programmes that include DNA analysis alongside IRT testing (IRT/DNA vs IRT/IRT) make the CF diagnosis at a younger age (median 16 vs 28 days).[10] The median age in our study using IRT-DNA-IRT is

Table 3 Details of patients (n=10) missed by newborn screening (NBS) but subsequently diagnosed with CF during the 4-year study period

Age at diagnosis	Gender/ ethnicity	History	Reason NBS missed diagnosis	Genotype
NBS results negative but diagnosed before becoming symptomatic (n=3)				
7 weeks	Male White British	Mother had CF and father was a carrier, so patient was tested. Abnormal sweat test (Cl^- 57 mmol/L) & genotyping.	Normal IRT (43 mcg/L).	p.Arg117His (5 T)/p. Ile1269Asn
5 months	Male White British	Parents requested testing after screening isolating one gene. Child asymptomatic. Abnormal sweat test (72 mmol/L), 2nd gene on extended genotyping.	1st IRT 101 mcg/L. One gene isolated and 2nd IRT was low (58 mcg/L), reported as 'low likelihood CF/ probable carrier'.	p.Phe508del/p.Leu206Trp
2 months	Male White British	Parents requested testing after screening isolating one gene. Child asymptomatic. Abnormal sweat test (66 mmol/L), 2nd gene on extended genotyping.	1st IRT 70 mcg/L. One gene isolated and 2nd IRT was low (41 mcg/L), reported as 'low likelihood CF/ probable carrier'.	p.Phe508del/ c.3140-26A>G
NBS results negative but subsequently presenting with symptoms (excluding meconium ileus) (n= 7)				
Age at diagnosis	Gender	History	Reason NBS missed diagnosis	Genotype
7 weeks	Male Egyptian	Prolonged conjugated hyperbilirubinaemia and poor weight gain. Abnormal sweat test (85 mmol/L) & extended genotyping.	IRT raised>99.9th % (173 mcg/L) and no genes found, so specimen for 2nd IRT requested by NBS lab. However, no sample received, so incomplete screening.	c.1302delA/c.1302delA *†
6 months	Female Bangladeshi	Productive cough and failure to thrive. Diagnosed on extended genotyping, abnormal sweat test (57 mmol/L).	Normal IRT (no value reported).	p.Ile502Thr/p.Ile502Thr†
9 months	Male Bangladeshi	Older sister has CF but following negative NBS, the patient was not tested further. Cough and failure to thrive. Abnormal sweat test (91 mmol/L) & extended genotyping.	Normal IRT (62 mcg/L).	p.Arg709X/p.Arg709X†
14 months	Female White British	Recurrent chest infections. 2nd gene on extended genotyping. Sweat test just abnormal (30 mmol/L).	1st IRT 73 mcg/L. One gene isolated and 2nd IRT was low (29 mcg/L), reported as 'low likelihood CF/probable carrier'.	p.Phe508del/p.Thr582Ile and c.1117-26_25delTA
11 weeks	Female White Irish	Productive cough and poor weight gain. Abnormal sweat test (102 mmol/L) & genotyping.	Normal IRT (68 mcg/L).	p.Phe508del/p.Phe508del†
7 weeks	Female Afghanistani	Persistent cough and failure to thrive. Abnormal sweat test (93 mmol/L) & extended genotyping.	Raised IRT but level<99.9th % (105 mcg/L) and no genes found, so reported as 'CF not suspected'.	p.Gly178Arg/p.Gly178Arg†
2 years	Female Sri Lankan	Referred to CF centre a for recurrent chest infections. Abnormal sweat test (95 mmol/L) & extended genotyping.	Raised IRT but level<99.9th % (111 mcg/L) and no genes found, so reported as 'CF not suspected'.	p.Ile1295PhefsX33/p. Ile1295PhefsX33

*This was reported by the Manchester genetics laboratory as 'previously undescribed, highly likely to be pathogenic'. The child has Egyptian parents and sweat chloride was 85 mmol/L. Six patients were homozygous, with five being rare mutations; 5/6 had consanguineous parents (marked with †).
CF, cystic fibrosis; IRT, immunoreactive trypsinogen.

20.5 days. Even at such a young age, we found a significant proportion (48%) already had symptoms, mostly loose stools and/ or poor weight gain. Additionally, by 2 years of age (in the 104 patients with data) almost half had already had their first *P aeruginosa* infection and one-third their first *S aureus* infection (we should stress these figures do not necessarily represent chronic infection). This would suggest current infection control policies against *P aeruginosa* with careful attention to segregation are not as effective as anticipated; but it is also possible there are environmental factors at play.

CF screening is not infallible. It had been forecast that there would be three babies missed per year in our region; we found 10 in 4 years supporting this prediction. It is also likely there are still some children yet to be diagnosed, born in the 4-year period and missed on screening. We found our misses occurred in five places on the screening pathway (indicated with arrows in figure 1).

- *Infants, negative on screening, but with MI* (6 cases): IRT is considered unreliable in babies with MI in the first week of life.[2 11] Our data are a reminder that all babies with MI should have a DNA analysis and sometimes a sweat test.
- *IRT less than initial cut-off* (4 cases). Of the 'biological' false negative cases, one even had the classic p.Phe508del/p. Phe508del genotype. Known reasons for falsely low IRT levels are acute gastroenteritis or respiratory illness; and some premature or small-for-dates babies.[2]
- *Probable carrier, low likelihood of CF* (3 cases). There is an average of 152 (range 131–171) babies falling into this screening category each year in England[8] This group receives genetic counselling to tell them that the possibility their child has CF cannot be ruled out completely. Although 'CF is not suspected', they are offered a sweat test. Two were tested and diagnosed at 2 months and 5 months of age. The parents of the third child declined the sweat test and he was diagnosed at 14 months of age with recurrent chest infections. We know of another child in the 'probable carrier' category, aged 3 years (diagnosed after the study period ended), whose parents did not proceed with a sweat test, but who was diagnosed after 4 months of diarrhoea and weight loss. The protocol could be altered to refer them all for sweat testing, and although this would be quite a logistical undertaking, perhaps this change should be considered.
- *IRT<99.9th centile with no mutation found—CF not suspected* (2 cases). This highlights the issue of using cut-offs designed to reduce the number of false positive babies referred for sweat tests, at the cost of missing some.
- *System error* (1 case). A second IRT sample (as there were no genes found and the IRT was >99.9th%), was never received. The baby was diagnosed following prolonged conjugated hyperbilirubinaemia aged 7 weeks.

Table 4 Details of CF patients with normal (<30 mmol/L) and intermediate (30–60 mmol/L) sweat chloride results

Sweat C^{l-} (mmol/L)	Genotype	1st IRT (mcg/L)	2nd IRT (mcg/L)	Ethnicity
16	p.Phe508del/p.Asp1152His	167	–	White British
19	p.Phe508del/p.Arg117His	77	–	White Other
22	p.Phe508del/p.Arg117His	64	–	White British
29	p.Phe508del/p.Asp1152His	73	–	White British
30	p.Phe508del/p.Thr582Ile and c.1117-26_25delTA	73	29	White British
32	p.Phe508del/p.Arg117His	81	–	White British
35	p.Phe508del/c.3717 +10kbC>T	75	–	White British
35	p.Phe508del/p.Arg117His	88	–	White British
35	p.Phe508del/p.Arg117His	121	–	White British
40	p.Phe508del/p.Arg117His	79	–	White British
41	p.Gly551Asp/p.Arg117His	94	–	White British
46	p.Phe508del/p.Arg117His	70	–	White British
52	p.Phe508del/p.Leu1156Leu	94	69	White Other
55	E1124del/E1124del	303	182	Pakistani
57	p.Arg117His/p.Ile1269Asn	43	–	White British
57	p.Ile502Thr/p.Ile502Thr	Low	–	Bangladeshi

CF, cystic fibrosis; IRT, immunoreactive trypsinogen.

These missed babies illustrate that if there is clinical suspicion of CF in a previously screened child, a sweat test must be performed.

The birth prevalence of CF was 1 in 3991 live births (for 2 of the years), which is lower than the expected figure for the UK of 1 in 2415.[12] Aside from the undiagnosed children, there is a greater ethnic mix in the London region than the country overall, hence the incidence in the region was always likely to be lower than the national figure. The exact ethnic breakdown of the screened population in London and South East England is not available, although it is known that in 2006–2007, 51% of births in Greater London were to women born outside the UK,[13] and in 2009 in Inner London the figure was 60%.[14] One of the reasons behind the IRT-DNA-IRT protocol is to increase the chance of detecting CF in non-Caucasian babies.[7]

This study demonstrates the success of CF screening in reducing the age of diagnosis in our area. As expected, some babies are missed by the process, and clinicians still need to consider the diagnosis when symptoms are suggestive of CF. Finally, a significant proportion of screened infants had clinically important bacteria isolated from respiratory samples within the first 2 years, highlighting the importance of microbiological vigilance in a screened cohort.

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Contributors MTCL collected and analysed the data. IMB-L was PI and wrote the paper with CW. Other authors all reviewed the paper and provided data from their centres.

Competing interests None.

Ethics approval UK National Research Ethics Committee (REC reference number 07/MRE09/56).

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