Challenges in Diagnosing Asthma in Children

Practice Pointer - Challenges in Diagnosing Asthma in Children

Kendra Chisholm[1], Luke Daines[2], Steve Turner[1]

[1] Women and Children's Division, NHS Grampian, Aberdeen, UK

[2] Usher Institute, University of Edinburgh, Edinburgh, UK

Correspondence to:

Prof Steve Turner

Child Health, Royal Aberdeen Children's Hospital, Aberdeen, AB25 2ZG

Email: s.w.turner@abdn.ac.uk

Phone: +44 1224 554 587

Word count 2128

How this article was created

We focussed the article on the four most commonly cited and most recently updated guidelines for the diagnosis of asthma in children.

Contributorship and the guarantor

ST conceived the article and is the guarantor. ST and KC wrote the first draft of the article. All authors made meaningful contributions to and reviewed the article. KC created the box.

Acknowledgements

None

How patients were involved in the creation of this article

No patients were involved.

Conflicts of Interest

The *BMJ* has judged that the authors have no disqualifying financial ties to commercial companies that are relevant to this paper. None of the authors has a conflict to declare.

Licence

What you need to know

- Asthma in children is a clinical diagnosis based on history and examination, and in many cases a response to a trial of inhaled corticosteroid treatment.
- Asthma can be diagnosed in children aged under five years but is unlikely to explain recurrent respiratory symptoms in under two-year-olds
- Test can be done to help support (or exclude) a clinical diagnosis but should not be used solely to make (or exclude) a diagnosis of asthma.

Education into practice

- The article gives suggestions to clinicians about how they might explain to parents some of the uncertainties faced when diagnosing asthma (box three).
- A trial of treatment with low-dose inhaled corticosteroids (ICS) should be offered rather than a trial of short-acting beta agonists (SABA).
- A normal test, e.g. spirometry, does not exclude a diagnosis of asthma and not every child with an abnormal test has asthma.

INTRODUCTION

Asthma is characterised by recurrent episodes of cough and wheeze and difficulty in breathing and affects more than 10% of children in the UK [1]. Despite being so common, there is no universally agreed definition or diagnostic test for asthma in children, or in adults.[2] Diagnosing asthma in children relies on a suggestive history and response to a trial of preventer treatment. The lack of objectivity in diagnosing asthma leads to both overdiagnosis and underdiagnosis.[3, 4] Clinicians and researchers have explored the role of objective tests, such as spirometry, peak flow variability and exhaled nitric oxide in diagnosing asthma. Despite the lack of evidence, a number of organisations have incorporated objective testing into diagnostic algorithms. But how helpful are these algorithms and objective tests?

This review will

(1) Describe current diagnostic algorithms (also called pathways) for childhood asthma
(2) Consider the feasibility of the proposed diagnostic algorithms in "real world" healthcare settings for children aged over five years
(3) Describe areas of remaining uncertainty in diagnosing asthma in children

Diagnosing asthma – What do the guidelines say?

This review will focus on algorithms from four recent and commonly cited guidelines: European Respiratory Society (ERS), British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN), National Institute for Health and Care Excellence (NICE) and Global Initiative for Asthma (GINA).[5-8] At the time of writing a joint BTS/SIGN and NICE asthma guideline is being created, but this article considers them separately.

Table one summarises the characteristics and recommendations for each of the guidelines.

Symptoms

All four guidelines acknowledge that asthma is a clinical diagnosis based on the combination of symptoms (recurrent cough, wheeze and difficulty in breathing), see Box one. These symptoms are not specific to asthma; they are all also commonly seen in acute lower respiratory tract infections (LRTI). What is different between asthma and LRTI is that with the former, symptoms Cough has a sensitivity and specificity for asthma of between 0.71-0.89 and 0.27-0.45, respectively.[5] The sensitivity of wheeze (as an isolated symptom) for asthma is similar to cough, i.e. between 0.55-0.86, but the specificity is relatively higher, i.e. between 0.48-0.90.[5] The low sensitivity of wheeze is in part due to the variability in how wheeze is reported by parents, and then interpreted by clinicians. When parents and paediatricians look at videos of children making different breathing sounds, they often label a sound as "wheeze" when experts agree the sound is not wheeze.[11] There is a "library" of standard respiratory sounds which can be listened to in order to reduce the ambiguity of "wheeze".[12] Difficulty in breathing, or shortness of breath, is also a subjective concept – it is normal to get relatively short of breath on exercise. However, parents will usually recall if their child has had difficulty breathing at rest, whilst also coughing and wheezing; parents of a young child may describe their child's "ribs sucking in" and "tummy sticking out" (i.e. subcostal recession) and those of an older child may report "sucking in around their neck" (i.e. tracheal tug).

Tests

All four guidelines (and NHS England's 2021 National Bundle of Care for Children and Young People with Asthma) recommend that clinical diagnosis should be supported by objective testing, ideally before starting preventer treatment since this may affect test results. The hierarchy of testing (i.e. FEV_1 first, FeNO or bronchodilator testing second, PEF last) in guidelines is determined by the available evidence and sensitivities and specificities at the time the guideline was published. In the interests of feasibility, it would be reasonable to do whichever tests are available, remembering that diagnosing asthma remains based primarily on symptoms. Table two describes the tests.

Box 1

Box one: Clinical Pearls

History Taking:

- Asthma involves recurrent episodes of cough and wheeze and difficulty in breathing
- A history of only cough or wheeze or difficulty in breathing is not consistent with asthma
- Cough is typically dry and especially noted on exercise and a few hours after the child has gone to sleep
- Features suggesting an alternative diagnosis in children include: daily symptoms, symptoms present since birth and a persistent wet cough[6]
- Personal history of eczema, hayfever or food allergies
- First degree family history of asthma
- Exposures which cause symptoms, e.g. exposure to second hand smoke, can be sought but are common in all children. These exposures typically increase the odds of asthma by only two-fold so should not carry much weight when making a diagnosis[13]

Examination:

- Examination is usually normal (unless the child is having an asthma exacerbation)
  Examination findings suggestive of alternative diagnosis include clubbing, (acquired) chest wall deformity (e.g. Harrison sulcus), failure to thrive and fine crackles on auscultation[6, 8]

A high probability of asthma[6] would meet these criteria:

- a history of recurrent episodes (attacks) of symptoms
- of wheeze and cough and difficulty in breathing recorded observation of wheeze heard by a healthcare professional
- personal history of other atopic conditions
- first-degree family history of asthma
- no symptoms/signs to suggest alternative diagnoses.

Specialist Referral:

- Unclear diagnosis after thorough history and examination and watchful waiting is not appropriate
- Presence of clubbing, (acquired) chest wall deformity, failure to thrive and (persistent) fine crackles on auscultation
- Poor response to a trial of preventer treatment
- Severe/life-threatening asthma attack

Spirometry.

All guidelines recommend spirometry as the primary diagnostic test for children. Spirometry in children with asthma is usually normal.[10] This is likely due to poor specificity and sensitivity compounded by testing outside of an exacerbation (when reduced spirometry has recovered). However, there is no consensus on which spirometric measurement should be done, nor the optimal cut-off values (Table three). Spirometry can be more challenging to measure in children than adults, but with training and adequate time, acceptable spirometry can be measured in children aged 5 and older.[14] Most guidelines recommend that bronchodilator reversibility (BDR) should be determined in the presence of abnormal (also called obstructed) spirometry.[5, 7, 8] The BTS/SIGN guideline

suggests BDR should be done in all individuals doing spirometry.[6] All guidelines agree that an FEV_1 improvement of ≥12% is a significant BDR test, but do not state what dose of bronchodilator should be used (commonly 400 micrograms of inhaled salbutamol).

Fractional exhaled nitric oxide (FeNO).

When spirometry is normal or inconclusive, FeNO is the next test recommended by ERS and NICE with respective values of above 25 and 35 parts per billion suggesting a diagnosis of asthma, Table two.[5, 7] The BTS/SIGN guideline recommends FeNO as one of several tests which could be used after spirometry, along with peak flow variability, blood eosinophils and allergy testing.[6] The GINA guideline does not recommend FeNO in its diagnostic algorithm.[8]

Peak expiratory flow (PEF) variability.

PEF charting is recommended by GINA and BTS/SIGN guidelines after spirometry.[6, 8] The ERS and NICE guidelines place PEF after spirometry and FeNO.[5, 7] Definitions of "abnormal" PEF variability include >12%[5], >13%[8] and >20%[7]. PEF lacks specificity in diagnosing asthma (Table two) when compared to spirometry, but may be the only test available in primary care in the UK and in many other nations.[8, 14]

Other testing.

ERS and BTS/SIGN guidelines recommend challenge testing, e.g. exercise or methacholine tests, but in the UK, these tests are only available in specialist centres.[5, 6] The BTS/SIGN guideline states that allergy testing (including IgE and skin prick testing) can be done where there is an intermediate probability for asthma.[6]In contrast, the ERS guideline provides evidence that allergy tests lack sensitivity and specificity for diagnosing asthma. [5]

Table 1: Comparison of commonly used asthma guidelines: European Respiratory Society (ERS), British Thoracic Society/ Scottish Intercollegiate Guideline Network (BTS/SIGN), National Institute for Health and Care Excellence (NICE) and Global Initiative for Asthma (GINA).
BDR = bronchodilator response. FeNO = Fractional Exhaled Nitric Oxide. PEF = peak expiratory flow.

	Guideline (date published)			
	ERS (March 2021)	BTS/SIGN (July 2019)	NICE (March 2021)	GINA (June 2022)
Number of objective tests required for diagnosis	2	1 - 2 †	2	2
Suggested order in which objective tests should be done	i. Spirometry ii. BDR (if spirometry abnormal) iii. FeNO iv. Diurnal PEF x 2 weeks/ Challenge test	i. Spirometry + BDR ii. Variability tests/ tests for eosinophilic inflammation or atopy	i. Spirometry ii. BDR (if spirometry obstructed) iii. FeNO iv. PEF variability	i. Spirometry/ PEF with BDR ii. Diurnal PEF x 2 weeks/ exercise challenge test
Age range covered by diagnostic algorithm	5 – 16 years	≤18 years	≤ 17 years	5 – ≤ 16 years
What do the guidelines say about under-fives?	"We did not include children aged <5 years in these guidelines, because diagnostic tests for asthma on young children are rarely performed"	"Consider monitored initiation of treatment or watchful waiting according to the assessed probability of asthma"	"Treat symptoms based on observation and clinical judgement, and review the child on a regular basis"	"A probability-based approach using symptom pattern during and between respiratory infections may be helpful"
Sensitivity Specificity of algorithm ‡	Not available	Not available	Sensitivity (69%) Specificity (67%)	Sensitivity (42%) Specificity (90%)

† Where there is ahigh probability of asthma (based on symptoms) spirometry before and after starting preventer treatment is recommended

‡ From a Swiss study of children referred to outpatient clinic [9]. A second study, which used an epidemiological definition for asthma, concluded that the NICE diagnostic algorithm should not be used in children.[10]

Table two. A summary of the tests which can be done to support a diagnosis of asthma in children. These tests can be carried out in children aged under five years but only usually in centres with expertise. International consensus statements describe the methodology more fully.

		How is it done?	What does it detect?
Spirometry		Forced expiratory manoeuvre – a big breath in and a fast breath out for as long as possible	Airflow obstruction (both fixed and reversible)
Fractional exhaled nitric oxide		Depending on age, six or ten second exhalation and slow and contacts flow (50ml/sec)	Airway eosinophilia
Peak flow variability		A big breath in and explosive breath out. Usually done twice daily over a two week period.	Airway variability
Other tests	Bronchodilator response	Spirometry before and after inhaling a short acting beta agonist	The level of reversible airway obstruction
	Airway challenge, e.g. with methacholine	Spirometry before and after inhaling increasing concentrations or doses of chemical known to induce bronchspasm	The level of airway reactiveness
	Exercise test	Spirometry before, during and after exercise	The level of airway reactiveness to exercise

Table three: Comparison of tests used in the diagnosis of asthma in children. European Respiratory Society (ERS). British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN). National Institute for Health and Care Excellence (NICE). Global Initiative for Asthma (GINA).

		ERS	BTS/SIGN	GINA	NICE
Spirometry (FEV_1/FVC ratio)	+ve threshold	< 80% or < LLN *	< 70% or < LLN *	< 90% or < LLN *	<70% or < LLN *
	sensitivity	12 – 52% (mean = 32%)	52%	-	-
	specificity	72 – 93% (mean = 83%)	73%	-	-
	PPV	-	75%	-	-
	NPV	-	49%	-	-
Bronchodilator Response (FEV_1)	+ve threshold	≥ 12% and/or ≥ 200 mls	≥ 12%	≥ 12%	≥ 12%
	sensitivity	35.6%	50%	-	-
	specificity	89.5%	86%	-	-
	PPV	-	75%	-	-
	NPV	-	49%	-	-
Fractional Exhaled Nitric Oxide	+ve threshold	≥ 25 ppb	≥ 35 ppb	Not recommended	≥ 35 ppb
	sensitivity	57% (mean)	57%	-	-
	specificity	81% (mean)	87%	-	-
	PPV	-	90%	-	-
	NPV	-	49%	-	-
Peak Expiratory Flow	+ve threshold †	≥ 12%	> 12.3%	> 13%	> 20%
	sensitivity	50% ‡	50%	-	-
	specificity	72% ‡	72%	-	-
	PPV	-	48%	-	-
	NPV	-	74%	-	-
Exercise Challenge Test	+ve threshold	> 10% fall in FEV_1 §	> 15% fall in FEV_1 §	> 12% fall in FEV_1 or >15% fall in PEF §	Not recommended
	sensitivity	37 – 77% (mean = 57%)	69 – 72%	-	
	specificity	68 – 77% (mean = 73%)	69 – 72%	-	
	PPV	-	90 – 99%	-	
	NPV	-	5 – 73%	-	

- Data/values not specified

† ERS and GINA = twice daily (diurnal) PEF over 2 weeks; BTS and NICE = twice daily (diurnal) PEF over 2 – 4 weeks

‡ Sensitivity and specificity yielded from testing over a 2 week period

§ Refers to a fall from the baseline value

***** The lower limit of normal is considered equal to the 5th centile of a given population or, using a z-score, is a value of -1.64. A z-score is a statistical measurement that describes a value's relationship to a group of values.

How do these guidelines work in real life?

Can testing be done in children?

Research in central England found that spirometry and FeNO could be measured respectively in 94 and 77% of children aged 5-16 years outside of hospital.[14] The World Health Organisation (WHO) identified that out of 194 countries surveyed, only 42% have spirometry available in primary care, Figure one.[15] In many countries access to spirometry is limited by funding and availability of trained staff.[14, 17]

How accurate are the algorithms in practice?

A study in Switzerland applied the GINA and NICE diagnostic algorithms to 514 children and young people (5-17 years) referred to respiratory clinics with suspected asthma, of whom 70% were diagnosed with asthma on clinical grounds.[9] The sensitivity and specificity of the NICE algorithm were 69% and 67%, and corresponding values for GINA were 42% and 90%. A second study applied the cut-off values recommended for children by NICE (see Table two) to a birth cohort and found cut-offs for FEV_1/FVC, FEV_1 and BDR had sensitivities of <10% and specificities of >90% for asthma; the sensitivity and specificity of the FeNO cut-off were 44% and 84% respectively.[18]

Applying prediction models to routinely acquired primary care data to help support an asthma diagnosis has been attempted, but lack the necessary precision to be applied in clinical practice. Reasons for this include a lack of objective historical data, and the absence of a standard definition and diagnostic testing for asthma.[19]

The clinical diagnosis of asthma requires episodic cough and wheeze and difficulty in breathing. The decisional balance shifts towards asthma if there is also a personal history of eczema, food allergy or hay fever and one parent who uses an inhaler for asthma.

Areas of uncertainty in diagnosing asthma in children

Does Cough Variant Asthma exist in children?

No. Whilst cough variant asthma (i.e. cough which responds to inhaled corticosteroids) is well described in adults, there is virtually no evidence to suggest it exists in children. All guidelines advise against diagnosing and treating asthma based on a single symptom, e.g. cough.

Should a trial of treatment be with a short-acting beta agonist or low-dose inhaled corticosteroid?

Whilst SABA is used to demonstrate reversibility in the context of lung function testing, it is not recommended for conducting a trial of treatment. Both NICE and BTS/SIGN recommend a two month diagnostic trial should be done with ICS and not a SABA.[6, 7] Symptoms should be reviewed at the end of the ICS trial and the treatment continued if symptoms are substantially better; there is no definition of what is a "substantial improvement". Increasingly, guidelines are moving to all bronchodilator asthma treatment being combined with ICS. The evidence-base for this includes the National Review of Asthma Deaths which found many fatal cases treated with SABA alone. LTRAs are not recommended for use as a diagnostic trial.

Can you diagnose asthma in under 5s?

Yes. Asthma can emerge before a child's fifth birthday. The BTS/SIGN guideline says "*In general, the earlier the onset of wheeze, the better the prognosis. Cohort studies show a break point at around two years; most children who present before this age become asymptomatic by mid-childhood*".[6] Put another way, asthma is unlikely to explain recurrent respiratory symptoms in under two-year-olds. Given that testing rarely yields reliable results in the under-fives, the diagnosis is wholly clinically based. If the child's quality of life (QOL) is not affected by their symptoms, e.g. no regular night-time cough or exertional wheeze, then watchful waiting is the best action. If QOL is being impacted, a two-month trial of low-dose ICS with clinical review would be appropriate in over two year olds; a trial of ICS would be unusual in younger children.[3, 4, 6] Resolution of symptoms after two months

could be explained by treatment being effective or by the resolution of non-asthmatic symptoms. Stopping treatment in the late spring months (when the respiratory virus season comes to an end) to see if symptoms return is recommended, to be restarted if symptoms recur.[4]

Is viral-induced wheeze different to asthma?

No – in most children. We have all cared for preschool children who only wheeze with a respiratory tract infection; when they are well they are very well, but when they are bad they are awful. Such individuals have traditionally been labelled as "viral wheezers". Studies of "viral wheezers" and "typical asthmatics" demonstrate that over time many young children move between the two phenotypes[21, 22] i.e. viral induced wheeze is the same as asthma in most young wheezy children. A patient-centred approach should not dwell on what the diagnosis is, but on the prevention and management of symptoms. A "watchful waiting" approach should be considered. A trial of asthma preventers can be discussed, along with an action plan for managing acute episodes, e.g. use up to ten puffs of a SABA inhaler (with spacer), when to seek medical attention.

Is it safe to use inhaled corticosteroids (ICS) in children with asthma for prolonged periods?

Yes. There is no doubt that ICS improve asthma control and reduce asthma attacks in children.[6-8] Less potent ICS molecules such as beclomethasone dipropionate and budesonide have an excellent safety record. Any effect on growth has been found to be approximately 1 cm loss in final adult height. [23] ICS molecules such as fluticasone dipropionate and mometasone are twice as potent microgramme-for-microgramme as beclomethasone and budesonide and all high dose ICS treatment may increase the very small risk of clinically-relevant adrenal suppression.[6] Local side effects of ICS, i.e. hoarse voice or oral thrush, can be reduced by rinsing out the mouth or brushing teeth after using the inhaler. Child-onset asthma is steroid responsive, so if symptoms persist despite good adherence and inhaler techniques then an alternative diagnosis should be considered.

What is the impact of repeated course of oral corticosteroids (OCS) in children with recurrent respiratory exacerbations? Children may receive courses of OCS for symptoms ahead of an asthma diagnosis. The harm from repeated short OCS courses is not described. Guidelines recommend a short OCS course for a child with an asthma exacerbation.[6] There is clinical uncertainty about giving OCS to children who do not have an asthma diagnosis; OCS have side effects (most commonly vomiting[24]) and do not work in many young children with acute wheeze.[25] If a child has a high probability of asthma (see box one) they could have a trial of ICS treatment. Pragmatically it seems reasonable to give OCS to a child who has previously had a clear positive response to a short OCS course and also in a child with more severe symptoms.

Conclusion

Asthma remains a clinical diagnosis based on recurrent episodes of cough and wheeze and difficulty in breathing. In children aged over five, testing can be helpful in nudging a decision one way or another. Guidelines are not always consistent in which tests they recommend (Table one) and their definitions of "abnormal" (Table two). This article has hopefully succeeded in identifying the strengths and weaknesses of current diagnostic algorithms and resolving some clinical uncertainties. Box two give hints for colleagues in communicating these uncertainties.

Box two. Hints for communicating uncertainties to parents and carers.

- Asthma is one of many conditions which has no diagnostic test. Similarly, there is no test for migraine, ADHD and irritable bowel syndrome, but like asthma these common conditions are diagnosed and treated on a daily basis.
- Since the symptoms of asthma (recurrent episodes of cough and wheeze and difficulty in breathing) can be heard or seen, the is absence of a reliable test for asthma is not a major problem.
- Although different guidelines have different recommendations for which tests should be done, in which order and what they define as abnormal, all guidelines are highly consistent in stating the asthma is a clinical diagnosis based on history.
- The tests which can be done to help support (or exclude) an asthma diagnosis are not infallible; many children with asthma have normal tests (even before starting treatment) and there are many children with no asthma symptoms who have abnormal test results.

REFERENCES

1. Asthma + Lung UK. [Internet]. Available from: https://www.asthmaandlung.org.uk/.

2. Saglani S, Menzie-Gow AN. Approaches to Asthma Diagnosis in Children and Adults. Front Pediatr. 2019 Apr 17;7:148.

3. Kavanagh J, Jackson DJ, Kent BD. Over-and under-diagnosis in asthma. Breathe. 2019;15(1):e20-e7.

4. Bush A, Fleming L. Is asthma overdiagnosed? Arch Dis Child. 2016;101(8):688-9.

5. Gaillard EA, Kuehni CE, Turner S, Goutaki M, Holden KA, de Jong CC, et al. European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years. European respiratory journal. 2021;58(5).

6. British Thoracic Society Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. 2019. ISBN 978 1 909103 70 2. Available from: https://www.sign.ac.uk/media/1773/sign158-updated.pdf.

7. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. 2021. Available from: www.nice.org.uk/guidance/ng80

8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2023. Available from: www.ginasthma.org.

9. de Jong CC, Pedersen ES, Mozun R, Müller-Suter D, Jochmann A, Singer F, et al. Diagnosis of asthma in children: findings from the Swiss Paediatric Airway Cohort. Eur RspirJ. 2020;56(5).

10. Murray C, Foden P, Lowe L, Durrington H, Custovic A, Simpson A. Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. LancetChild Adol Health. 2017;1(2):114-23.

11. Saglani S, McKenzie SA, Bush A, Payne D. A video questionnaire identifies upper airway abnormalities in preschool children with reported wheeze. ArchDisChild. 2005;90(9):961-4.

12. Pasterkamp H, Brand PL, Everard M, Garcia-Marcos L, Melbye H, Priftis KN. Towards the standardisation of lung sound nomenclature. Eur Respir J. 2016;47(3):724-32.

13. Dick S, Friend A, Dynes K, AlKandari F, Doust E, Cowie H, Ayres JG, Turner SW. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. BMJ Open 2014;4(11):e006554.

14. Lo D, Beardsmore C, Roland D, Richardson M, Yang Y, Danvers L, et al. Spirometry and FeNO testing for asthma in children in UK primary care: a prospective observational cohort study of feasibility and acceptability. Br J Gen Pract. 2020;70(700):e809-e16.

15. Jat KR. Spirometry in children. Prim Care Respir J. 2013;22(2):221-9.

16. World Health Organisation (WHO). The Global Health Observatory. [online] General availability of spirometry at the primary health care level. 2022. Available from:

https://www.who.int/data/gho/data/indicators/indicator-details/GHO/general-availability-of-peak-flow-measurement-spirometry-at-the-primary-health-care-level.

17. Masekela R, Zurba L, Gray D. Dealing with access to spirometry in Africa: a commentary on challenges and solutions. Int J Envir Res Public Health. 2019;16(1):62.

18. The Lancet. Global Health Metrics. Global Burden of Disease Study 2019. [Internet]. 2020. Available from: https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/asthma.pdf.

19. Daines L, McLean S, Buelo A, Lewis S, Sheikh A, Pinnock H. Systematic review of clinical prediction models to support the diagnosis of asthma in primary care. NPJ Primary Care Respiratory Medicine. 2019;29(1):19.

20. Chang AB, Landau LI, Van Asperen PP, Glasgow NJ, Robertson CF, Marchant JM, Mellis CM. Cough in children: definitions and clinical evaluation. Med J Australia 2006;184(8):398-403.

21. Schultz A, Devadason S, Savenije O, Sly P, Le Souef P, Brand P. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. Acta Paediatrica. 2010;99(1):56-60.

22. Van Wonderen K, Geskus R, van Aalderen W, Mohrs J, Bindels P, van Der Mark L, Ter Riet G. Stability and predictiveness of multiple trigger and episodic viral wheeze in preschoolers. Clin Exp Allergy. 2016;46(6):837-47.

23. Loke YK, Blanco P, Thavarajah M, Wilson AM. Impact of Inhaled Corticosteroids on Growth in Children with Asthma: Systematic Review and Meta-Analysis. PLoS One 2015;10(7):e0133428.

24. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child 2016 ;101(4):365-70.

25. Wallace A, Sinclair O, Shepherd M, Neutze J, Trenholme A, Tan E, Brabyn C, Bonisch M, Grey N, Johnson DW, McNamara D, Thompson JMD, Asher I, Dalziel SR. Impact of oral corticosteroids on respiratory outcomes in acute preschool wheeze: a randomised clinical trial. Arch Dis Child. 2021;106(4):339-344.

FIGURE LEGEND

Figure 1. Availability of spirometry at the primary healthcare level internationally in 2021. Data gathered from 194 countries surveyed as part of the WHO Global Health Observatory.