

# Use of Management Pathways or Algorithms in Children With Chronic Cough

## CHEST Guideline and Expert Panel Report

*Anne B. Chang, MBBS, PhD, MPH; John J. Oppenheimer, MD; Miles M. Weinberger, MD, FCCP;  
Bruce K. Rubin, MD; Kelly Weir, BSpThy, MSpPath, PhD, CPSP;  
Cameron C. Grant, MBChB, PhD; Richard S. Irwin, MD, Master FCCP; on behalf of the  
CHEST Expert Cough Panel*

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## e-Appendix 1.

All data relating to key questions 1 to 3 were previously published.<sup>1</sup> Key data are repeated in this supplementary file for ease of reading.

### Key question 1 (KQ1)

In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), does the use of cough management protocols (or algorithms) improve clinical outcomes?

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> <li>Humans</li> <li>Children with chronic cough (<math>&gt; 4</math> weeks)</li> </ul>	Adults (aged $>14$ years)
Index Test	<ul style="list-style-type: none"> <li>Cough management protocols or pathways</li> </ul>	None
Comparator	<ul style="list-style-type: none"> <li>Non use of cough management protocols or pathways</li> </ul>	None
Target Condition	<ul style="list-style-type: none"> <li>Chronic Cough</li> </ul>	None
Timing	<ul style="list-style-type: none"> <li>Timing not limited</li> </ul>	None
Setting	<ul style="list-style-type: none"> <li>Inpatient and outpatient</li> </ul>	None
Study design	<ul style="list-style-type: none"> <li>Evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Not a clinical study (e.g., editorial, non-systematic review, letter to the editor, case series)</li> </ul>
Publications	<ul style="list-style-type: none"> <li>English-language only</li> <li>Peer-reviewed articles</li> <li>Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)</li> </ul>	<ul style="list-style-type: none"> <li>Non-English-language publications</li> </ul>

**e-Table 1: Prospective studies that have used cough management protocols (or algorithms) in children (key question 1)**

First author, publication yr Country	Setting	Guideline base	Inclusion criteria; Exclusion	N enrolled, N completed, Age	Primary outcome	Diagnoses a-priori defined; FU length	*Period effect considered	Main findings (top 3 diagnoses)
<b><u>Randomized controlled trial or systematic review</u></b>								
Chang <sup>2</sup> 2013 Australia	Multicentre esp OPD	Modified ACCP 2006 <sup>3</sup> and TSANZ <sup>4</sup>	Aged <18 years, >4 weeks cough, newly referred; Excl: chronic respiratory illness	270, 253 Mean=4.5 yrs, SD=3.7	At 6 wks: <sup>+</sup> Cough resolution by cough diary, <sup>5</sup> PC-QOL <sup>6</sup>	Yes; FU: max 12 mo for Dx and 6 mo post Dx	Yes, 2 wks of treatment	Absolute risk reduction with early use of algorithm=24.7%, 95%CI 13-35. Mean difference between groups in PC-QOL=0.6 (PBB, asthma, resolved without specific Dx)
McCallum <sup>7</sup> 2014	Cochrane review							Data same as above study <sup>2</sup> as it was the sole study in the review
<b><u>Cohort studies</u></b>								
Asilsoy, <sup>8</sup> 2008 Turkey	Single centre, Pediatric OPD	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: none reported	108, 108 mean=8.4 yrs	Cough - unspecified	Partial; FU:NR	Not specified	94.5% success (Asthma, PBB, UACS)

Chang <sup>9</sup> 2012 Australia#	Multicentre, Resp OPD	Modified ACCP 2006 <sup>3</sup> and TSANZ <sup>4</sup>	Aged <18 years >4 weeks cough newly referred Excl: chronic respiratory illness	range 6-14 yrs 346, 346 mean=4.5 yrs, SD 3	Cough resolution by cough diary, <sup>5</sup> PC-QOL <sup>6</sup>	Yes; FU:max 12 mo for Dx and 6 mo post Dx	Yes, 2 wks of treatment	Diagnoses differed in age groups (PBB, asthma, resolved without specific Dx)
Karabel, <sup>10</sup> 2014 Turkey	Single centre, Resp OPD	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: NM, cardiac, syndromes, RTI in last 4 wks	270, 270, mean=6.5 yrs range 7 mo- 17 yr	Not described	Partial; FU:12 mo	Not specified	Standardized approach "increases possibility for fast and accurate diagnoses..." (Asthma, asthma- like, GERD)
Marchant <sup>11</sup> 2006 Australia	Single centre, Resp OPD	Modified ACCP 1998 <sup>12</sup>	>3 wks cough Age <18 yrs Newly referred Excl: NR	108, 103 median=2.6 yr IQR 1.2-6.9	Cough diary, <sup>5</sup>	Yes; FU:max 12 mo for Dx, post Dx NR	Yes, 2 wks of treatment,	91% success (PBB, natural resolution, bronchiectasis)
Rehman, <sup>13</sup> 2009 Pakistan	Single centre, Pediatric OPD	Locally designed algorithm with Mantoux test	Aged 6-59 mo >4 wks cough Excl: Use of ACE inhibitors	172, 161 Summary not reported	Parents reporting - unspecified	NR; FU:until cough resolved (max 18 mo)	No,	Underlying cause identified in 92% of children (asthma, post-viral, tuberculosis)
Spelman, <sup>14</sup> 1991 Ireland	18 general practices	Asthma protocol^	>4 wks Excl: wheeze, previously on bronchodilators	106 Final=81 Range 0.5- 10 yrs	Parents reporting - unspecified	NR; FU:20 wks then 2 yrs	Unclear, visits 4 wks apart,	By visit-1, 71% cough gone/much better (73% diagnosed as

Usta, <sup>15</sup> 2014 Turkey	Single centre, pediatric allergy OPD	British Thoracic Society	Inclusion: NR Excl: ~	156, 156, Mean=8.4 yr SD 2.6	Cough- unspecified	Partial; FU: max 18 mo for Dx, NR post Dx	Not specified	asthma) Diagnoses changed from initial to final assessment (postnasal drip + asthma, postnasal drip, asthma, PBB <sup>§</sup> )
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ACCP=American College of Chest Physicians, ACE=angiotensin converting enzyme, Dx=diagnosis, Excl=exclusion criteria, FU=follow up period, GERD=gastroesophageal reflux disease, NR=not reported, OPD= respiratory outpatients, PBB=protracted bacterial bronchitis, PC-QOL= Parent Cough-Specific Quality of Life, Resp=Respiratory, TSANZ=Thoracic Society of Australia and New Zealand, UACS=upper airway cough syndrome

\*Period effect considered i.e use of 'time to response': the temporal relationship between use of medication and outcome was defined *a-priori*

#Children in this study were also in the RCT<sup>2</sup>

@improvement of  $\geq 75\%$  or total resolution according to parental reports and cough diary data for  $\geq 3$  days

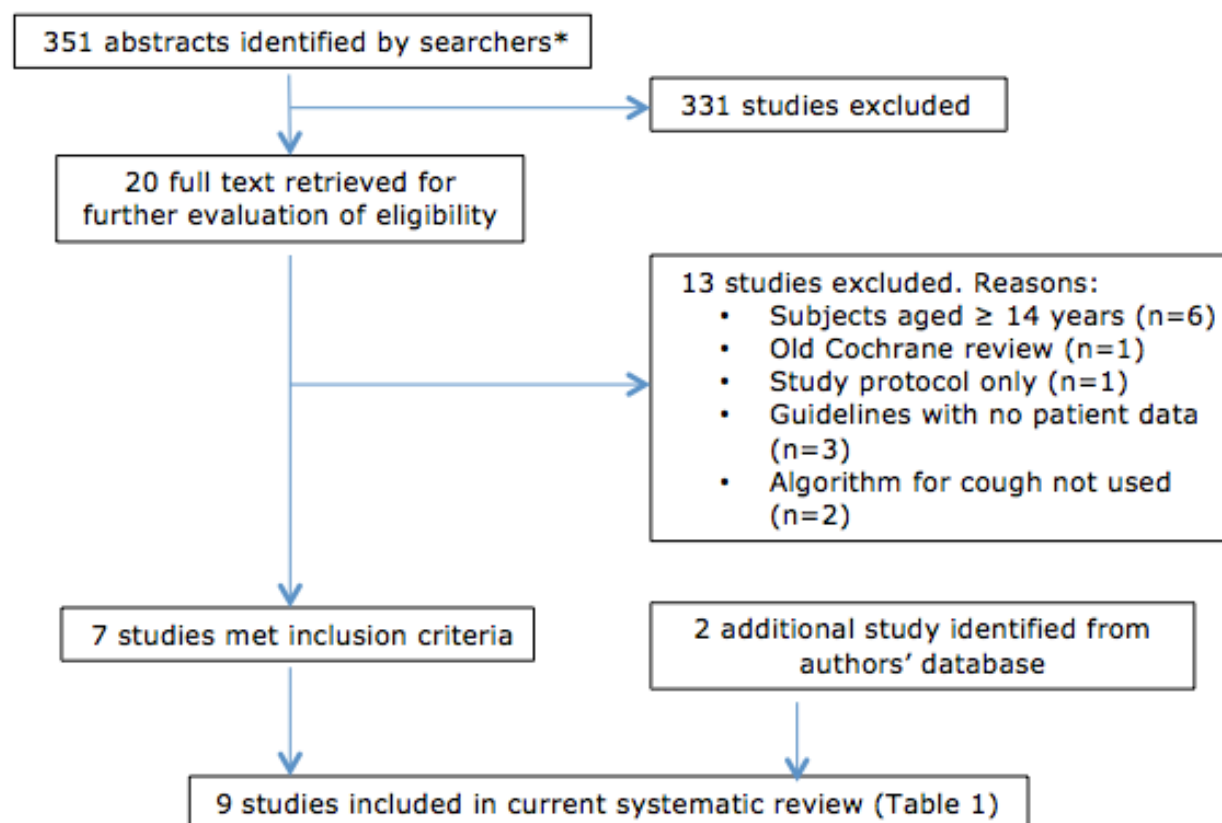
~"premature birth, neuromotor development retardation, development-growth retardation, chest wall deformity, a smoking habit, clubbing, cardiac disease, any known chronic disease and/or a pulmonary disease, and those who could not cooperate in pulmonary function test"<sup>15</sup>

<sup>§</sup>equal number of children with 'asthma' and PBB

^First visit: Age <2yr given oral orciprenaline, aged >3 yrs given oral salbutamol. Second visit: If "cough gone or much better" medications continued; if not, children given theophylline. Third visit: If "cough gone or much better" medications ceased; if not, children given oral prednisolone. Fourth visit: If "cough gone or much better" medications ceased; if not, children given inhaled sodium cromoglycate. Fifth visit: If "cough gone or much better" medications ceased; if not, children given oral prednisolone. Those on sodium cromoglycate, medications continued.

**e-Figure 1**

Selection of studies that addresses key question 1: In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), does the use of cough management protocols (or algorithms) improve clinical outcomes?



\*Searchers were undertaken by Nancy Harger, MLS and Judy Nordberg, MLS, Education and Clinical Services Librarians working in the University of Massachusetts Medical School Library in Worcester, MA

## Key question 2

In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), should the cough or testing algorithm differ depending on the duration and/or severity?

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> <li>Humans</li> <li>Children with chronic cough</li> </ul>	Adults (aged $>14$ years)
Index Test	<ul style="list-style-type: none"> <li>Duration (<math>&gt;4</math> but <math>&lt;8</math> weeks) and/or</li> <li>Severity cough (cough impacting activities)</li> </ul>	None
Comparator	<ul style="list-style-type: none"> <li><math>&gt;8</math> weeks</li> <li>Cough not impacting on activities</li> </ul>	None
Target Condition	<ul style="list-style-type: none"> <li>Chronic cough</li> </ul>	None
Timing	<ul style="list-style-type: none"> <li>Timing not limited</li> </ul>	None
Setting	<ul style="list-style-type: none"> <li>Inpatient and outpatient</li> </ul>	None
Study design	<ul style="list-style-type: none"> <li>Evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Not a clinical study (e.g., editorial, non-systematic review, letter to the editor, case series)</li> </ul>
Publications	<ul style="list-style-type: none"> <li>English-language only</li> <li>Peer-reviewed articles</li> <li>Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)</li> </ul>	<ul style="list-style-type: none"> <li>Non-English-language publications</li> </ul>

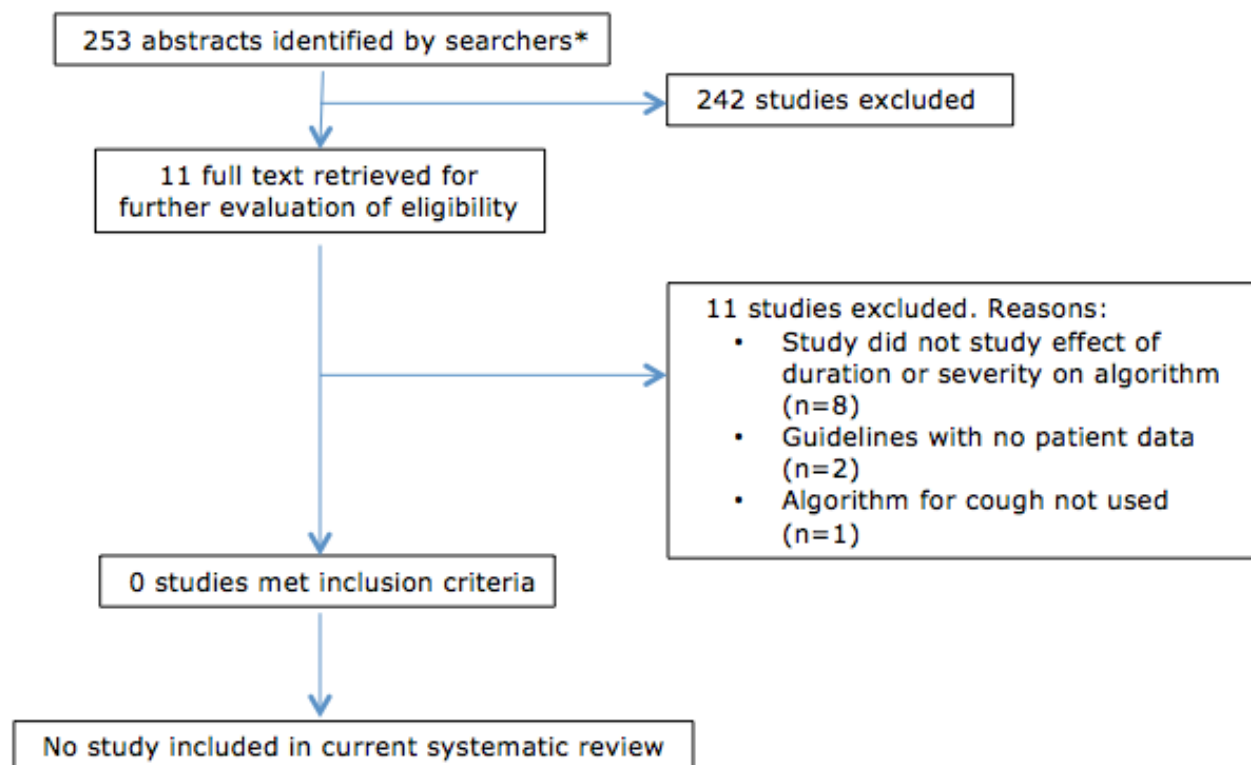
**e-Table 2: Summary of pediatric chronic cough guidelines relating to whether the cough or testing algorithm should differ depending on the duration and/or severity**

<b>First author, publication year</b>	<b>Country</b>	<b>Society</b>	<b>Definition of chronic cough</b>	<b>Severity</b> Assessment mentioned? If so, how	<b>Severity used to determine pathway?</b>
Chang <sup>4</sup> 2006	Australia	Thoracic Society of Australia & New Zealand	>4 weeks	Yes, non-specific effects on child and parents, expectations and burden	No
Chang <sup>3</sup> 2006	USA	American College of Chest Physicians	>4 weeks	Yes, non-specific effects on child and parents, expectations and burden	No
Gibson <sup>16</sup> 2008	Australia	Australia Lung Foundation	>4 weeks (pediatric component)	Yes, non-specific effects on child and parents	No
Kohno <sup>17</sup> 2006	Japan	Japanese Respiratory Society	>4 weeks (pediatric component)	No	No
Shields <sup>18</sup> 2008	England	British Thoracic Society	>8 weeks	Yes, non-specific effects on child and parents	No
Leconte <sup>19</sup> 2008	Belgium	Primary care	>4 weeks	Yes, quality of life, expectations, non-specific effects	No
Lu <sup>20</sup> 2014	China	Multiple societies	>4 weeks	No (based on translated article)	No
Zacharasiewicz <sup>21</sup> 2014	Austrian	Austrian Society of Pediatrics, Austrian Society Pneumology	>4 weeks	Yes, parental understanding	No



**e-Figure 2**

Selection of studies that addresses key question 2 - In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), should the cough or testing algorithm differ depending on the duration and/or severity?



\*Searchers were undertaken by Nancy Harger, MLS and Judy Nordberg, MLS, Education and Clinical Services Librarians working in the University of Massachusetts Medical School Library in Worcester, MA

### Key question 3 (KQ3)

In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), should the cough or testing algorithm differ depending on the associated characteristics of the cough and clinical history?

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> <li>Humans</li> <li>Children with chronic cough</li> </ul>	Adults (aged $>14$ years)
Index Test	<ul style="list-style-type: none"> <li>Use of cough characteristics (e.g wet cough, productive cough) and/or</li> <li>Use of associated clinical history (e.g feeding difficulties, recurrent pneumonia)</li> </ul>	None
Comparator	<ul style="list-style-type: none"> <li>Not using cough characteristics or associated clinical history</li> </ul>	None
Target Condition	<ul style="list-style-type: none"> <li>Chronic cough</li> </ul>	None
Timing	<ul style="list-style-type: none"> <li>Timing not limited</li> </ul>	None
Setting	<ul style="list-style-type: none"> <li>Inpatient and outpatient</li> </ul>	None
Study design	<ul style="list-style-type: none"> <li>Evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Not a clinical study (e.g., editorial, non-systematic review, letter to the editor, case series)</li> </ul>
Publications	<ul style="list-style-type: none"> <li>English-language only</li> <li>Peer-reviewed articles</li> <li>Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)</li> </ul>	<ul style="list-style-type: none"> <li>Non-English-language publications</li> </ul>

**e-Table 3a: Prospective studies that have evaluated the use of characteristics of the cough and/or clinical history to determine cough management or testing algorithm (key question 3)**

First author, publication year Country	Setting	Guideline base	Inclusion criteria, Exclusion	Main characteristic used	N enrolled, N completed, Age	Primary outcome	*Period effect considered; FU period	Main findings related to key question
<b><u>Randomized controlled trial or systematic review</u></b>								
Chang <sup>2</sup> 2013 Australia	Multi-centre, Resp OPD	Modified ACCP 2006 <sup>3</sup> and TSANZ <sup>4</sup>	Aged <18 years >4 weeks cough newly referred Excl: chronic respiratory illness	Non-specific and specific cough pointers	270, 253 Mean=4.5 yrs SD=3.7	At 6 wks: @Cough resolution by cough diary, <sup>5</sup> PC-QOL <sup>6</sup>	Yes, 2 wks of treatment; FU: max 12 mo for Dx and 6 mo post Dx	Non-specific cough: 'self-resolved' was the most common. Specific cough: PBB, asthma were most common
Marchant <sup>22</sup> 2012 Australia	Single centre, Pediatric and resp OPD	Not applicable	Aged 0.5-18 yrs Wet cough >3 wks Doctor-observed wet cough	Wet cough	50, 47 Mean=1.8-2.8 IQR=0.9-5.3	@Cough resolution by cough diary <sup>5</sup>	Yes; FU: 2 wks	Amoxycillin-clavulanate effective for wet cough, bronchoalveolar lavage findings in subgroup indicate PBB
<b><u>Cohort studies</u></b>								
Asilsoy, <sup>8</sup> 2008 Turkey	Single centre, Pediatric OPD	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: none reported	Non-specific and specific cough pointers	108, 108 mean=8.4 yrs range 6-14 yrs	Cough - unspecified	Not specified; FU: NR	'Watch and wait approach' as part of non-specific cough particularly beneficial

Chang, <sup>23</sup> 2015 Australia#	Multicentre, Resp OPD	Modified ACCP 2006 <sup>3</sup> and TSANZ <sup>4</sup>	Aged <18 years >4 weeks cough newly referred Excl: chronic respiratory illness	Non-specific and specific cough pointers	346, 326 mean=4.5 yrs, SD 3	Cough resolution by cough diary, <sup>5</sup> PC-QOL <sup>6</sup>	Yes, 2 wks of treatment; FU:max 12 mo for Dx and 6 mo post Dx	Children with chronic dry cough without any 'cough pointers' can be safely managed using the watchful waiting approach. High positive LR of cough pointers
Karabel, <sup>10</sup> 2014 Turkey	Single centre, Resp OPD	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: cardiac, neuromuscular syndromes, RTI in last 4 wks	Non-specific and specific cough pointers	270, 270, mean=6.5 yrs range 0.6-17	Not described	Not specified; FU:12 mo	Use of specific cough in this study less successful as 22 children in cohort had bronchiectasis and were identified through abnormal CXR pathway
Marchant, <sup>24</sup> 2006	Single centre, Resp OPD	Not applicable	>3 wks cough Age <18 yrs Newly referred Excl: NR	Non-specific and specific cough pointers	100 100 Median=2.8 yr IQR=1.0-6.5	+Cough resolution by cough diary	Yes; FU:max 12 mo for Dx, NR post Dx	Most useful clinical marker in predicting specific cough is the presence of a daily moist cough
Rehman, <sup>13</sup> 2009 Pakistan	Single centre, Pediatric OPD	Locally designed algorithm, includes Mantoux test	Aged 6-59 mo >4 wks cough Excl: Use of ACE inhibitors	Signs of heart disease	172, 161 Summary age not reported	Parents reporting - unspecified	No; FU:until cough resolved (max 18 mo)	Country-specific flow chart

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Usta, <sup>15</sup> 2014 Turkey	Single centre, pediatric allergy OPD	British Thoracic Society	Inclusion: NR Excl: ~	Non-specific and specific cough pointers	156, 156, Mean=8.4 yr SD 2.6	Cough- unspecified	Not specified; FU: max 18 mo for Dx, NR post Dx	Presence of rhinitis & allergic salute considered as a specific cough pointer. Asthma described as most common cause of non-specific cough
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ACCP=American College of Chest Physicians, ACE=angiotensin converting enzyme, Dx=diagnosis, Excl=exclusion criteria, FU=follow-up; GERD=gastroesophageal reflux disease, mo=months, NR=not reported, OPD= respiratory outpatients, PBB=protracted bacterial bronchitis, PC-QOL= Parent Cough-Specific Quality of Life, Resp=Respiratory, TSANZ=Thoracic Society of Australia and New Zealand, UACS=upper airway cough syndrome, yr=year

\*Period effect considered: temporal relationship between use of medication and outcome was defined a-priori

#Children in this study were from same study<sup>9</sup> and hence only one paper presented

+improvement of  $\geq 75\%$  or total resolution according to parental reports and cough diary data for  $\geq 3$  days

~"premature birth, neuromotor development retardation, development-growth retardation, chest wall deformity, a smoking habit, clubbing, cardiac disease, any known chronic disease and/or a pulmonary disease, and those who could not cooperate in pulmonary function test"<sup>15</sup>

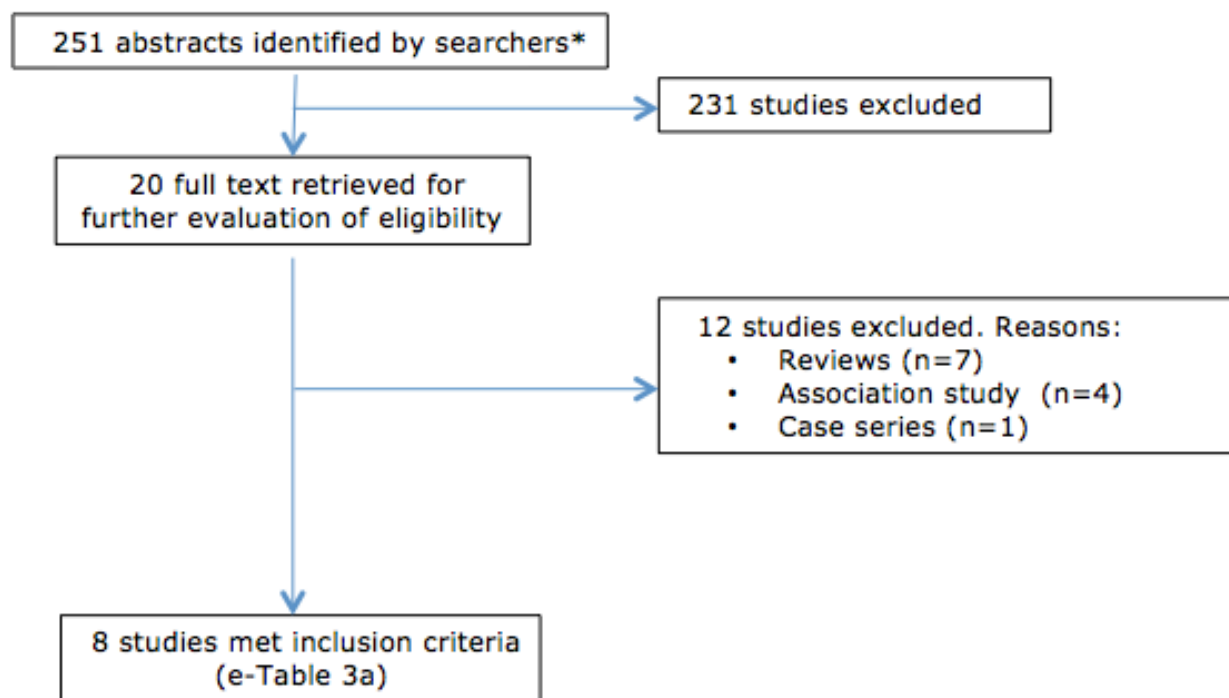
·Differentiation of specific from non-specific cough is presence of cough pointers, first described in a review paper<sup>25</sup>

**e-Table 3b: Summary of pediatric chronic cough guidelines advocating different management based on associated characteristics of the cough and clinical history**

<b>First author, publication year</b>	<b>Country</b>	<b>Society</b>	<b>Mx based on cough characteristics? If so, what?</b>	<b>Mx based on other clinical history? If so, what?</b>
Chang <sup>4</sup> 2006	Australia	Thoracic Society of Australia & New Zealand	Yes Cough constructs and pointers	Yes Non-specific and specific cough
Chang <sup>3</sup> 2006	USA	American College of Chest Physicians	Yes Cough constructs and pointers	Yes Non-specific and specific cough
Gibson <sup>16</sup> 2008	Australia	Australian Lung Foundation	Yes Cough constructs and pointers	Yes Non-specific and specific cough
Kohno <sup>17</sup> 2006	Japan	Japanese Respiratory Society	Partial Algorithm not presented	Yes Age, generic medical history
Leconte <sup>19</sup> 2008	Belgium	Primary care	Yes Cough constructs and pointers	Yes Non-specific and specific cough
Lu <sup>20</sup> 2014	China	Multiple societies	Yes Cough constructs	Yes (based on translated article) Non-specific and specific cough
Shields <sup>18</sup> 2008	England	British Thoracic Society	Yes Cough constructs and pointers	Yes Non-specific and specific cough
Zacharasiewicz <sup>21</sup> 2014	Austrian	Austrian Society of Pediatrics, Austrian Society Pneumology	Yes	Yes Unspecific and specific cough

**e-Figure 3**

Selection of studies that addresses key question 3 - In children aged  $\leq 14$  years with chronic cough ( $>4$  weeks duration), should the cough or testing algorithm differ depending on the associated characteristics of the cough and clinical history?



\*Searchers were undertaken by Nancy Harger, MLS and Judy Nordberg, MLS, Education and Clinical Services Librarians working in the University of Massachusetts Medical School Library in Worcester, MA

### Key question 4 (KQ4)

In children aged  $\leq 14$ -years, what testing or tests should be routinely done in clinical practice when evaluating chronic cough of at least 4-weeks duration?

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> <li>Humans</li> <li>Children with chronic cough (<math>&gt; 4</math> weeks)</li> </ul>	Adults (aged $>14$ years)
Index Test	<ul style="list-style-type: none"> <li>Any investigations</li> </ul>	None
Comparator	<ul style="list-style-type: none"> <li>No investigations</li> </ul>	None
Target Condition	<ul style="list-style-type: none"> <li>Chronic Cough</li> </ul>	None
Timing	<ul style="list-style-type: none"> <li>Timing not limited</li> </ul>	None
Setting	<ul style="list-style-type: none"> <li>Inpatient and outpatient</li> </ul>	None
Study design	<ul style="list-style-type: none"> <li>Evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Not a clinical study (e.g., editorial, non-systematic review, letter to the editor)</li> </ul>
Publications	<ul style="list-style-type: none"> <li>English-language only</li> <li>Peer-reviewed articles</li> <li>Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)</li> </ul>	<ul style="list-style-type: none"> <li>Non-English-language publications</li> </ul>



**RESULTS OF SEARCHERS FOR KQ4**

(undertaken by librarians (Nancy Harger, MLS and Judy Nordberg, MLS) from the University of Massachusetts Medical School, USA on 4<sup>th</sup> Aug 2015)

**PubMed**

("chronic cough" OR ((cough[mh] OR cough[tiab]) AND chronic disease[mh])) AND ("chest x-ray"[tiab] OR "chest radiograph"[tiab] OR radiography, thoracic[mh] OR evaluation[tiab] OR diagnosis[tiab] OR diagnosis[mh] OR diagnostic tests, routine[mh] OR testing[tiab] OR tests[tiab]) NOT (editorial[pt] OR letter[pt] OR comment[pt]) *Filters: Humans; English; Child: birth-18 years*

**Results: 659**

**SCOPUS**

TITLE-ABS-KEY(("chronic cough" OR (cough AND "chronic disease")) AND ("chest x-ray" OR "chest radiograph" OR "thoracic radiography" OR evaluation OR diagnosis OR "routine diagnostic tests" OR testing OR tests) AND (child OR adolescent OR infant OR children OR neonate OR toddler OR preschool)) AND (human OR humans ) AND ( LIMIT-TO(DOCTYPE,"ar" ) OR LIMIT-TO(DOCTYPE,"re" ) OR LIMIT-TO(DOCTYPE,"cp" ) OR LIMIT-TO(DOCTYPE,"ip" ) ) AND ( LIMIT-TO(LANGUAGE,"English" ) )

**Results: 806**

**After deduplication against "All References" in EndNote, Results = 320**

**CENTRAL (Cochrane)**

((("chronic cough" OR (cough AND "chronic disease")) AND ("chest x-ray" OR "chest radiograph" OR "thoracic radiography" OR evaluation OR diagnosis OR "routine diagnostic tests" OR testing OR tests) AND (child OR adolescent OR infant OR children OR neonate OR toddler OR preschool))

**Results: 42**

**After deduplication against "All References" in EndNote (with non-English removed), Results = 7**

**Web of Science**

TOPIC: (((("chronic cough" OR (cough AND "chronic disease")) AND ("chest x-ray" OR "chest radiograph" OR "thoracic radiography" OR evaluation OR diagnosis OR "routine diagnostic tests" OR testing OR tests) AND (child OR adolescent OR infant OR children OR neonate OR toddler OR preschool))) *Refined by: LANGUAGES: ( ENGLISH ) AND DOCUMENT TYPES: ( ARTICLE OR PROCEEDINGS PAPER OR MEETING ABSTRACT OR REVIEW )*

**Results: 282**

**After deduplication against "All References" in EndNote, Results = 113**

**e-Table 4**

**Prospective and retrospective studies that have included routine testing in all children with chronic cough and reported on outcomes (key question 4)**

<b>First author, publication yr Country</b>	<b>Setting</b>	<b>Guideline base</b>	<b>Inclusion criteria, Exclusion</b>	<b>Tests used</b>	<b>N enrolled, N completed, Age</b>	<b>Primary cough outcome</b>	<b>*Period effect considered; FU period</b>	<b>Main findings related to key question at initial visit</b>
Asilsoy, <sup>8</sup> 2008 Turkey	Single centre, Pediatric OPD, Prosp	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: none reported	Spiro +/- salbutamol, CXR	108, 108 mean=8.4 yrs range 6-14 yrs	Cough - unspecified	Not specified; FU:NR	BDR n=20 (18.5%) CXR abn n=3 (all later found to have bronchiectasis)
de Benedictis, <sup>26</sup> 1986 Canada	Single center, Resp lab, retros review of notes	Not applicable	MCH test done, >6 wk cough, normal physical exam, available FU data. Excl: Hx of wheeze, dyspnea, BD use, URTI in last 6 wk	See e-Table 2 for lung function. CXR, sinus XR and SPT (10 allergens) in some	58, mean=11 yrs range 7-16 yrs	Cough response (undefined) to 4 wk SABA (oral or inhaled) or theophylline	No, FU period not specified	CXR abnormal in 6 of 54 (11.1%), SPT+ in 16 of 48 (33.3%), sinus XR abnormal in 4 of 34 (11.8%)
Callahan <sup>27</sup> 1996 USA	Single center, Resp OPD, retros review of notes	Not applicable	Chronic cough >3 wk Excl: NR	Unclear what tests were done in all children	95, Age NR	Unspecified	No, FU: NR	Spiro diagnostic in 11 (11.6%). Study also reported some children had CT, barium meal but no data on how tests were selected
Chang <sup>2</sup> 2013 Australia	Multicenter Resp OPD, Randomized	Modified ACCP 2006 <sup>3</sup> and	Aged <18 yr, >4 wk cough, newly referred;	Spiro +/- salbutamol, CXR. Further Ix	270, 253 Mean=4.5	<sup>+</sup> Cough resolution by cough diary, <sup>5</sup>	Yes, 2 wks of treatment FU: max 12	Absolute risk reduction with early use of

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	controlled trial <sup>#</sup>	TSANZ <sup>4</sup>	Excl: chronic respiratory illness	undertaken when indicated	yrs, SD=3.7	PC-QOL <sup>6</sup>	mo for Dx, 6 mo post Dx	algorithm=24.7%, 95%CI 13-35. Mean difference between groups in PC-QOL=0.6
Chang, <sup>23</sup> 2015 Australia	Multicenter, Resp OPD, Prosp	Modified ACCP 2006 <sup>3</sup> and TSANZ <sup>4</sup>	Aged <18-yr, chronic cough >4-wk cough, newly referred Excl: chronic respiratory illness	Spiro +/- salbutamol, CXR. Further Ix undertaken when indicated	346, 326 mean=4.5 yrs, SD 3	Cough resolution by cough diary, <sup>5</sup> PC-QOL <sup>6</sup>	Yes, 2 wks of treatment; FU: max 12 mo for Dx and 6 mo post Dx	Spiro abn n=8 ‡(OR 2.4, 95%CI 0.14-42.7; LR+ Infinity; LR- 0.97, 95%CI 0.95-0.99) CXR abn n=58 ‡(OR 20.3, 95%CI 1.2-335; LR+ Infinity; LR- 0.8, 95%CI 0.75-0.85)
Cloutier <sup>28</sup> 1981 USA	Single center, resp OPD, Prosp	Not applicable	Chronic cough (>2 mo), able to do PFT and exercise test, normal exam, ENT, CXR and sweat test Excl: wheeze, BD use, Hx of croup bronchiolitis, pneumonia, aspiration, tobacco smoking	See e-Table 2 for PFT, IgE levels, SPT to local antigens, blood and nasal eosinophils	15 Mean=10.9 yr SD 2.9	Cough resolution (unspecified)	No, FU after Rx with theophylline and 6 mo without theophylline	All IgE levels normal, SPT+ n=2 Blood and nasal eosinophils elevated n=2
Dani <sup>29</sup> 2002 India	Single center, ped OPD, Prosp	Not applicable	consecutive, immunocompetent, aged 1-12 yr, chronic cough >3 wk, unknown etiology Excl: heart disease	"Sequential incorporation of routine Ix e.g., FBC, ESR, Mantoux test, sputum, throat swab, CXR. Further Ix (e.g.	94 Age NR	NR	No, FU NR	Dx by history and physical examination and routine Ix n=82 (87%). Data on what was useful not provided. 37% Asthma n=35 (37%) Tuberculosis n=21

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				bronchoscopy, HIV, CT scan, barium swallow) when indicated				(22.3%)
Karabel, <sup>10</sup> 2014 Turkey	Single centre, Resp OPD	ACCP 2006 <sup>3</sup>	>4 wks cough Excl: cardiac, neuromuscular syndromes, RTI in last 4 wks	FBC, CXR, spiro +/- salbutamol. Further Ix undertaken when indicated	270, 270, mean=6.5 yrs range 0.6-17	Not described	Not specified; FU:12 mo	74 (27%) children diagnosed with asthma based on clinical, CXR and spiro and cough resolved with asthma therapies
Marchant, <sup>24</sup> 2006	Single centre, Resp OPD, Pros	Not applicable	>3 wks cough, Age <18 yrs, consecutive newly referred Excl: NR	Spiro +/- salbutamol, CXR Further Ix undertaken when indicated	100 100 Median=2.8 yr IQR=1.0-6.5	<sup>+</sup> Cough resolution by cough diary	Yes; FU: max 12 mo for Dx, NR post Dx	CXR abn predicting specific cough OR=3.2 (95%CI 1.3, 7.6), LR+ 1.7, spiro abn LR+ 2.3
Turkas, <sup>30</sup> 2002 Turkey	Single center, Allergy asthma OPD, Prosp	Not applicable	Chronic cough +/- episodic wheeze and dyspnea >4 wk Excl: NR	See e-Table 2 for PFT. CXR and sinus X-rays, SPT (30 inhaled allergens)	133 (81 with cough only), mean=10.1 yr, SD 2.2	Cough (undefined)	No, FU: unclear for the children with cough alone	Atopy no effect on AHR prediction. Data on SPT and sinus XR in relation to cough not given
Usta, <sup>15</sup> 2014 Turkey	Single centre, pediatric allergy OPD	British Thoracic Society	Inclusion: NR Excl: ~	Spiro with albuterol	156, 156, Mean=8.4 yr SD 2.6	Cough-unspecified	Not specified; FU: max 18 mo for Dx, NR post Dx	21 children diagnosed with asthma based on spiro and cough resolved with asthma therapies
Yilmaz <sup>31</sup> 2014 Turkey	Single centre, pediatric asthma, allergy OPD	ACCP	Aged <18 yr, chronic cough >4 wk. Excl: presence of specific cough	SPT (house dust mites, pollens, alternaria, animal dander, latex), FBC	109 Median=5 yr IQR 3.5, 9	Cough on diary card	No, FU: mean 21 mo (SD 5)	Children with asthma on FU more likely to have atopy (16 of 31, 52%) than those without (20 of 77,

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			pointer, wet cough, characteristic cough pattern, CXR or PFT abnormality, chronic resp illness, previous use of corticosteroid, LTRA, ACE-I					26%). No difference between groups on blood eosinophilia
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ACCP=American College of Chest Physicians, ACE-I=angiotensin converting enzyme inhibitor, AHR+=positive airway hyper-responsiveness, BD=bronchodilator, BDR=bronchodilator, responsiveness, CXR=chest xray, Dx=diagnosis, Excl=exclusion criteria, FBE=full blood examination, FU=follow-up; Hx=history, LR+=positive likelihood ratio, LR-=negative likelihood ratio, MCH=methacholine challenge, mo=months, NR=not reported, OPD=outpatients department, PC-QOL= Parent Cough-Specific, PFT=pulmonary function test, Pros=prospective study, Resp=Respiratory, SABA=short acting beta<sub>2</sub> agonist, Spiro=spirometry, SPT=skin prick test, XR=xray, yr=year

~"premature birth, neuromotor development retardation, development-growth retardation, chest wall deformity, a smoking habit, clubbing, cardiac disease, any known chronic disease and/or a pulmonary disease, and those who could not cooperate in pulmonary function test"<sup>15</sup>

‡compared to children whose cough resolved without specific treatment

#Children in this study included were subset of children from in another study<sup>23</sup>

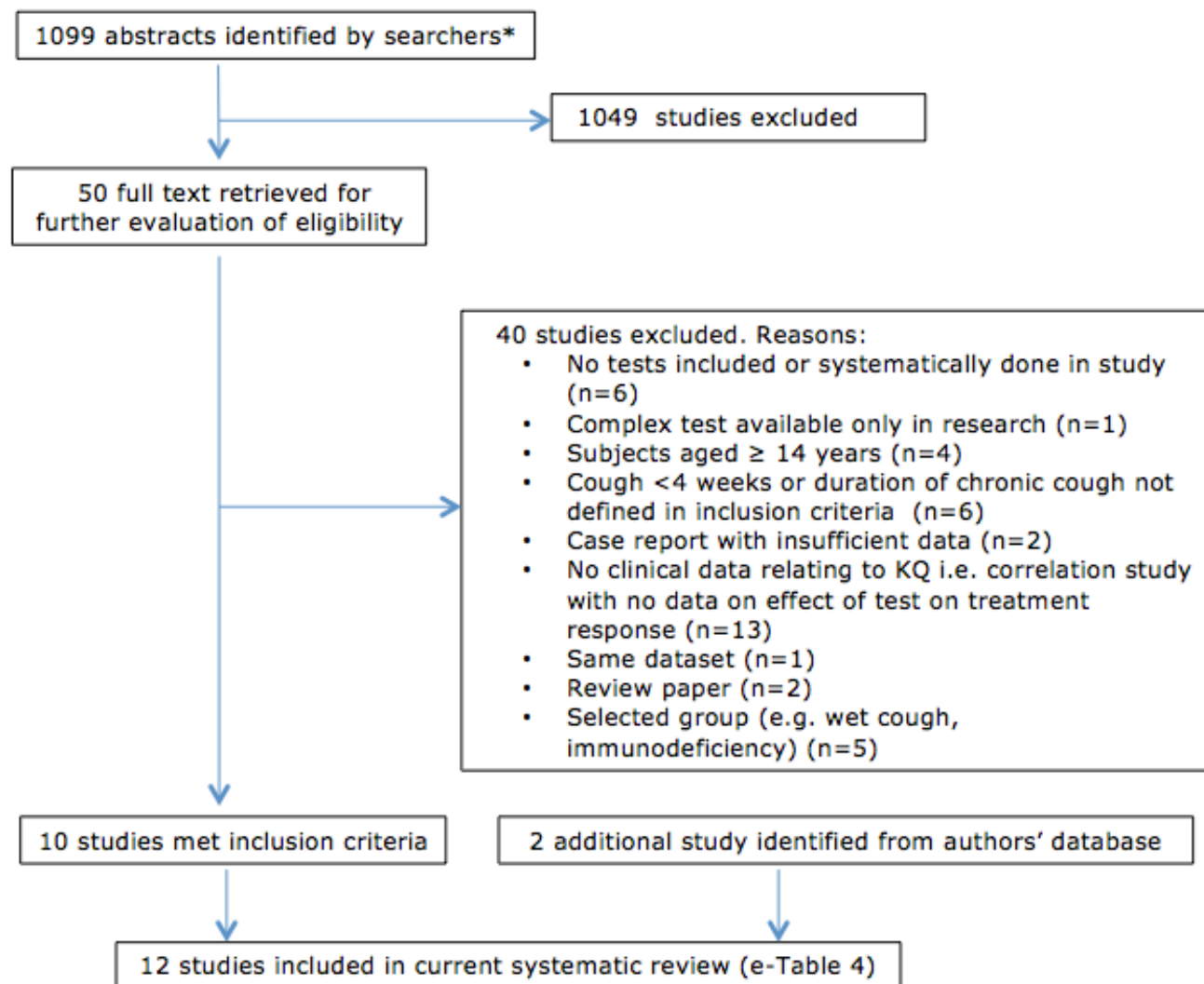
\*Period effect considered: temporal relationship between use of medication and outcome was defined a-priori

+improvement of ≥75% or total resolution according to parental reports and cough diary data for ≥3 days

·Differentiation of specific from non-specific cough is presence of cough pointers, first described in a review paper<sup>25</sup>

**e-Figure 4**

Selection of studies that addressed key question (KQ) 4 - In children with chronic (>4 weeks) cough, what testing or tests should be routinely done in clinical practice?



\*Searchers were undertaken by Nancy Harger, MLS and Judy Nordberg, MLS, Education and Clinical Services Librarians working in the University of Massachusetts Medical School Library in Worcester, MA

## Key question 5 (KQ5)

When evaluating children aged  $\leq 14$ -years with chronic cough (of at least 4-weeks duration), what is the role of pulmonary function studies and bronchial provocation in clinical practice?

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> <li>Humans</li> <li>Children with chronic cough</li> </ul>	Adults
Index Test	<ul style="list-style-type: none"> <li>Pulmonary function</li> <li>Bronchial provocation or test for airway hyperresponsiveness</li> </ul>	None
Comparator	<ul style="list-style-type: none"> <li>No test for pulmonary function or airway hyperresponsiveness</li> </ul>	None
Target Condition	<ul style="list-style-type: none"> <li>Chronic cough</li> </ul>	None
Timing	<ul style="list-style-type: none"> <li>Timing not limited</li> </ul>	None
Setting	<ul style="list-style-type: none"> <li>Inpatient and outpatient</li> </ul>	None
Study design	<ul style="list-style-type: none"> <li>Evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Not a clinical study (e.g., editorial, non-systematic review, letter to the editor)</li> </ul>
Publications	<ul style="list-style-type: none"> <li>English-language only</li> <li>Peer-reviewed articles</li> <li>Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)</li> </ul>	<ul style="list-style-type: none"> <li>Non-English-language publications</li> </ul>

## **RESULTS OF SEARCHERS FOR KQ5**

(undertaken by librarians (Nancy Harger, MLS and Judy Nordberg, MLS) from the University of Massachusetts Medical School, USA on 7<sup>th</sup> Aug 2015)

### **PubMed**

("chronic cough" OR ((cough[mh] OR cough[tiab]) AND chronic disease[mh])) OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "productive cough" OR "persistent cough") AND ("pulmonary function test"[mh] OR pulmonary function test[tiab] OR "bronchial provocation tests"[mh] OR bronchial provocation tests[tiab]) Filters: Humans; English; Child: birth-18 years

**Results: 51**

### **SCOPUS**

(TITLE-ABS-KEY(("chronic cough" OR (cough AND "chronic disease"))) OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "productive cough" OR "persistent cough")) AND (TITLE-ABS-KEY("pulmonary function test" OR "bronchial provocation tests") AND (child OR children OR infant OR neonate OR toddler OR preschool) AND (human OR humans)) AND ( LIMIT-TO(LANGUAGE,"English" ) ) AND ( LIMIT-TO(DOCTYPE,"ar" ) OR LIMIT-TO(DOCTYPE,"re" ) OR LIMIT-TO(DOCTYPE,"cp" ) )

**Results: 104**

**After deduplication against "All References" in EndNote, Results = 68**

### **CENTRAL (Cochrane)**

("chronic cough" OR (cough AND "chronic disease") OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "productive cough" OR "persistent cough") AND ("pulmonary function test" OR "bronchial provocation tests") AND (child OR children OR infant OR neonate OR toddler OR preschool) in Title, Abstract, Keywords

**Results: 18**

**After deduplication against "All References" in EndNote, Results = 12**

### **Web of Science**

TOPIC: (("chronic cough" OR (cough AND "chronic disease") OR "idiopathic cough" OR "refractory cough" OR "unresponsive cough" OR "intractable cough" OR "psychogenic cough" OR "unresolved cough" OR "unexplained cough" OR "productive cough" OR "persistent cough") AND ("pulmonary function test" OR "bronchial provocation tests") AND (child OR children OR infant OR neonate OR toddler OR preschool))

*Refined by: LANGUAGES: ( ENGLISH )*

**Results: 68**

**After deduplication against "All References" in EndNote, Results = 60**



**e-Table 5**

**Studies that have specifically evaluated the use of pulmonary function and/or bronchial provocation tests in children with chronic cough (key question 5)**

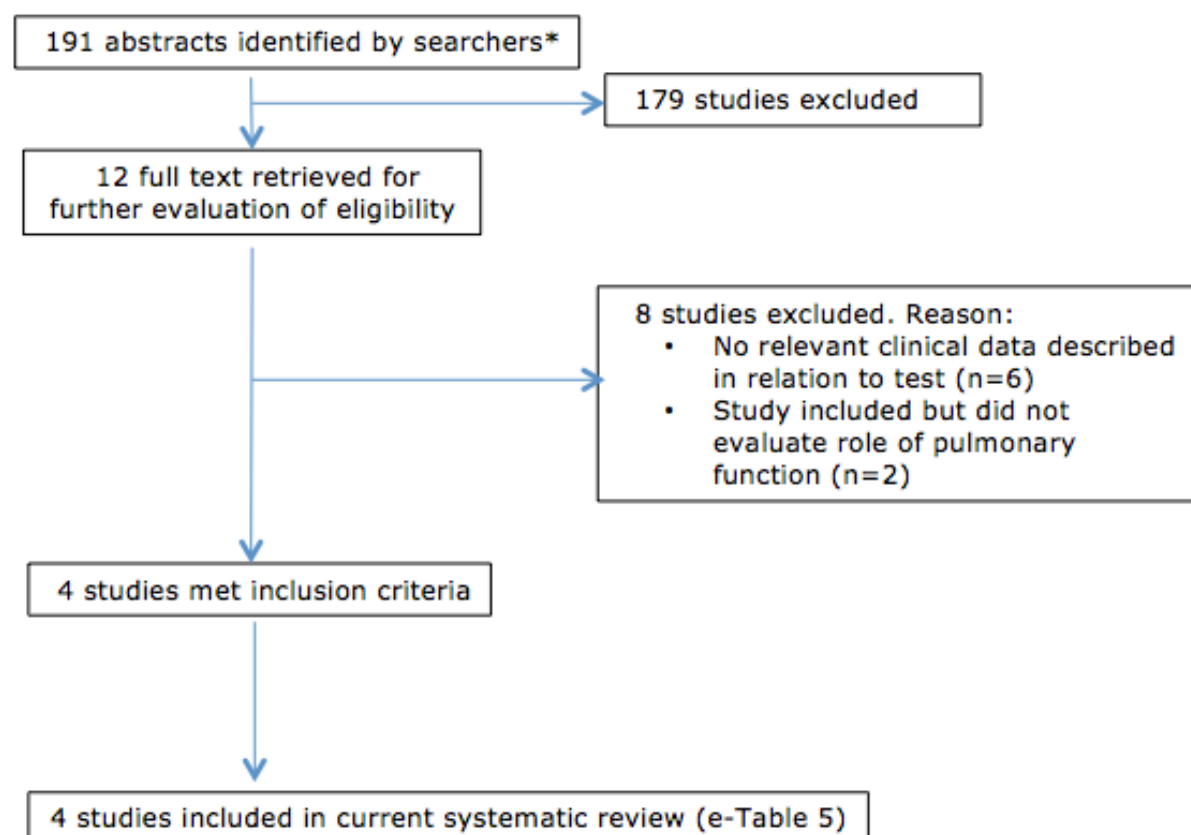
<b>First author, publication year Country</b>	<b>Setting</b>	<b>Inclusion criteria, Exclusion</b>	<b>Pulmonary function used, Definition of AHR</b>	<b>N enrolled, N completed (if relevant) Age</b>	<b>Findings</b>	<b>Clinical response</b>	<b>Comments</b>
Bentur, <sup>32</sup> 2004 Israel	Single center, resp OPD, prospective	Aged <24 mo, chronic cough (>2 mo), referred. Excl: any chronic or resp disease, steroids or acute illness in last 4 wk, BD in 2 wk	AHR to nebulized adenosine, AHR+ =recorded wheeze by computer analysis	30, Mean=8.3 mo SD 4.2 mo	AHR+ n=27 Cough quality not mentioned	All Rx with budesonide 200ug bd for 4 wk. At 3 yr, 14 of AHR+ had asthma (by questionnaire)	AHR+ for recurrent wheeze, sensitivity=100 %specificity=66.6%
Cloutier <sup>28</sup> 1981 USA	Single center, resp OPD, prospective	Chronic cough (>2 mo), PFT and exercise test, normal exam, ENT, CXR and sweat test Excl: wheeze, BD use, Hx of bronchiolitis, croup, pneumonia, aspiration, tobacco smoking	Spirometry, peak flow, lung volumes, threadmill exercise test, AHR+ not defined	15, Mean=10.9 yr SD 2.9	Normal lung volumes in all, Flow <sub>max</sub> 75%VC fall >33% in all post exercise. Cough was non-productive in all, family Hx of atopy, allergies or hay fever in 9	Isoproterenol given to 8 with no difference to baseline or post exercise test. All responded within 3-5 days to theophylline (15-20 mg/kg/day), 12 children reported improvement in exercise tolerance.11 coughed again within 6 mo off theophylline	In period off theophylline, 2 wheezed

de Benedictis, <sup>26</sup> 1986 Canada	Single center, resp lab, retrospective review of notes	MCH test done, >6 wk cough, normal physical exam, available FU data. Excl: Hx of wheeze, dyspnea, BD use, URTI in last 6 wk	Spirometry, MCH, blood gas, lung volumes AHR+ =20% fall in FEV <sub>1</sub> during test (max MHC 25mg/ml)	58, mean=11 yrs range 7-16 yrs	Increased RV/TLC in 11, low PaO <sub>2</sub> in 6, AHR+ n=31 (53%). AHR+ and AHR- similar in age, cough duration, personal or family Hx of atopy	27 of the 31 (87.1%) AHR+ cough responded rapidly (undefined) to 4 week trial of oral or inhaled SABA or theophylline, 4 no response; 9 of 17 (52.9%) AHR- also cough free after Rx above	Some incongruity between symptoms/signs and tests
Turkas, <sup>30</sup> 2002 Turkey	Single center, Allergy and asthma OPD, Prospective	Chronic cough +/- episodic wheeze and dyspnea >4 wk Excl: NR	Spirometry with SABA, MCH, AHR+ =PD <sub>20</sub> <8mg/ml	133 (81 with cough only), mean=10.1 yr, SD 2.2	AHR+ n=80, Cough only group had lower probability of being AHR+ (OR 0.7, 95%CI 0.3, 1.9)	Study described clinical response only in those with extra- thoracic AHR (EAHR)	EAHR non- standard and study included children with wheeze

AHR+=positive airway hyper-responsiveness, BD=bronchodilator, Dx=diagnosis, Excl=exclusion criteria, FU=follow-up; Hx=history  
MCH=methacholine challenge, mo=months, NR=not reported, OPD=outpatients department, Resp=Respiratory, SABA=short acting beta<sub>2</sub>  
agonist, yr=year

**e-Figure 5**

Selection of studies that addresses key question 5 – In the evaluation of children with chronic (>4 weeks) cough clinical practice, what is the role of pulmonary function studies and bronchial provocation?



\*Searchers were undertaken by Nancy Harger, MLS and Judy Nordberg, MLS, Education and Clinical Services Librarians working in the University of Massachusetts Medical School Library in Worcester, MA

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