Online data supplement

Assessing bronchodilator response in preschool children using spirometry

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Table E1: feasibility of Spirometry in Pre-schoolers

Study	Population	Setting	Number	Feasibility	Comment
Eigen [1]	Healthy pre-schoolers 36 to 87 mo old	USA, community	307 screened 259 eligible 187 white*	214/259 (82.6%)	Spirometry naïve No age breakdown of feasibility presented
Marostica [2]	Cystic fibrosis 3 to 6y old	USA, clinic	38	3y: 4/6 (66.6%) 4y: 9/11(81.8%) 5y: 10/10(100%) 6y:10/11 (90.9%)	At least 2 acceptable manoeuvres were required Patients not spirometry naive
Jeng [3]	Healthy pre-schoolers 36 to 83	Taiwan, community	248	3y: 33/45 (73.3%) 4y: 65/71 (91.5%) 5y: 65/71 (91.5%) 6y: 51/55 (92.7%)	not stated that no previous spirometry
Joseph-Bowen [4]	Longitudinal birth cohort	Australia, Community	1995	1735/1995 (87.0%)	No age breakdown of feasibility presented Population contained asthmatic children Most spirometry naïve
Kampschmidt [5]	Healthy pre-schoolers 3 to 5y	USA, community	200	3y: 23/51 (45.1%) 4y: 67/103 (65.0%) 5y: 40/46 (87.0%)	31 with known asthma and 8 diagnosed in the population One acceptable manoeuvre sufficient
Nystad [6]	Healthy pre-schoolers 3 to 6y	Norway, community	630	3y: 51%** 4y: 69% 5y: 76% 6y: 78%	3 acceptable manoeuvres required
Leung [7]	Healthy pre-schoolers	Hong Kong, Community	1909	<3y:63/155 (40.6%) 3y:333/532 (62.6%)	Asthmatic children included

	2 to 7y			4y:447/572(78.1%) 5y:449/534(84.1%) ≥6y:110/115(95.7%)	Likely to be spirometry naïve
Neve [8]	Asthmatics 3-5y	France, clinic	171	FET 0.75s ; >1s 3y: 45%; 73% 4y: 60%; 80% 5y: 76%; 97% Forced volume repeatability 3y: 26-57% 4y: 39-55% 5y: 53-100%	Only data from first spirometry used 14% who could not do 2 tests were excluded before study population selected.
Olaguibel[9]	Healthy 3-6y	Spain, clinic	102	59% of those who attended 64% of those who agreed on the day	Siblings of patients or non-respiratory patients recruited Prior training given.
Piccioni[10]	Healthy 3-6y	Italy, community	960	79.8% of those who attended 83.7% of those who agreed on the day	36.3% of acceptable tests had early termination and not used for FVC thus true success rate 50.8%.
Turner[11]	Longitudinal cohort 5y	Scotland, community	827	77.2% ≥2 acceptable 68.0% 3 acceptable 64.8% met all criteria	Cohort included wheezy children 20% FET < 1s
Vilnozi [12]	Healthy & asthmatic 2-6	Israel, community and clinic	341	3y: H 62%, A 65% 4y: H 69%, A 75% 5y: H 75%, A 82% 6y: H 78%, A 88%	75 children who could not perform spirometry were excluded before calculating success. Incentive programs used Asthmatics probably not spirometry naïve.

* These children who performed acceptable spirometry were used to calculate normative data; N/A: not available; FET: forced expiratory time; ** absolute numbers not presented; FET = forced expiratory time; H = healthy, A = asthmatic

Table E2: Determining Bronchodilator Response in Pre-schoolers

Study	Population	Setting	Definition of BDR	Lung function method	Positive BDR	comments
Borrego [13]	43 Asthmatics, 22 controls, 3-6y	Portugal, clinic	Mean difference pre and post placebo +2SD in healthy population	Spirometry	14% increase in $FEV_{0.75}$	Based on 22 healthy controls
Olaguibel[14]	33 asthmatics, 3-6y	Spain, clinic	SD Index (≥ 2 x of between test repeatability) Δ Baseline % Δ% predicted	IOS Spirometry sRaw	SD Index R5: -1.97±1.51 R20: -1.03±1.61 X5: 1.27±1.23 Δ Baseline % R5: -19±12.7 R20: -10.1±16 X5: 23.5±21.1 sRaw: -22±16.4 FEV_1: 7.5±12.7 Δ% predicted R5: -16.5±12.6 R20: -11.5±16.1 X5: 22.0±21.2 sRaw: -45.7±42.2 FEV_1: 7.6±11.8	One of the asthmatics had significant BDR based on the criteria defined.

Calogero[15]	Healthy, 2.9-6.1y	Italy, community	>5th % of change in R8 or >95% of change in X8 post salbutamol in healthy children	FOT	R8: >-1.88 Z-scores X8: >2.44 Z-scores	Not validated in children with asthma
Mele[16]	60 healthy, 2.5-5.7y 60 recurrent wheeze 2.9-6.1y	Italy, community and clinic	>5th % of change post salbutamol in healthy children	Rint	>0.26 KPa.s.L^{-1} or >1.25 Z-scores	
Oostveen[17]	311 longitudinal cohort	Belgium, community	>5th % change post salbutamol in never wheeze group	FOT R4	>5.5 h Pa.s.L^{-1}	
Thamrin[18]	78 healthy, 39 CF, 49 nCLD, 56 asthma, 66 recurrent wheeze, 4-8y	Australia, clinic	>5% change post salbutamol in healthy group	FOT	R6: 42% R8: 37% R10: 39%	

Table E3. English Translation of the Screening Questionnaire.

Does your child…	Never	Sometimes	A lot	Don't know
Q1. Develop coughs that won't go away?				
Q2. Wake up at night because of trouble breathing?				
Q3. Have a hard time taking a deep breath?				
Q4. Make noisy or wheezy sounds when breathing (awake)?				
Q5. Complain about a chest that feels tight or hurts after running, playing hard, or doing sports?				
Q6. Wake up at night coughing?				
Q7. Cough when running, climbing stairs or playing sports?				
Q8. Miss days of kindergarten (absent from kindergarten) because of breathing problems?				

	No	Yes	Don't know
Q9. Has a doctor or nurse told you that your child has asthma, reactive airway disease or wheezy bronchitis?			
Q10. Has your child stayed in the hospital overnight for asthma or for trouble breathing in the last year?			
Q11. Does your child take medicine or use an inhaler for asthma or other respiratory disease?			

Table E4. Spirometric data before and after inhaled bronchodilator in healthy children and those with asthma measured on the first visit. Data, as absolute values, are shown as group mean and standard deviation (SD) (asthmatic children prescribed ICS excluded).

Spirometry	Healthy children (n=364)*			Children with asthma (n=203)*		
	Baseline (mean ±SD)	Post bronchodilator (mean ±SD)	p-value	Baseline (mean ±SD)	Post bronchodilator (mean ±SD)	p-value
FVC (L)	1.17 ±0.16	1.21 ±0.06	0.720	1.14 ±0.22	1.23 ±0.12	0.039
FEV_1 (L)	1.11 ±0.12	1.16 ±0.07	0.567	0.98 ±0.17	1.11 ±0.10	0.026
$FEV_{0.75}$ (L)	1.01 ±0.10	1.06 ±0.05	0.482	0.89 ±0.14	1.02 ±0.13	0.020
$FEV_{0.5}$ (L)	0.90 ±0.09	0.94 ±0.05	0.538	0.78 ±0.11	0.90 ±0.12	0.025
FEF_{25-75} ($L.s^{-1}$)	1.50 ±0.31	1.65 ±0.28	0.568	1.11 ±0.41	1.53 ±0.46	0.014
FEF_{25} ($L.s^{-1}$)	0.99 ±0.20	1.09 ±0.19	0.564	0.72 ±0.28	1.01 ±0.34	0.022
FEF_{50} ($L.s^{-1}$)	1.93 ±0.26	2.11 ±0.38	0.535	1.43 ±0.51	1.99 ±0.58	0.015
FEF_{75} ($L.s^{-1}$)	1.26 ±0.14	1.38 ±0.25	0.508	0.94 ±0.37	1.32 ±0.39	0.022
PEF ($L.s^{-1}$)	2.47 ±0.27	2.69 ±0.44	0.501	2.10 ±0.62	2.60±0.88	0.039

*number of children with successful spirometry on the first visit.

Table E5. Baseline spirometry, reported as group mean Z-scores (mean), in healthy children and those with asthma measured on the first visit (asthmatic only without ICS). The difference between groups (mean and 95% confidence intervals (CI)) are also shown. Significance was assessed using pared t-tests.

	Asthma (n=203)	**Healthy (n=364)**	**Difference [mean (95% CI)]**	**p-value**
z-FVC	-0.21	0.09	-0.30 (-0.4 to 0.08)	0.09
z-FEV_1	-0.65	0.25	-0.90 (-0.99 to 0.28)	0.005
z-$FEV_{0.75}$	-0.90	0.09	-0.99 (-1.39 to 0.24)	0.005
z-$FEV_{0.5}$	-0.62	0.06	-0.68 (-1.38 to 0.32)	0.006
z-FEF_{25-75}	-1.11	-0.04	-1.07 (-1.01 to 0.21)	<0.001
z-FEF_{25}	-1.20	-0.05	-1.15 (-1.02 to 0.11)	0.003
z-FEF_{50}	-1.01	-0.01	-1.00 (-0.97 to 0.24)	0.000
z-FEF_{75}	-0.98	-0.01	-0.97 (-0.91 to 0.16)	0.004
z-PEF	-0.32	0.02	-0.34 (-0.32 to 0.02)	0.10

Baseline spirometry on visit 1. CI=confidence interval.

Table E6: Repeatability (Cintra) and Reproducibility (Cinter) of spirometry, calculated using absolute values, in healthy children and those with asthma from lung function measured on the first visit before and after receiving placebo (asthmatic only without ICS).

Spirometry	Healthy (n=181)			Asthma (n=103)		
	Cintra	Cinter	p-value	Cintra	Cinter	p-value
FVC	12.0%	12.3%	0.699	13.1%	18.4%	0.121
FEV_1	11.6%	11.9%	0.711	12.0%	19.5%	0.201
$FEV_{0.75}$	11.8%	11.9%	0.891	12.3%	23.4%	0.101
$FEV_{0.5}$	12.1%	12.3%	0.812	12.2%	24.5%*	0.031

Within session repeatability (Cintra) calculated from children randomized to receive placebo inhalation on visit one; between session reproducibility (Cinter) calculated from baseline spirometry performed at each visit. *Statistically significant difference ($p<0.05$) between Cintra and Cinter.

Table E7. Change in lung function after salbutamol in healthy children and those with asthma measured on the first visit (asthmatic only without ICS). Data are shown as group mean change [mean (SD)%] within the asthmatic and healthy groups and the difference [mean (95% confidence intervals) between groups].

	Asthma (n = 103)	**Healthy (n = 181)**	**Difference [mean (95% CI)]**	**p-value**
FVC	7.9 (9.9)	3.2 (5.2)	4.7 (0.3 to 8.4)	0.028
FEV_1	13.2 (9.5)	4.3 (6.3)	8.9 (-2.1 to 10.9)	0.006
$FEV_{0.75}$	14.6 (12.0)	4.6 (4.9)	10.0 (-5.2 to 15.3)	<0.001
$FEV_{0.5}$	15.4 (13.2)	5.1 (6.0)	10.3 (-2.1 to 12.4)	0.001

Table E8: Change in lung function after placebo in healthy children and those with asthma. Data are shown as group mean change [mean (SD)%] within the asthmatic and healthy groups and the difference [mean (95% confidence intervals) between groups.

	Asthma (n=124)	**Healthy (n=181)**	**Difference Mean (95% CI)**	**p-value**
FVC	1.2 (7.7)	0.9 (6.2)	0.3 (-2.1 to 1.8)	0.986
FEV_1	2.4 (6.9)	2.2 (6.0)	0.2 (-2.7 to 3.0)	0.967
$FEV_{0.75}$	1.9 (4.9)	1.1 (6.2)	0.8 (-2.1 to 2.3)	0.765
$FEV_{0.5}$	1.7 (4.2)	1.0 (6.8)	0.7 (-1.9 to 2.1)	0.883

Table E9. Thresholds for positive bronchodilator response defined from repeatability of spirometry in healthy children (Cintra) and from ROC curve analyses. The numbers of healthy and asthmatic children classified as having a positive bronchodilator response are also shown. (asthmatic only without ICS)

	Cintra			ROC		
	Threshold	BDR, n (%)		Threshold	BDR, n (%)	
		Asthma (n = 103)	Healthy (n =181)		Asthma (n = 103)	Healthy (n =181)
FVC	13.3%	24 (23.3%)	9 (5.0%)	5%	25 (50.5%)	52 (28.7%)
FEV_1 (L)	14.2%	27 (26.2%)	13 (7.2%)	7%	51 (49.5%)	34 (18.8%)
$FEV_{0.75}$	13.5%	49 (47.6%)	12 (6.6%)	11%	54 (52.4%)	21 (11.6%)
$FEV_{0.5}$	14.6%	45 (43.7%)	18 (9.9%)	12%	54 (52.4%)	39 (21.5%)

Table E10: Ability of change in spirometric variable following salbutamol to discriminate between asthma and healthy children (asthmatic only without ICS)

Spirometry	**Area**	**Threshold**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
FVC	0.53	5%	50.5%	71.3%	50.0%	71.7%
FEV_1	0.68	7%	49.9%	81.0%	34.4%	89.1%
$FEV_{0.75}$	0.72	11%	52.3%	88.4%	47.1%	89.3%
$FEV_{0.5}$	0.68	12%	52.7%	78.2%	32.7%	89.2%

Area = area under the Receiver-Operator-Characteristic curve; Threshold = value of spirometric variable giving the best balance between sensitivity and specificity; PPV = positive predictive value for detecting asthma; NPV = negative predictive value for excluding asthma.

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