BMJ

BMJ 2012;344:e4224 doi: 10.1136/bmj.e4224 (Published 3 July 2012)

RESEARCH

Derivation and validation of age and temperature specific reference values and centile charts to predict lower respiratory tract infection in children with fever: prospective observational study


OPEN ACCESS

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Abstract

Objectives To develop reference values and centile charts for respiratory rate based on age and body temperature, and to determine how well these reference values can predict the presence of lower respiratory tract infections (LRTI) in children with fever.

Design Prospective observational study.

Participants Febrile children aged at least 1 month to just under 16 years (derivation population, n=1555; validation population, n=671) selected from patients attending paediatric emergency departments or assessment units in hospitals.

Setting One hospital in the Netherlands in 2006 and 2008 (derivation population); one hospital in the Netherlands in 2003-05 and one hospital in the United Kingdom in 2005-06 (validation population).

Intervention We used the derivation population to produce respiratory rate centile charts, and calculated 50th, 75th, 90th, and 97th centiles of respiratory rate at a specific body temperature. Multivariable regression analysis explored associations between respiratory rate, age, and temperature; results were validated in the validation population by calculating diagnostic performance measures, z scores, and corresponding centiles of children with diagnoses of pneumonic LRTI (as confirmed by chest radiograph), non-pneumonic LRTI, and non-LRTI.

Main outcome measure Age, respiratory rate (breaths/min) and body temperature (°C), presence of LRTI.

Results Respiratory rate increased overall by 2.2 breaths/min per 1°C rise (standard error 0.2) after accounting for age and temperature in the model. We observed no interactions between age, temperature, and respiratory rates. Age and temperature dependent cut-off values at the 97th centile were more useful for ruling in LRTI (specificity 0.94 (95% confidence interval 0.92 to 0.96), positive likelihood ratio 3.66 (2.34 to 5.73)) than existing respiratory rate thresholds such as Advanced Pediatrics Life Support values (0.53 (0.48 to 0.57), 1.59 (1.41 to 1.80)). However, centile cut-offs could not discriminate between pneumonic LRTI and non-pneumonic LRTI.

Conclusions Age specific and temperature dependent centile charts describe new reference values for respiratory rate in children with fever. Cut-off values at the 97th centile were more useful in detecting the presence of LRTI than existing respiratory rate thresholds.

Introduction

Bacterial pneumonia is now the most common serious bacterial infection among children presenting with fever to paediatric emergency departments in industrialised countries.[1] To identify children at risk of lower respiratory tract infection, several clinical signs and symptoms have been reported as potential predictors.[1-5] Respiratory rate is the clinical feature with the most consistent and strongest evidence for predicting lower respiratory tract infection.[1-10] However, other reports have failed

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Web appendix 1: Age and temperature specific L, M, and S values (as calculated with LMSChartMaker Pro (Medical Research Council, UK))
Web appendix 2: Number of patients for different age groups and temperature bands (derivation population)
Web appendix 3: Diagnostic performance of temperature dependent reference values to detect presence of lower respiratory tract infection: (A) pneumonic LRTI vs. non-LRTI, and (B) non-pneumonic LRTI vs non-LRTI
Web appendix 4: Diagnostic performance of temperature dependent reference values, and Fleming and APLS reference values to detect presence of lower respiratory tract infection: pneumonic LRTI vs. non-pneumonic LRTI
Web appendix 5: Patient characteristics of patients of the derivation population with and without measured respiratory rate

to identify tachypnoea as a useful clinical predictor of the disease.[8] Tachypnoea might not always be associated with lower respiratory tract infection, since children with the disease are also typically febrile, and the separate contributions of fever and the underlying infection to the presence of tachypnoea are unclear.[11 12] Furthermore, even if the effect of fever is discounted, the increased respiratory rate might not be categorised as tachypnoea, owing to inaccurate threshold values.[3 6 13-19] Fleming and colleagues suggested that commonly used threshold values for respiratory rate, such as those of the Advanced Pediatrics Life Support (APLS) guidelines, could cause considerable misclassification.[20]

The predictive value of vital signs is probably best shown by using modelling strategies that incorporate both their continuous nature and the effect of body temperature.[21] To our knowledge, no such reference values are available for respiratory rate. We did a prospective observational study to determine the associations between age, body temperature, and respiratory rate, and use this information to derive reference values and centile charts for respiratory rate in children according to age and body temperature. Finally, we evaluated the predictive ability of these reference values to discriminate lower respiratory tract infections in children with fever in emergency care settings.

Methods

Design, setting, and participants

Population used for deriving reference values

We recruited children with fever, aged at least 1 month to just under 16 years, presenting to the paediatric emergency department of the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands, in 2006 and in 2008. This university hospital receives 9000 emergency care visits every year (of which 90% are basic paediatric emergencies).[22]

Clinical signs and symptoms were registered in a standardised electronic patient record.[23] Temperature and respiratory rate were measured at the discretion of the attending physician or nurse. Body temperature was measured rectally. Trained emergency care nurses measured respiratory rate by using a standard approach that involved clinical counting of respiratory movements for 30 seconds. Children with measurements for both temperature and respiratory rate were eligible. Children whose respiratory rate was recorded while they were crying or distressed were excluded. We also excluded children with an acute exacerbation of a primary pulmonary condition (including lower tract respiratory infections), metabolic (including dehydration) or neurological disease potentially interfering with respiratory rate, "immediate" triage urgency according to the Manchester triage system, or a chronic disease (requiring at least two hospital visits per year). We considered outliers to be children whose respiratory rate was more than three standard deviations from the mean rate for their age group and temperature band, and excluded them from the derivation of normative reference values (fig 1⇓).

Populations used for validation study

To validate the reference values, we selected children at risk of lower respiratory infectious disease from two populations that differed from the derivation population in both setting and time.[9 10 24] The first population consisted of children, aged at least 1 month to just under 16 years, with fever (axillary temperature >38.0°C) and signs of lower respiratory tract infection (cough, difficulty breathing, or wheeze), who presented to the paediatric assessment unit of the University Hospital Coventry and Warwickshire NHS trust in Coventry, United Kingdom, between 2005 and 2006.[9] The Coventry hospital is an inner city hospital delivering emergency care to about 25 000 children every year.

The second validation population included children aged from 1 month up to 16 years, with fever (rectal temperature >38.0°C) and cough, who presented to the paediatric emergency department of the Erasmus MC-Sophia Children's Hospital in 2003-05.[10 24] We excluded children with an increased risk of recurrent serious infections, such as iatrogenic immunosuppression, malignancies, severe psychomotor retardation, or cystic fibrosis. We included children in whom both temperature and respiratory rate were measured.

Final diagnoses of lower respiratory tract infection were divided into pneumonic lower respiratory tract infection (LRTI), non-pneumonic LRTI, and non-LRTI. Pneumonic LRTI was defined as radiological changes consistent with pneumonia—that is, the presence of micronodular or macronodular infiltrations or consolidation in chest radiographs (Coventry: single radiologist, unblinded; Erasmus MC-Sophia: two radiologists, blinded). Non-pneumonic LRTI was defined as the presence of clinical signs of lower respiratory tract infection, such as chest wall retractions, decreased oxygen saturation, crackles, or grunting, but without chest radiograph changes consistent with pneumonic LRTI. If the final diagnosis was inconclusive or the chest radiograph was absent, the investigators reached a consensus diagnosis (Coventry: MT; Erasmus MC-Sophia: HM, RO). The final consensus diagnoses were established using all available information from the medical records and additional tests. We made follow-up visits or telephone calls at one week and did a medical records check for reattendance within one week to rule out the possibility of missed diagnoses and to avoid verification bias.[25]

Ethical approval

The study was approved by the local medical ethics committee of the Erasmus MC-Sophia Children's Hospital and requirement of informed consent was waived. For the Coventry population, the Coventry local research ethics committee (04/Q2802/115) approved the study and informed consent was required and given.[9 23]

Derivation of reference values and centile charts for respiratory rate

Univariate and multivariable linear regression analyses

We calculated Spearman's ρ correlation coefficients for respiratory rate (breaths/min), body temperature (°C), and age (years) using R statistical software, version 12.1.2 (cor.test function).[26] We evaluated age as a continuous variable and in clinically relevant categories (1 month to <12 months, 12 to <24 months, 24 months to <5 years, and 5 to <16 years).[14 27] To compare the correlation coefficients for temperature and respiratory rate of the different age groups, we used the Fisher r to z transformation.[28 29] We used multivariable linear regression analysis (SPSS, version 17.0) to determine the relation between respiratory rate, temperature, and age.

Age and temperature dependent centiles for respiratory rate, and minimum sample size

We calculated median and upper centiles (75th, 90th, and 97th) of respiratory rate at a specific temperature for children in each age group using LMSChartMaker Pro (Medical Research

Council, UK), based on the method of Cole and Green.[30] We checked the final models using z score graphs, detrended Q-Q plots, and Q statistic curves for the parameters in the model (L, M, S). In each age group, we aimed to recruit 30-60 children for each relevant temperature bands (≤37.9°C, 38.0-38.9°C, 39.0-39.9°C, ≥40.0°C), according to recommendations of Virtanen and colleagues.[31]

Validation of the predictive ability of temperature dependent centiles to identify lower respiratory tract infections

We calculated individual z scores for children who had pneumonic LRTI, non-pneumonic LRTI, and non-LRTI by using the following formula: ((respiratory rate/μ)λ−1) /(λ×σ) (in which μ, λ, and σ are age group and temperature specific parameters; web appendix 1).[32] We compared z scores using the non-parametric test of Kruskal-Wallis. We then calculated the diagnostic performance (sensitivity, specificity, positive and negative likelihood ratios) and discriminative ability (area under receiver operating characteristics curve) of centile cut-off values (50th, 75th, 90th, and 97th). Finally, we calculated the diagnostic performance and discriminative ability of the APLS threshold values,[27] and the continuous reference values of Fleming and colleagues.[20] We did all calculations using the Epi, verification, and Hmisc package in R.[26]

Results

Table 1⇓ describes characteristics of the derivation population (n=1555) and two validation populations (Erasmus MC-Sophia: n=311; Coventry: n=360).[9 10 24]

Univariate and multivariable linear regression analysis

Respiratory rate had a significantly negative correlation with age (r=−0.64) and positive correlation with temperature (r=0.27). The correlation between respiratory rate and temperature was significantly smaller in children aged at least 1 month to just under 12 months (r=0.13) than in those in the other age groups (12 to <24 months (r=0.34); 24 months to <five years (r=0.36); and five to <16 years (r=0.41)). We found an overall increase of 2.5 breaths/min per 1°C rise in temperature (standard error 0.3; model 1, table 2⇓), which decreased after we added age to the model (β=2.2 (standard error 0.2), P<0.01; model 2, table 2). We observed no interaction between the age groups and temperature.

Age specific and temperature dependent centiles for respiratory rate

We achieved a minimum sample size of 30 or more in all but one of the temperature bands and age groups (web appendix 2). Table 3⇓ shows reference values of respiratory rate at the median, 75th, 90th, and 97th centiles, indicating values that were outside APLS threshold values. Upper limits of APLS threshold values corresponded with the 75th centile in febrile children at least 12 months old and with the 50th centile in febrile children younger than 12 months. The upper centile regions of the higher temperature bands differed from the Fleming reference values in particular. Figure 2⇓ plots all centiles.

Diagnostic performance of age specific and temperature dependent centiles to identify lower respiratory tract infection

The mean z score of children with pneumonic LRTI was 1.16 (95% confidence interval 0.96 to 1.37), corresponding to the 88th centile. The mean z score for those with non-pneumonic LRTI was 1.01 (0.80 to 1.23; 84th centile). These two z scores were significantly higher than the z score of children with non-LRTI (0.34 (0.25 to 0.43); 63rd centile), but did not differ significantly from each other (P=0.31).

Table 4⇓ compares the diagnoses of all lower respiratory tract infections (pneumonic and non-pneumonic LRTI combined) with non-LRTI for each centile cut-off value. Cut-off values at the 50th centile had a moderate sensitivity of 0.84 (0.79 to 0.89) and negative likelihood ratio of 0.40 (0.29 to 0.56), and could not rule out presence of lower respiratory tract infections. Cut-off values at the 97th centile had a high specificity (0.94 (0.92 to 0.96)) and positive likelihood ratio (3.66 (2.34 to 5.73)) and were useful to rule in lower respiratory tract infections. Cut-off values at higher centiles had a lower sensitivity but a higher specificity and positive likelihood ratio than cut-off values at lower centiles. The centile cut-off values were able to distinguish both pneumonic and non-pneumonic LRTI from non-LRTI (web appendix 3), but could not differentiate between pneumonic and non-pneumonic LRTI (web appendix 4A). The centile cut-off values performed better than the Fleming and APLS reference values in detecting lower respiratory tract infection (table 5⇓). The APLS threshold values and cut-off values at the lower centiles (50th and 75th) performed similarly. Neither the Fleming or APLS reference values proved useful in differentiating between pneumonic and non-pneumonic LRTI (web appendix 4B).

Discussion

Principal findings

This study provides reference values and centile charts for respiratory rate based on the body temperature in children of different age groups, and their diagnostic value to predict lower respiratory tract infections. We observed an independent association between respiratory rate and both age and temperature. Respiratory rate, adjusted for age, increased by around 2.2 breaths/min per 1°C rise in body temperature without significant contributions from specific age groups. Cut-off values at the 90th and 97th centiles were useful for ruling in the presence of all lower respiratory tract infections (specificity 0.86 (95% confidence interval 0.82 to 0.89) and 0.94 (0.92 to 0.96), respectively). Cut-off values at the 50th centile had only a moderate sensitivity (0.84 (0.79 to 0.89)) and negative likelihood ratio (0.40 (0.29 to 0.56)), and could not rule out the presence of lower respiratory tract infections.

Our findings accord with others who reported an increase, unadjusted for age, of 2.5 breaths/min per 1°C rise in temperature in two different paediatric populations.[6 33] Our results are also supported by previous observations of an increase of about 20 breaths/min between the fifth and 95th centiles adjusted for age and temperature in resting, healthy children.[34] However, none have provided reference values or centile charts for respiratory rate in children of different age groups that are based on body temperature. Based on our results, we conclude that a previously reported rise of five to 11 breaths/min per 1°C rise in temperature overestimates the true increase.[35]

Our centiles provide threshold values on a continuous scale. They differed considerably from the APLS threshold values, especially for children with high fever.[21] Our centiles reduced misclassification and outperformed both the APLS threshold values and the continuous reference values of Fleming and colleagues for ruling in the presence of lower respiratory tract infections. This improvement accords with previous reports evaluating the usefulness of the temperature dependent centiles for heart rate.[36] Only the 50th centile cut-off value of the Fleming reference values, with no correction for body temperature and which had similar sensitivity, showed moderate value for ruling out the presence of lower respiratory tract infection.

Our centile charts are preferred as a clinical tool in febrile children, especially if respiratory rate is measured in the upper centiles, in order to identify lower respiratory tract infections. Smart phone applications or computer programmes that automatically adjust the respiratory rate for age and temperature could facilitate their use in clinical settings.

We found no difference between the mean z scores for the pneumonic and non-pneumonic LRTI groups. This result complies with the now widely accepted opinion of paediatric respiratory specialists that chest radiographs discriminate poorly between bacterial, viral, and atypical infections.[37] In addition to our respiratory rate centiles, more sophisticated diagnostic tools are needed to decide on further diagnostic and therapeutic management of children with lower respiratory tract infection. These tools should incorporate other important clinical signs and symptoms (such as age, grunting, wheezing, duration of disease, and signs of general illness[38]) and possibly the concentrations of inflammatory markers, such as C reactive protein and procalcitonin.[10 39]

Strengths and weaknesses of the study

The main strength of our study was the large cohort of children visiting a paediatric emergency department, reflecting the general population of febrile children. We also validated the diagnostic performance of our centiles in different time periods and clinical settings using two large validation samples including children with lower respiratory tract infections. We did not assess validity or diagnostic performance of the centile charts in primary care or in low or middle income countries, and we recommend further validation to ensure generalisability.

A study limitation was that respiratory rate was measured by clinical counting, which is known to vary with the expertise of the observer and is less accurate than either the clinical gold standard method of counting for two periods of 30 seconds and averaging, or objective devices that measure chest wall movements or exhaled air.[40-42] However, we thought that measuring respiratory rate consistently by trained nurses would limit measurement variability and would probably reflect common clinical practice, increasing the face validity of the centile charts.

In addition, we had to exclude a high percentage of children from our derivation population due to missing values. Temperature and respiratory rate were measured at the discretion of an attending nurse or physician and thus depended on age and severity of disease (web appendix 5). Although we excluded children without fever or with low triage urgency more often, they were still represented well and offered sufficient power for analysis. Finally, we excluded children who were crying or distressed, because these factors could contribute to individual variation and unreliable measurements.[41] A more detailed description of the child's wellbeing, other than just crying or distress, would have added to the validity of the centiles. However, these data were not available, and would have decreased the external generalisability to typical clinical settings in which these factors cannot be controlled and children will often be crying or upset during clinical assessment.

Contributors: All authors contributed substantially to the writing of the manuscript. RN developed the protocol, was responsible for the data analysis, and was the main author of the paper. MT developed the protocol and was responsible for data acquisition and critical revision of the manuscript. RP contributed to protocol development, statistical analysis, and revision of the manuscript. MV was responsible for data acquisition and protocol development. HM and RO supervised the protocol development, data analysis, and writing of the manuscript. All authors read and approved the final manuscript. All authors had full access to all of the data in the study and can take full responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: The study was received no funding.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; RN is supported by ZonMW, a Dutch organisation for health research and development, and Erasmus MC Doelmatigheid; RO is supported by an unrestricted grant of Europe Container Terminals BV and by a fellowship grant of the European Society of Pediatric Infectious Diseases in 2010; MT is supported by a National Institute for Health Research (NIHR) programme grant (MaDOx), and the MaDOx programme presents independent research commissioned by NIHR under its Programme Grant for Applied Research funding stream (RP-PG-0407-10347).

Ethical approval: Ethical approval obtained from local Erasmus MC-Sophia Children's Hospital ethics committee and Coventry local research ethics committee 04/Q2802/115.

Patient consent: Erasmus MC-Sophia's Children's Hospital ethics committee waived the requirement of informed consent for the development population. Informed consent was required and given for the two validation populations.

Data sharing: No additional data available.

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What is already known on this subject

Respiratory rate is an important predictor of lower respiratory tract infections, and is affected both by underlying respiratory disease and the presence of fever

Existing thresholds values that define tachypnoea do not adjust for the presence of fever

What this study adds

Age specific and temperature dependent reference values for respiratory rate reduce misclassification of tachypnoea in children with fever

These reference values are more useful than existing threshold values for ruling in the presence of lower respiratory tract infections

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Accepted: 14 May 2012

Cite this as: *BMJ* 2012;344:e4224

Tables

Table 1| Patient characteristics of derivation and validation populations. Data are median (interquartile range) or no (%) unless stated otherwise

	Derivation population (Erasmus MC 2006, 2008; n=1555)	Validation populations (children at risk of lower respiratory tract infection)	
		Erasmus MC, 2003-05 (n=311)	Coventry, 2005-06 (n=360)
Age (years)	1.60 (0.52 to 4.46)	1.61 (0.82 to 2.86)	2.33 (1.17 to 5.96)
Sex (male)	881 (57)	153 (49)	208 (58)
Temperature (ºC)	37.8 (37.2 to 38.8)	39.1 (38.5 to 39.9)	38.1 (37.4 to 39.0)
Respiratory rate (breaths/min)	30 (24 to 40)	40 (30 to 48)	32 (26 to 40)
Final diagnosis of lower respiratory tract infection			
Pneumonic LRTI	Not applicable*	61 (20)	55 (15)
Non-pneumonic LRTI	Not applicable*	48 (15)	46 (13)
Non-LRTI	Not applicable*	202 (65)	259 (72)

*Patients with lower respiratory tract infections excluded from the derivation population.

Table 2| Multivariable linear regression model of temperature, age, and respiratory rate

	Model 1 (temperature only)		Model 2 (temperature and age)	
	β (standard error)	P	β (standard error)	P
Body temperature (ºC)	2.5 (0.3)	<0.01	2.2 (0.2)	<0.01
Age group				
1 month to <12 months	—	—	17.8 (0.7)	<0.01
12 to <24 months	—	—	10.8 (0.9)	<0.01
24 months to <5 years	—	—	3.3 (0.8)	<0.01
5 to <16 years	—	—	Reference	—
Intercept (standard error)	−62.7 (10.4)	—	−59.4 (8.5)	—
Model performance characteristics				
F test	83.85	<0.01	247.26	<0.01
Partial F test	—	—	286.33	<0.01
R^2 (change in R^2)	0.05	—	0.39 (0.34)	—

Table 3| Respiratory rate values expected at different temperatures in children (aged 1 month to <16 years)

	Respiratory rate centiles (breaths/min)			
Temperature (°C), by age group	**50th**	**75th**	**90th**	**97th**
Age 1 to <12 months				
36.0 to 36.9	37	45*	55*	65*
37.0 to 37.9	38	48*	57*	69*
38.0 to 38.9	40*	50*	60*	72*
39.0 to 39.9	42*	52*	63*	75*
Age 12 to <24 months				
36.0 to 36.9	28	35	41*	49*
37.0 to 37.9	32	39*	47*	55*
38.0 to 38.9	35	42*	50*	60*
39.0 to 39.9	36*	44*	53*	62*
Age 24 months to <5 years				
36.0 to 36.9	23	27	31*	36*
37.0 to 37.9	25	30	35*	40*
38.0 to 38.9	27	32*	38*	44*
39.0 to 39.9	29	35*	41*	48*
Age 5 to <16 years				
36.0 to 36.9	19	23	27*	32*
37.0 to 37.9	21	26*	30*	36*
38.0 to 38.9	23	28*	34*	41*
39.0 to 39.9	24	30*	36*	44*

*Values that lie above age specific upper thresholds of respiratory rate as defined by APLS values (<1 year: >40 breaths/min; 1 to <2 years: >35 breaths/min; 2 to <5 years: >30 breaths/min; 5 to <16 years: >25 breaths/min).[27]

Table 4| Diagnostic performance of temperature dependent reference values to detect presence of lower respiratory tract infection.* Data are estimate (95% confidence interval)

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Area under receiver operating characteristics curve
50th centile	0.84 (0.79 to 0.89)	0.39 (0.35 to 0.44)	1.38 (1.26 to 1.52)	0.40 (0.29 to 0.56)	0.62 (0.55 to 0.68)
75th centile	0.62 (0.55 to 0.69)	0.65 (0.61 to 0.70)	1.80 (1.53 to 2.12)	0.58 (0.48 to 0.69)	0.64 (0.56 to 0.72)
90th centile	0.41 (0.34 to 0.48)	0.86 (0.82 to 0.89)	2.86 (2.17 to 3.77)	0.69 (0.61 to 0.78)	0.63 (0.56 to 0.71)
97th centile	0.21 (0.16 to 0.28)	0.94 (0.92 to 0.96)	3.66 (2.34 to 5.73)	0.83 (0.77 to 0.90)	0.58 (0.52 to 0.64)

*Analysis compares all diagnoses of lower respiratory tract infection (pneumonic and non-pneumonic LRTI combined) with non-LRTI.

Table 5| Diagnostic performance of Fleming and APLS reference values to detect presence of lower respiratory tract infection.* Data are estimate (95% confidence interval)

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Area under receiver operating characteristics curve
APLS threshold values[27]	0.75 (0.69 to 0.81)	0.53 (0.48 to 0.57)	1.59 (1.41 to 1.80)	0.47 (0.37 to 0.60)	0.64 (0.57 to 0.71)
Fleming and colleagues[20]					
50th centile	0.87 (0.81 to 0.91)	0.34 (0.30 to 0.39)	1.32 (1.22 to 1.44)	0.39 (0.27 to 0.56)	0.61 (0.54 to 0.67)
75th centile	0.72 (0.65 to 0.78)	0.53 (0.48 to 0.57)	1.52 (1.34 to 1.73)	0.53 (0.42 to 0.67)	0.62 (0.55 to 0.70)
90th centile	0.60 (0.54 to 0.67)	0.66 (0.61 to 0.70)	1.76 (1.49 to 2.09)	0.60 (0.50 to 0.72)	0.63 (0.55 to 0.71)
99th centile	0.45 (0.38 to 0.52)	0.78 (0.75 to 0.82)	2.13 (1.69 to 2.68)	0.70 (0.61 to 0.79)	0.62 (0.54 to 0.70)

*Analysis compares all diagnoses of lower respiratory tract infection (pneumonic and non-pneumonic LRTI combined) with non-LRTI.

Figures

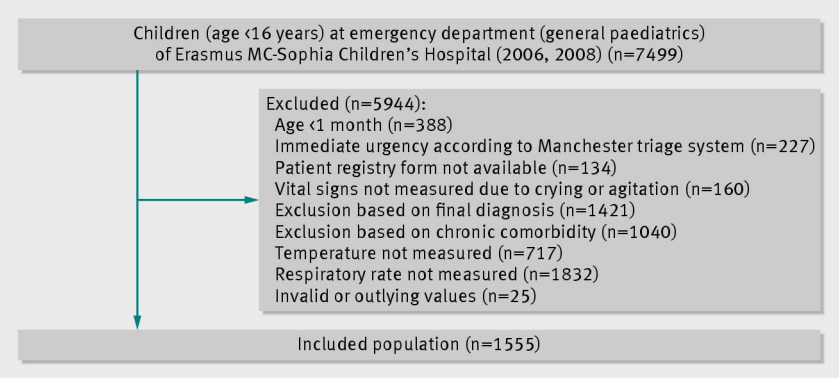

Fig 1 Inclusion and exclusion of derivation population

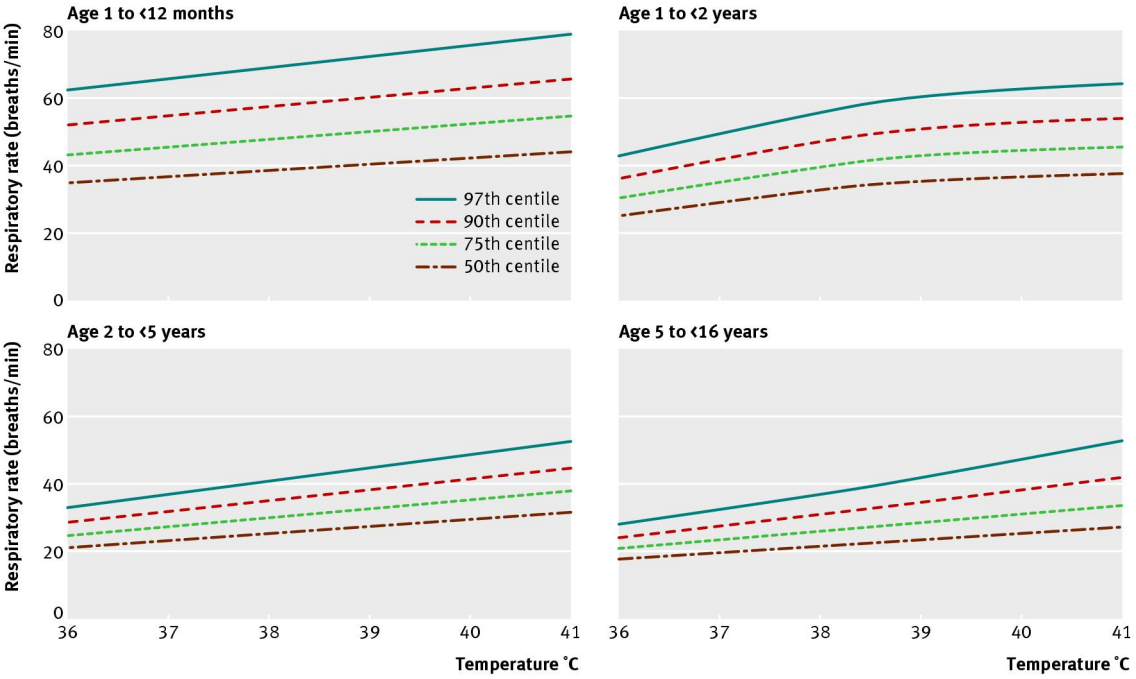

Fig 2 Median and upper centiles of respiratory rate expected at different temperatures for children of different age groups