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Preschool wheezing and asthma in children: a systematic review of guidelines and quality appraisal with the Agree II Instrument

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The authors declare no conflict of interest.

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Authors' contributions

M.R. and W.F. initially conceptualized this study. All authors contributed to the data collection, data analysis, data interpretation, and preparation of the report. M.R., T.J.& W.F.assumed the main responsibility for the manuscript writing. All authors contributed to (and agreed upon) the final version.

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Appendices 1, 2 and 3

KEY MESSAGE

Wheezing and shortness of breath in preschool children is a heterogeneous condition, and one of the most commonly presented symptoms in everyday pediatric practice. A systematic review mapping the currently available guidelines for the diagnosis and management of preschool wheeze and/or asthma was necessary to provide a baseline for further development of EAACI recommendations. There is an abundance of guidelines targeting asthma in children, and their quality is rather good. However, the number of guidelines for preschool wheezing is lacking. Future guidelines for Preschool Wheezing should and will aim to identify EARLY individuals who are at risk for subsequent asthma inception and to provide them appropriate management and treatment.

ABSTRACT

Background. Asthma-like symptoms in preschool children, such as wheezing and dyspnea,are common time-, and resource-consuming diagnostic and management challenges. Quality of wheezing and asthma recommendations vary. The purpose of this study, carried out by the EAACI Task Force for Preschool Wheeze, was to systematically review and assess the quality of guidelines for diagnosis and treatment of preschool wheezing and/or asthma.

Methods. The Cochrane Library, MEDLINE, and EMBASE were searched untilJune 2018. The methodological rigor, quality, and transparency of relevant guidelines were assessed with the use of the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool.

Results. We identified 26 guidelines. The quality scores for each domain varied. Of all domains, clarity and presentation had the highest mean score, whereas applicability and stakeholder involvement had the lowest.The scores (median) for individual domains were as follows: Score and purpose 86%; Stakeholder involvement 49%; Rigor of development 54%; Clarity of presentation 85%; Applicability 51%; and Editorial independence 63%.

Conclusion. Although several guidelines on asthma management in children are available; however, their quality varies. Additionally, there is a considerable gap in reliable recommendations on the management and treatment of non-asthmatic preschool wheeze.

Key words: preschool wheezing, asthma, children, guidelines, AGREE, systematic review

INTRODUCTION

Wheezing and shortness of breath in preschool children is one of the most commonly presented symptoms in everyday pediatric practice.A considerable minority of children

will continue to experience wheezing in school years and beyond, diagnosed as "asthma" [1]. Preschool wheeze has been classified in several different ways, based on time of appearance, natural history, comorbidities and triggers.Some of these children with different phenotypes of wheezing will develop asthma later in life. However, until the diagnosis is confirmed, decision-making regarding the proper treatment is uncertain and challenging. [2, 3].

The term "preschool wheeze" has not been appropriately defined, and it varies considerably between countries (e.g. a 2-5 years gap according to the CDC, <4 years in the U.K., and <7 in Scandinavian countriesand Poland). Nonetheless, majority of birth cohorts show that significant changes in the epidemiology of recurrent wheeze take place around the age of 6 years [1-3], so we assumed the age of 6, as the most commonly accepted.

The relative prevalence of these phenotypes varies with the age of the child and partially overlap.All the above-mentioned factors suggest that our understanding of wheezing needs revision.[4]

There is a tremendous demand to propose an effective diagnostic approach and management of preschool wheezing/early-life asthma for at least three reasons. Firstly, pre-schoolers have the highest rate of unscheduled medical visits for wheezing and asthma symptoms, compared with all other age groups.[5] Secondly, episodes of wheezing, difficulty in breathing and cough usually lead to more limitations of every-day activities than in older children.[1] Thirdly, early life wheezing and repeated and cumulative lung injury due to viral respiratory infections (mainly rhinovirus or respiratory syncytial virus) may be causally associated with reduced lung function at six years of age,which might persist until adulthood.[6] Furthermore, these children consume a disproportionally high number of medications (mostly bronchodilators, and steroids)since the diagnosis of asthma in preschoolers is difficult and depend on many factors, including persistence of symptoms of wheezing at the age of 6 years.

Given the significant burden of disease and the magnitude of pediatric health-care utilization, several national and international consortia have published guidelines to

assist the clinical management of preschool wheezing/asthma and to improve resource use over the past 20 years. In 2017 the European Academy of Allergy and Clinical Immunology established a Task Force on Preschool Wheeze, to assess the quality of present guidelines and to propose new clinical practice recommendations. A joint working group was formed with the mandate to develop an EAACI position on the diagnosis and management of wheezing in pre-schoolers. The international multidisciplinary group included academic and non-academic clinicians, clinician-scientists, scientists, physicians trained in the evidence-based medicine and medical students from 10 countries (D, D.K., FIN, GR, NL, N, P.L., S, T.R., U.K.). This multidisciplinary team aimed to evaluate (critically appraise) all existing guidelines on asthma or preschool wheeze, published in English over the past 20 years and their use of evidence in making clinical recommendations.

METHODS

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement (Appendix 1), according to a pre-defined protocol and search strategy(Appendix 2 and 3)

Our team searched through MEDLINE, EMBASE, and the Cochrane Libraryuntil June 2018. In July 2019, a cross-reference with subsequent manual search was repeated in order to identify recommendations and/or guidelines on the diagnosis and management of wheezing and asthma in children, published in English, over the past 20 years. The search strategy was prepared by a professional librarian. Main search terms included wheezing, bronchiolitis, bronchitis, obstructive lung disease, obstructive airway disease, asthma, in children (aged 0-18 years). We excluded review papers, commentaries, guidelines summaries, old versions of included guidelines, conference abstracts and letters.

The search and selection of the publications were conducted independently by 5 reviewers, each time, the discrepancies between reviewers were solved by the

discussion, We retained all the potentially relevant articles and critically reviewed their full texts.

Our aim was to assess the process of guideline development and reporting; thus, we used the AGREE II, which is an internationally accepted standard for evaluation of the methodological quality of clinical practice guidelines. We used an electronic, online version of the AGREE II tool(available at: http://www.agreetrust.org/). This 23-items questionnaireaddresses six domains, which are guideline qualityrelated prepared and disseminated by the the AGREE Research Trust. [7], as follows:

1. *Scope and purpose:* **i**n this domain overall aim of the guideline, specific health questions and target of the guideline is addressed.
2. *Stakeholder involvement:*The second domain focuses on questions connected with stakeholders and views of potential users.
3. *Rigor of development:*In thethird domain number, the process of collecting, synthesizing the evidence, formulation of the recommendations, and updating are reviewed.
4. *Clarity of presentation:*Language, structure, format, and presentation are assessed in the fourth domain.
5. *Applicability:* Identification of possible barriers and facilitators in the guideline implementation process and presenting strategies of uptake improvement and guideline application are addressed in the fifth domain.
6. *Editorial independence:*The last domain deals with conflict of interest presentation.

Altogether, there are 23 questions rated on the 7-point Likert scale which ranges from "strongy agree" to "strongly disagree", in a six-domain tool. AGREE II tool incorporates two additional items.The first one, called the Overall Guidelines Assessment in which the reviewer again, using the 7-point Likert scale, judges the overall quality of the guideline. The second one adressesthe question as to whether the assessed guideline should be used.The possible answers are ''*yes*'', ''*yes with modification*'' or ''*no*''.

The number of reviewers recommended by the AGREE II consortium consists of at least two and preferably four people. In this paper, each guideline was appraised by at least three and up to eight reviewers independently.

Scores, for each question, were summed up, and then calculated as the percentage of the maximum possible score, using the AGREE II formula: [(score obtained – minimum possible score)/(maximum possible score – minimum possible score)] x 100. Scores range from 0% to 100%, however, there is no range or threshold provided by the AGREE II consortium that enables differentiation between high or low-quality guidelines.We arbitrarily set quality cut off at 60% as other authors used it.[8]

Four to eight reviewers independently assessed the methodology of the guidelines using the AGREE II instrument. Two of the authors had previous experience with the AGREE II instrument, while the rest of the team underwent online AGREE II training, that consists of a tutorial and practice exercise's available at www.agreetrust.org. Any disagreement, resulting in a difference in scoring by >2 points was resolved by discussion and second reassessment. All other disagreements between the reviewers were resolved via discussions until a consensus was reached. A change of the quality of guidelines over time was also assessed.

Additionally, all guidelines were reviewed for the grading method used.

Statistical analysis

We (M.R., W.F.) used descriptive statistics, for the basic features of the data in a study. Continuous non-parametric data was presented as a median followed by range, first and third interquartiles, and interquartiles range,whereas parametric data was presented as a mean ± standard deviation (S.D.), we calculated it with the use of Microsoft Excel (ver. 2019 16.0.6742.2048**)**.The agreement among reviewers/appraisers was calculated using the alpha Cronbach score,and SPSS software (ver. 26). [9]

RESULTS

Guidelines identification and interobserver agreement

For a flow diagram documenting the identification process for the eligible documents, see **Figure 1**. Overall, 26 guidelines were included.[2, 3, 10-33]We identified 26 guidelines, ten of which were developed by international societies or international consortia.[2, 3, 12, 17, 19, 25, 28-30, 33] The rest of identified guidelines were developed either by expert groups or national health organizations.

Cronbach`s alpha reliability coefficient varied from 0.68 to 0.93, with the mean value across all guidelines 0.834 (0.08 standard deviation) and median 0.865. In one case, all reviewers agreed with 100% of the answers. Therefore, calculating the Cronbach`s alpha was impossible due to lack of variance between answers.[10]

The AGREE II quality scores

Scores for each domain, overall assessment and Cronbach`s alpha coefficient and grading method are presented in **Table 1** and **Table 2,** respectively. Median for various domains ranged from 49% up to 86%. Domain 1 (scope and purpose) and domain 4 (clarity and presentation) were scored the highest (medians: 86% and 85% respectively), while domain 2 (stakeholder involvement) and domain 5 (applicability) were scored the lowest (medians 49% and 51%)

Scope and purpose: For the scope and purpose domain, the median was 86%; range: 28% to 100%). The highest scores in the first domain earned the Australian book of asthma and NICE guidelines [10, 13], while three guidelines scored below 60%. [27, 28, 31] Lack of proper reporting - which means that authors did not address thoroughly issues connected with scope and purpose (such for example target users of the guideline etc.) of the assessed guideline was the reason for such low scoring.

Stakeholder involvement: Patient and public involvement (stakeholders),hada median score of 49%; range: 10% to 100%). Two guidelines received the highest score for this domain (100%) (the Australian book of asthma, and NICE guidelines).[10, 13] Score for this

domain was among the two lowest scored domains. The main reason for this was again due to lack of reporting.

Rigor of development: In the third domain, the median was 54%(range: 8% to 100%). The highest score for this domain was 100% and was scored by Australian guidelines.[10] Twelve guidelines received scores below 60%. The lowest score was 15% and was related to Japanese guidelines. [32] Consistently, the lack of adequate information provided by authors justified such a low scoring.

Clarity of presentation: For the clarity of presentation domain, the median for the score was 85%; range 34% to 100%. The highest (100%) score was granted for GINA and GEMA guidelines. [12, 15] This domain proved to be one of the two most effectively addressed domains with only two guidelines scoring below 60% (ranging from 34% to 37%). Low scores were again due to limited reporting. [3, 33]

*Applicability:*In the fifth domain, the median for the score was 51%; range: 3% to 100%) with the highest score of 100% being granted only for the Australian guidelines. [10]The lowest score accounted for 3%.[3] Again, the lack of proper reporting was the reason for low scores in this domain.

Editorial independence: For this domain, the median was 63% (range: 2% to 100%). 100% was the highest score, and only two guidelines achieved it: again, the Australian book of asthma guidelines and EPR-3 guidelines. [10, 16] The lowest score (2%) in this domain came for French guidelines. [30]

Change of overall quality score in time. Interestingly, the overall quality of the guidelines shows an improvement trend to improve over the last 20 years. (in the 20 years), even though it was statisticallynot significant. Correlation coefficient (r) equals 0.3036, and r squared equals 0.0921. P=0,13. (Fig. 2)

DISCUSSION

We systematically reviewed the quality of guidelines concerning preschool wheezing and asthma as part of the EAACI Task Force preparation of new clinical practice recommendations for diagnosis and management of preschool wheeze by using one method – AGREE II. Our inclusion criteria fulfilled 26 guidelines published in English. Using the AGREE II, the National Council of Asthma Australia received top ratings, followed by an international expert consortium 'GINA', and other guidelines, signed by the British national organizations – NICE and BTS. [10, 12-14]

The quality scores for each domain varied. Almost all guidelines have correctly introduced their scope and purpose, and clearly presented their recommendations, and therefore, gained the highest scores (domain 1 and 4 with medians of 86% and 85%, respectively). On the other hand, the broad involvement of stakeholders, including patients' groups (domain 2) as well as ease of guideline applicability with identification of possible costs and barriers (domain 5), were most troublesome and gained the lowest scores of 49%, and 51% respectively. In our search there several guidelines for asthma (23), while there were only four guidelines focused solely on wheezing. Those guidelines had considerably variedquality indicating a considerable gap in current recommendations in this clinical field.

"Overallquality score" reflects more reviewers opinion of the reviewers on quality of each guideline, than actual credibility. We are aware that the robustness of guidelines, is more than just any AGREE II score, and it has been the common pitfall of putting undue emphasis on any aggregate "overall score". Therefore we decided not to show this specific result. Moreover,it should be emphasized thatno guideline was perfect. Therefore we present all results in detail in Table 2, to show separate results for each of 23 - AGREE II question for every identified guideline.

A critical assessment of asthma and wheezing guidelines has not been fully elucidated so far.

Acuña-Izcarayet al. have published a systematic review of available clinical guidelines for asthma management published between 2000 and 2010. [34]. In this the review, authorsidentified 18 guidelines, and their scores were markedly lower in comparison to ours.Although the authors conclude that the quality of guidelines improves over time, a similar observation was made by Lytras et al. in their systematic review [35]. Armstrong et al. also observed improvement in the quality of guidelines marked over time., in their publication. [36] In our review, the majority of the guidelines (16 of 26) are published after 2010.

In 2017,Bakel et al. published a systematic review of guidelines for asthma and bronchiolitis in children, focusing on quantification of agreement among the above-mentioned guidelines using weighted and unweighted K score. [37] In their report, the authors concluded that different guidelines for asthma show low consistency. The main discrepancy between this study and ours is the number of guidelines included(9 vs 26 in our study), which may be due to different scopes and different exclusion criteria in their review. Moreover, our study is more detailed in terms of results regarding the AGREE domains.

The AGREE II instrument was used in the appraisal of several guidelines,consistently showing differences in quality between different guidelines. [34-40] Strikingly, a substantial portion of the publishedguidelines remains at least, average quality.Moreover, there is a visible scarcity in guidelines regarding preschool wheezing.

Recently, Sun et al. have analyzed 50 different pediatric guidelines (not explicitly addressed to asthma), by using AGREE II method.[39] Their results are similar to oursand show deficiencies and strengths in corresponding domains. Similarly, domain 2 (involvement of stakeholders) and domain 5 (guideline applicability) were the lowest scored domains, while domains 1 and 4 scored the highest. There were negligible numerical differences between our results and those of Sun and colleagues.

Limitations

Firstly, we limited our search to thepast 20 years, even though most authors suggestthat an update is generally required after 3 to 5 years.[41]

Our search was also significantly limited to English guidelines. Thus, high-quality guidelines but published in other than English languages might have been omitted in our search, resulting in language bias.

In our methodology, there was no blinding to neither authors nor organizations who developed these guidelines – which may be another potential source of bias. However, sincewe were already familiar with the majority of the identified guidelines, thus true blinding was not possible.

In this paper, we used AGREE II, as only one method of assessment. However, other assessment systems exist such as GRADE or GIN. The use of one of those systems considerably increasesthe quality of the guidelines. Therefore, the lack of full GRADE assessment in our study may be regarded as a potential limitation of our study.

Finally, some of the reviewers/appraisers had no previous experience with the AGREE II instrument.Therefore,all reviewers were asked to take part in the recommended AGREE II consortium online training, which was in accordance with other AGREE evaluation groups.[34,40]

Another possible drawback is that, even though the AGREE II tool is considered both valid and reliable, this instrument has its limitations, such as lack of clear criteria for applying each point on the Likert scale. We could see tendency in our scoring to score either low or high - which is result of rather dichotomic answer to many AGREE questions. Moreover, it is focused mostly on the methodological side of guidelines, even though it also deals with the quality of evidence, and one may feel that this part of guidelines preparation is not covered enough. [41] Moreover, it is worth mentioning that there is no range or threshold provided by the AGREE II consortium, to enable differentiation between high or low-quality guidelines. Therefore, in our paper, we decided not to show overall quality results, but we showed scores not only for each domain but also for each of the 23 questions as well. [8]Last but not least, an analysis of

changes over time has shown atrend for guideline quality improvement. For that reason, adopting any objective values may inaccurate.

Last but not least among the limitations should be mentioned, that understanding of the term“preschool wheeze”, that has not been adequately defined yet. In our Task Force activities, we arbitrarily assumed “preschool” as children between the ages of 2 and 6, reflecting age differences in school systems and the epidemiology of recurrent wheezing.

CONCLUSIONS AND IMPLICATIONS

Early wheezing episodes are heterogeneous conditions, and we believe that their management should be based on good recommendations, resulting from a more personalized approach. A thorough history and physical examination in wheezy preschoolers may help to identify children with a risk of asthma/atopy since it will guide the likelihood of symptoms persisting. In these patients, a treatment basing on the well-prepared guidelines can be applied, since many of them are good enough to instruct how to control clinical symptoms of wheezing.

Clinical practice guidelines play a tremendous role in healthcare decision-making. This review uses current evidence to highlight the impact of standardization in guideline development on their quality. The AGREE II tool is not only helpful in assessing guidelines but also in improving quality if used during the planning and preparation of guidelines. Also, it should be emphasized that the recommendations rarely consider the views of the patient and the public.

We conclude that, even though there is an abundance of guidelines targeting asthma in children, the number of guidelines for preschool wheezing remains low.It seems essential that future guidelines for wheezy pre-schoolers would aim to identify individuals who may suffer from asthma in older age, in order to provide appropriate management and treatment.

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396 University of Warsaw for her assistance in optimizing the search strategy.

Country/organization	Year	Guideline Reference number]	Grading	Method od grading	GIN	Domain numbers						Would you use it?	Cronbach α
						1	2	3	4	5	6	yes/ywm/no	
Australian	2019	Australian book of asthma [10]	Yes	NHRMC grading methond	Not reported	100%	100%	100%	94%	100%	100%	4/0/0	no variance
International	2017	Global Initiative for Asthma 2018. Global strategy for asthma management and prevention [12]	Yes	**GRADE**	Not reported	99%	79%	94%	100%	97%	95%	5/0/0	0,79
UK/NICE	2016	National Institute for Health and Care Excellence (NICE). Quality standard for asthma. London: NICE [13]	Yes	**GRADE**	Not reported	100%	100%	99%	90%	99%	42%	2/1/0	0,68
UK/BTS	2016	British Thoracic Society and Scottish Intercollegiate Guidelines Network (2016) British guideline on the management of asthma. SIGN clinical guideline [14]	Yes	**GRADE**	Not reported	98%	86%	93%	96%	90%	87%	6/0/0	0,79
Spain	2016	GEMA 2016 (Spanish guideline on the management of asthma) [15]	Yes	GEMA based on GRADE	Not reported	79%	97%	86%	100%	83%	60%	3/1/0	0,88
USA/NHLBI	2007	Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report [16]	Yes	Based on Jadad	Not reported	90%	89%	83%	94%	98%	100%	3/0/0	0,87
International	2012	International consensus on (ICON) pediatric asthma [17]	Yes	ICON	Not reported	92%	36%	57%	97%	57%	92%	3/2/0	0,73
Canada/CTS	2012	Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults [26]	Yes	Based on ACCP grading	Not reported	97%	75%	77%	94%	88%	88%	3/1/0	0,93
USA/ATS	2012	Official American thoracic society clinical practice guidelines: Diagnostic evaluation of infants with recurrent or persistent wheezing. [19]	Yes	**GRADE**	Not reported	92%	53%	71%	80%	47%	67%	4/1/0	0,93
International	2007	Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. [1]9	Not reported	Not reported	Not reported	88%	52%	34%	96%	75%	67%	4/1/0	0,89
Finland	2015	Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children [22]	Yes	Own method	Not reported	90%	44%	80%	89%	20%	60%	1/3/0	0,72
USA/NASPGHAN	2002	Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: Recommendations of the North America Society for Pediatric Gastroenterology and Nutrition. Journal of Pediatric Gastroenterology and Nutrition 2001 [20]	Yes	Own method/unknown	Not reported	91%	60%	62%	91%	57%	5%	3/2/0	0,92
Netherlands	2012	Assessment of Controversial Pediatric Asthma Management Options Using GRADE [21]	Yes	**GRADE**	Not reported	96%	53%	73%	72%	60%	92%	3/1/0	0,76
South Africa/SACAWG	2013	Guideline for the management of acute asthma in children: 2013 [23]	Yes	Own method based on GINA 2009	Not reported	66%	22%	50%	83%	48%	50%	2/3/0	0,9
USA	2009	V.A./DoD clinical practice guideline for management of asthma in children and adults. Department of Defense [11]	Yes	U.S. Preventative Services Task Force grading system	Not reported	100%	40%	51%	100%	68%	10%	2/2/0	0,8

Canada/CTS	2015	Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Pediatric Society position paper [24]	Not reported	Not reported	Not reported	92%	65%	34%	90%	74%	88%	1/6/0	0,927
International/ERS	2008	Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. [25]	Yes	Own, bades on GRADE	Not reported	81%	29%	63%	73%	13%	38%	0/5/0	0,86
Saudi Arabia	2019	The Saudi initiative for asthma - 2012 update: Guidelines for the diagnosis and management of asthma in adults and children. [27]	Yes	Own method	Not reported	59%	48%	50%	87%	52%	70%	3/0/2	0,92
International/IPCRG	2006	International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care [28]	Not reported	Not reported	Not reported	58%	50%	32%	67%	53%	52%	0/0/4	0,9
International/IPCRG	2006	International Primary Care Respiratory Group (IPCRG) Guidelines: management of asthma [29]	Not reported	Not reported	Not reported	80%	57%	24%	77%	49%	65%	1/2/2	0,92
International/France/SPLF	2008	Asthma and allergy: short texts and recommendations of the expert conference of the French Speaking Pneumology Society (SPLF) [30]	Yes	Agence Nationale d'Accre ditation et d'Evaluation en Sante	Not reported	83%	67%	57%	67%	31%	2%	1/3/1	0,93
Spain/SEPAR	2015	Guidelines for severe uncontrolled asthma [31]	Yes	**GRADE**	Not reported	57%	38%	41%	78%	35%	42%	0/5/1	0,75
International	2014	Classification and pharmacological treatment of preschool wheezing: changes since 2008 [2]	Not stated	Not stated	Not reported	88%	19%	80%	92%	24%	67%	0/4/0	0,78
Japan	2017	Japanese guidelines for childhood asthma 2017 [32]	Not reported	Not reported	Not reported	73%	44%	15%	78%	35%	56%	1/1/5	0,76
International	2008	Treatment of asthma in young children: evidence-based recommendations Asthma research and practice [3]	Not reported	Not reported	Not reported	81%	10%	37%	34%	3%	94%	0/3/3	0,77
International/IPCRG	2006	International Primary Care Respiratory Group (IPCRG) Guidelines: integrating diagnostic guidelines for managing chronic respiratory diseases in primary care. [33]	Not reported	Not reported	Not reported	28%	22%	8%	37%	24%	47%	0/0/4	0,73
Median						86%	49%	54%	85%	51%	63%		
q1, q3						0,79, 0,95	0,38, 0,73	0,38, 0,8	0,77, 0,94	0,35, 0,81	0,47, 0,88		
IQR						0,15	0,34	0,42	0,16	0,46	0,40		

Table 1. Domain scores and overall assessment of guidelines using the AGREE II instrument

AGREE II question			Guideline number (from best to worst score)																						Results			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Median	q1	q3	IQR

1. The overall objective(s) of the guideline is (are) specifically described.	100%	100%	100%	98%	87%	100%	97%	96%	87%	87%	100%	93%	100%	80%	100%	93%	90%	67%	83%	87%	87%	67%	79%	81%	89%	17%	89%	84%	99%	15%
2. The health question(s) covered by the guideline is (are) specifically described.	100%	97%	100%	98%	67%	100%	83%	100%	97%	87%	83%	87%	100%	53%	100%	88%	63%	47%	33%	60%	97%	44%	100%	57%	89%	11%	87%	60%	99%	38%
3. The population (eg, patients, public) to whom the guideline is meant to apply is specifically described.	100%	100%	100%	100%	83%	71%	97%	96%	93%	90%	88%	93%	88%	63%	100%	95%	90%	63%	57%	93%	67%	61%	83%	81%	64%	56%	89%	67%	95%	27%
4. The guideline development group includes individuals from all relevant professional groups.	100%	73%	100%	95%	100%	92%	80%	83%	40%	57%	100%	83%	88%	43%	13%	86%	70%	50%	53%	67%	90%	42%	38%	45%	22%	6%	72%	43%	89%	45%
5. The views and preferences of the target population (eg, patients, public) have been sought.	100%	80%	100%	64%	90%	100%	7%	46%	47%	7%	0%	0%	4%	0%	8%	17%	0%	7%	0%	7%	50%	11%	0%	2%	3%	0%	7%	0,5%	49%	48%
6. The target users of the guideline are clearly defined.	100%	83%	100%	98%	100%	75%	20%	96%	73%	93%	33%	97%	67%	23%	100%	93%	17%	87%	97%	97%	60%	61%	21%	86%	6%	61%	85%	60%	96%	36%
7. Systematic methods were used to search for evidence.	100%	93%	100%	98%	87%	79%	0%	75%	53%	17%	100%	73%	100%	67%	46%	19%	83%	23%	20%	0%	47%	44%	8%	0%	81%	0%	60%	19%	85%	66%
8. The criteria for selecting evidence are clearly described.	100%	97%	100%	83%	83%	79%	13%	71%	73%	23%	100%	83%	92%	70%	8%	12%	80%	30%	30%	30%	33%	44%	0%	0%	61%	0%	66%	25%	83%	58%
9. The strengths and limitations of the body of evidence are clearly described.	100%	93%	100%	98%	93%	79%	13%	71%	97%	33%	100%	83%	96%	53%	67%	12%	80%	37%	63%	33%	80%	72%	0%	2%	36%	11%	72%	34%	93%	59%
10. The methods for formulating the recommendations are clearly described.	100%	97%	100%	90%	90%	79%	87%	83%	90%	30%	100%	83%	92%	27%	100%	60%	83%	50%	13%	7%	90%	14%	0%	0%	6%	0%	83%	17%	90%	73%
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	100%	97%	100%	95%	93%	92%	90%	88%	90%	97%	46%	90%	83%	87%	88%	52%	80%	83%	47%	77%	63%	69%	38%	48%	67%	33%	85%	64%	91%	25%
12. There is an explicit link between the recommendations and supporting evidence.	100%	97%	92%	95%	77%	100%	97%	75%	97%	60%	96%	80%	100%	73%	38%	21%	83%	63%	57%	47%	80%	75%	17%	21%	47%	17%	76%	49%	95%	46%
13. The guideline has been externally reviewed by experts before its publication.	100%	80%	100%	98%	93%	96%	90%	83%	63%	0%	96%	0%	0%	10%	0%	81%	0%	70%	23%	0%	63%	0%	0%	38%	0%	0%	51%	0	88%	88%
14. A procedure for updating the guideline is provided.	100%	100%	100%	83%	70%	58%	67%	71%	3%	10%	0%	0%	25%	17%	58%	12%	17%	40%	0%	0%	0%	6%	4%	10%	0%	0%	14%	0,8%	64%	63%
15. The recommendations are specific and unambiguous.	100%	100%	100%	95%	100%	100%	100%	92%	87%	97%	100%	93%	88%	83%	100%	93%	83%	90%	70%	73%	90%	81%	92%	81%	31%	39%	92%	83%	100%	17%

16. The different options for management of the condition or health issue are clearly presented.	100%	100%	96%	95%	100%	100%	97%	92%	67%	100%	71%	93%	83%	83%	100%	86%	77%	93%	63%	97%	60%	86%	92%	79%	56%	17%	92%	77%	96%	19%
17. Key recommendations are easily identifiable.	83%	100%	75%	98%	100%	83%	93%	100%	87%	90%	96%	87%	46%	83%	100%	93%	60%	77%	67%	60%	50%	67%	92%	74%	17%	56%	83%	66%	93%	26%
18. The guideline describes facilitators and barriers to its application.	100%	100%	100%	88%	90%	92%	53%	88%	57%	53%	0%	43%	92%	43%	50%	64%	23%	40%	67%	40%	47%	6%	71%	17%	0%	61%	55%	40%	87%	47%
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	100%	100%	100%	98%	100%	100%	63%	92%	27%	90%	4%	67%	54%	57%	71%	95%	13%	77%	57%	43%	3%	39%	17%	57%	0%	11%	60%	29%	94%	64%
20. The potential resource implications of applying the recommendations have been considered.	100%	87%	96%	83%	43%	100%	23%	83%	57%	60%	0%	43%	67%	30%	50%	50%	13%	37%	33%	37%	40%	25%	8%	2%	3%	11%	42%	23%	65%	41%
21. The guideline presents monitoring and/or auditing criteria.	100%	100%	100%	90%	97%	100%	87%	88%	47%	97%	4%	73%	29%	63%	100%	88%	3%	53%	57%	77%	33%	69%	0%	71%	8%	11%	72%	36%	95%	58%
22. The views of the funding body have not influenced the content of the guideline.	100%	97%	13%	81%	47%	100%	87%	100%	43%	47%	13%	7%	88%	10%	17%	95%	20%	73%	50%	67%	3%	6%	46%	24%	100%	0%	47%	13%	87%	73%
23. Competing interests of guideline development group members have been recorded and addressed.	100%	93%	71%	93%	73%	100%	97%	75%	90%	87%	0%	3%	96%	90%	4%	81%	57%	67%	53%	63%	0%	78%	88%	88%	89%	94%	84%	64%	92%	28%
Legend: 100%-81%, 80-61%,60-40%,39-20%,<20%																														

Table 2. Assessment of guidelines using the AGREE II instrument – all questions (percentages)

Figure 1. Flow chart (study selection)

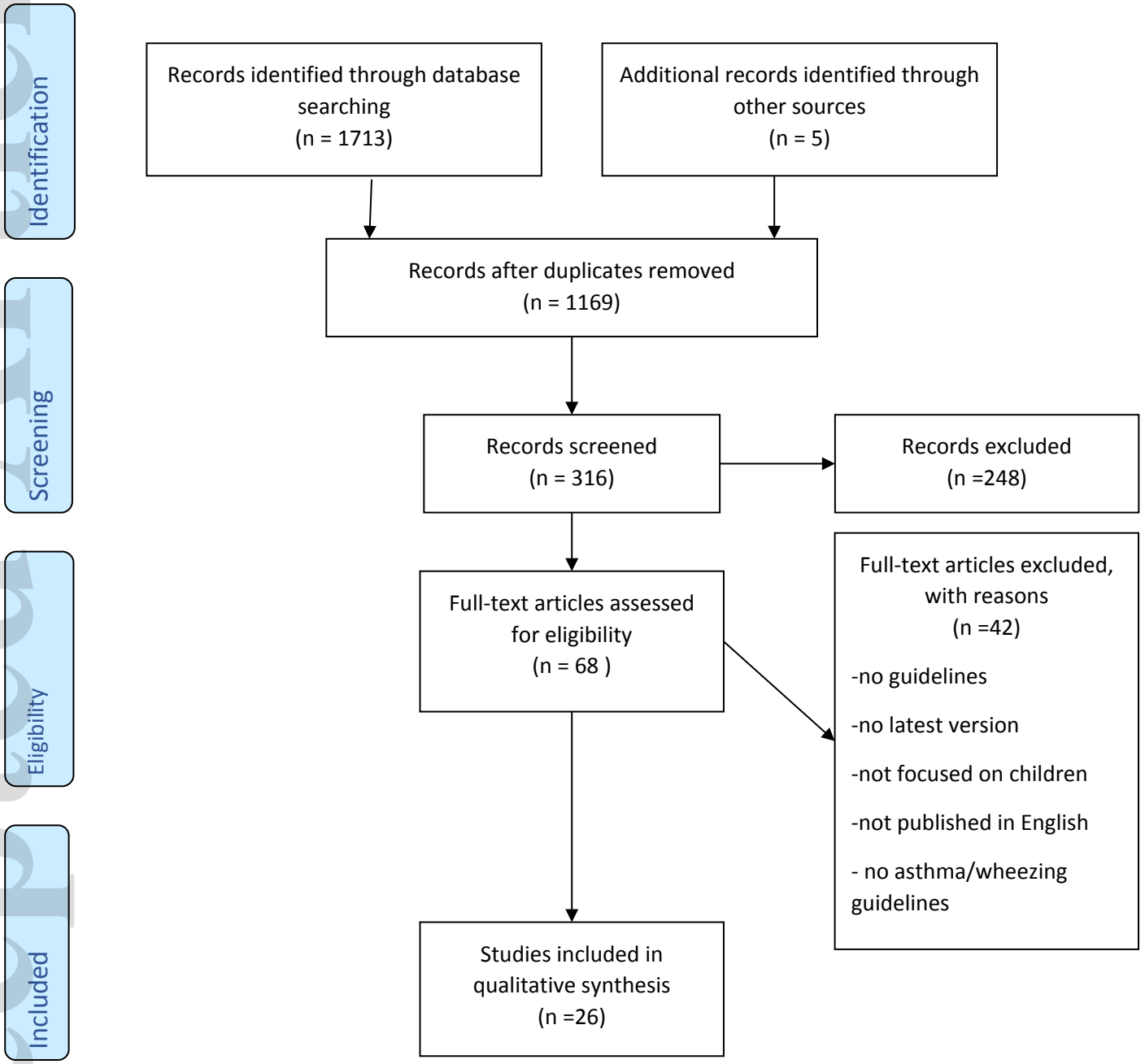
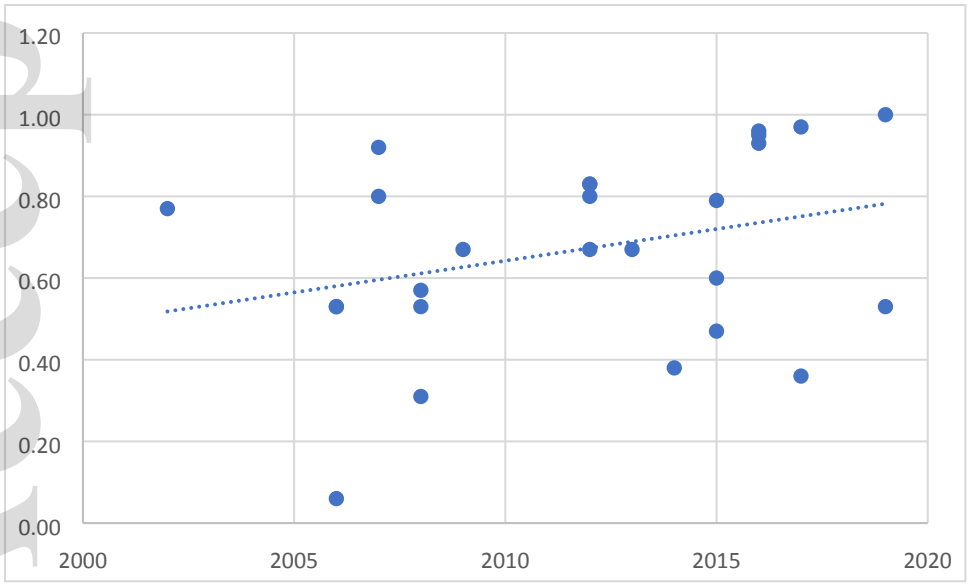


Figure 2. An overalquality of guidelines (AGREE score change) over time.



95CI: – 0,0049 0,03604, p=0,13, Beta: 5,71

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PRISMA 2009 Checklist

P1 I1Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 and 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	NA Objectives on page:P4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Protocol published online
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4 and 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Search strategy link:
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4 and 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5 AGREE

PRISMA 2009 Checklist

			tool
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Pages 4-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See attached flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable, for grading method see table 1.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable, For detailed outcomes see Table 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable

PRISMA 2009 Checklist

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Warsaw, 31 June 2018

STUDY PROTOCOL

Preschool wheezing and asthma in children: a systematic review of guidelines and quality appraisal with the Agree II Instrument – a protocol.

Marek Ruszczyński [1], Dominika Ambrożej [2], Aleksander Adamiec [2], Klaudia Ryczaj [3], Varpu Elenius [4], Ozlem Cavkaytar [5], Paraskevi Maggina [6], Heidi Makrinioti [7], Nikolaos Papadopoulos [6,8], Gunilla Hedlin [9,10], Jon R Konradsen [9,10], Bianca Schaub [11], Hermelijn Smits [12], Tuomas Jartti [4], Wojciech Feleszko [3], EAACI Task Force on Clinical Practice Recommendations on Preschool Wheeze.

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[12] Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands

Running title: *Wheezing and asthma guidelines AGREE appraisal*

Background:

Asthma-like symptoms in preschool children, such as wheezing and dyspnea, are common time-, and resource-consuming diagnostic and management challenges. Quality of numerous wheezing and asthma recommendations vary. The purpose of this study, carried out by the EAACI Task Force for Preschool Wheeze, was to assess the quality of guidelines for diagnosis and treatment of preschool wheezing and/or asthma.

Review question:

To systematically review and evaluate methodological quality of existing wheezing and asthma guidelines for children in last 20 years.

Warsaw, 31 June 2018

Searches:

Following electronic databases will be searched for published guidelines that fulfill our criteria: Medline, Embase, Cochrane library.

The search will be carried out independently by at least 3 reviewers, it will be restricted to English language only. We will use following strategies, prepared by trained librarian:

EMBASE: respiratory AND sounds OR bronchitis OR 'obstructive lung diseases' OR wheez* OR bronchiolitis OR 'obstructive airways disease' OR asthma AND guideline*:ti OR recommendations:ti OR 'health planning guideline':ti OR 'care pathway':ti OR 'critical pathway':ti OR 'consensus development conference':ti AND ([english]/lim) AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim)

MEDLINE (via PubMed): (("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields]) OR ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields]) OR ("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "lung"[All Fields] AND "disease"[All Fields]) OR "obstructive lung disease"[All Fields]) OR (wheez[All Fields] OR wheeze[All Fields] OR wheeze'[All Fields] OR wheeze1[All Fields] OR wheezed[All Fields] OR wheezed'[All Fields] OR wheezemd[All Fields] OR wheezer[All Fields] OR wheezers[All Fields] OR wheezers'[All Fields] OR wheezes[All Fields] OR wheezes'[All Fields] OR wheezies[All Fields] OR wheezin[All Fields] OR wheezin'[All Fields] OR wheeziness[All Fields] OR wheezing[All Fields] OR wheezing'[All Fields] OR wheezing,[All Fields] OR wheezings[All Fields] OR wheezingul[All Fields] OR wheezy[All Fields] OR wheezy'[All Fields]) OR ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields]) OR ("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "airway"[All Fields] AND "disease"[All Fields]) OR "obstructive airway disease"[All Fields])) AND ((guideline[title] OR guideline'[title] OR guideline'pregnancy[title] OR guideline's[title] OR guidelineon[title] OR guideliner[title] OR guideliner'[title] OR guidelinertrade[title] OR guidelines[title] OR guidelines'[title] OR guideliness[title] OR guidelinestrade[title]) OR (recommendation[title] OR recommendation's[title] OR recommendations[title] OR recommendations'[title] OR recommendationsa[title] OR recommendationsdagger[title] OR recommendationsfrom[title] OR recommendationsthe[title]) OR health planning[title] OR care pathway[title] OR ("critical pathways"[MeSH Terms] OR ("critical"[All Fields] AND "pathways"[All Fields]) OR "critical pathways"[All Fields] OR ("critical"[All Fields] AND "pathway"[All Fields]) OR "critical pathway"[All Fields]) OR consensus development conference[title]) AND (English[lang] AND ("infant"[MeSH Terms:noexp] OR "infant"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR "child"[MeSH Terms:noexp]))

COCHRANE:

#1 respiratory sounds

#2 bronchitis

#3 obstructive lung disease

#4 wheez*

#5 bronchiolitis

#6 obstructive airway disease

#7 asthma

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 MeSH descriptor: [Child] explode all trees

#10 MeSH descriptor: [Infant] explode all trees

#11 #8 and (#9 or #10)

Types of publications to be included:

Guidelines and recommendations will be included.

Condition or domain being studied.

. In 2017 the European Academy of Allergy and Clinical Immunology established a Task Force on Preschool Wheeze, to assess the quality of present guidelines and to propose new clinical practice recommendations. A joint working group was formed with the mandate to develop an EAACI position on the diagnosis and management of wheezing in preschoolers. The international multidisciplinary group included academic and non-academic clinicians, clinician-scientists, scientists, physicians trained in the evidence-based medicine and medical students from 10 countries (D, DK, FIN, GR, NL, N, PL, S, TR, UK). This multidisciplinary team aimed to evaluate (critically appraise) all existing guidelines on asthma or preschool wheeze, that have been published in English over the past 20 years and their use of evidence in making clinical recommendations.

Inclusion criteria:

recommendations and/or guidelines on the diagnosis and management of wheezing and asthma in children, published in English, over the past 20 years

Exclusion criteria:

review papers, commentaries, guidelines summaries, old versions of included guidelines, conference abstracts and letters.

Main outcome:

Guidelines methodological quality assessed with AGREE II tool.

Data extraction:

All relevant data will be extracted with the use of online AGREE II questionnaire.

Statistical analysis and data synthesis

Methodological quality scores will be calculated with the use of online AGREE II tool.

Continuous non-parametric data will be presented as a median followed by range, whereas parametric data were presented as a mean ± standard deviation (SD). The agreement among reviewers/appraisers will be calculated using the alpha Cronbach score, utilizing with the use of SPSS software.

EMBASE

respiratory AND sounds OR bronchitis OR 'obstructive lung diseases' OR wheez* OR bronchiolitis OR 'obstructive airways disease' OR asthma AND guideline*:ti OR recommendations:ti OR 'health planning guideline':ti OR 'care pathway':ti OR 'critical pathway':ti OR 'consensus development conference':ti AND ([english]/lim) AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim)

MEDLINE (via PubMed)

(("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields]) OR ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields]) OR ("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "lung"[All Fields] AND "disease"[All Fields]) OR "obstructive lung disease"[All Fields]) OR (wheez[All Fields] OR wheeze[All Fields] OR wheeze'[All Fields] OR wheeze1[All Fields] OR wheezed[All Fields] OR wheezed'[All Fields] OR wheezemd[All Fields] OR wheezer[All Fields] OR wheezers[All Fields] OR wheezers'[All Fields] OR wheezes[All Fields] OR wheezes'[All Fields] OR wheezies[All Fields] OR wheezin[All Fields] OR wheezin'[All Fields] OR wheeziness[All Fields] OR wheezing[All Fields] OR wheezing'[All Fields] OR wheezing,[All Fields] OR wheezings[All Fields] OR wheezingul[All Fields] OR wheezy[All Fields] OR wheezy'[All Fields]) OR ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields]) OR ("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "airway"[All Fields] AND "disease"[All Fields]) OR "obstructive airway disease"[All Fields])) AND ((guideline[title] OR guideline'[title] OR guideline'pregnancy[title] OR guideline's[title] OR guidelineon[title] OR guideliner[title] OR guideliner'[title] OR guidelinertrade[title] OR guidelines[title] OR guidelines'[title] OR guideliness[title] OR guidelinestrade[title]) OR (recommendation[title] OR recommendation's[title] OR recommendations[title] OR recommendations'[title] OR recommendationsa[title] OR recommendationsdagger[title] OR recommendationsfrom[title] OR recommendationsthe[title]) OR health planning[title] OR care pathway[title] OR ("critical pathways"[MeSH Terms] OR ("critical"[All Fields] AND "pathways"[All Fields]) OR "critical pathways"[All Fields] OR ("critical"[All Fields] AND "pathway"[All Fields]) OR "critical pathway"[All Fields]) OR consensus development conference[title]) AND (English[lang] AND ("infant"[MeSH Terms:noexp] OR "infant"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR "child"[MeSH Terms:noexp]))

COCHRANE

ID	Search Hits
#1	**respiratory sounds**
#2	**bronchitis**
#3	**obstructive lung disease**
#4	**wheez***

#5	**bronchiolitis**
#6	**obstructive airway disease**
#7	**asthma**
#8	**#1 or #2 or #3 or #4 or #5 or #6 or #7**
#9	**MeSH descriptor: [Child] explode all trees**
#10	**MeSH descriptor: [Infant] explode all trees**
#11	**#8 and (#9 or #10)**