CLINICALLY DIAGNOSING PERTUSSIS-ASSOCIATED COUGH IN ADULTS AND CHILDREN: CHEST GUIDELINE AND EXPERT PANEL REPORT

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ABSTRACT:

Background: The decision to treat a suspected case of pertussis with antibiotics is usually based on a clinical diagnosis rather than waiting for laboratory confirmation. The current guideline focuses on making the clinical diagnosis of pertussis-associated cough in adults and children.

Methods: The American College of Chest Physicians (CHEST) methodologic guidelines and the Grading of Recommendations, Assessment, Development, and Evaluation framework were used. The Expert Cough Panel based their recommendations on findings from a systematic review that was recently published on the topic; final grading was reached by consensus according to Delphi methodology. The systematic review was carried out to answer the Key Clinical Question: *In patients presenting with cough, how can we most accurately diagnose from clinical features alone those who have pertussis-associated cough as opposed to other causes of cough?*

Results: In adults, after pre-specified meta-analysis exclusions, pooled estimates of sensitivity and specificity were generated for only four clinical features: paroxysmal cough, post-tussive vomiting, inspiratory whoop and absence of fever. Both paroxysmal cough and absence of fever had high sensitivity (93.2% [CI, 83.2-97.4] and 81.8% [CI, 72.2-88.7], respectively) and low specificity (20.6% [CI, 14.7-28.1] and 18.8% [CI, 8.1-37.9]). Inspiratory whoop and post-tussive vomiting had a low sensitivity (32.5% [CI, 24.5-41.6] and 29.8% [CI, 8.0-45.2]) but high specificity (77.7% [CI, 73.1-81.7] and 79.5% [CI, 69.4-86.9]). In children, after pre-specified meta-analysis exclusions, pooled estimates of sensitivity and specificity were generated for only one clinical feature in children (0-18 years); post-tussive vomiting. Post-tussive vomiting in children was only moderately sensitive (60.0% [CI, 40.3-77.0]) and specific (66.0% [CI, 52.5-77.3]).

Conclusions: In adults with acute (< 3 weeks) or subacute (3-8 weeks) cough, the presence of whooping or posttussive vomiting should rule in a possible diagnosis of pertussis, whereas the lack of a paroxysmal cough or the presence of fever should rule it out. In children with acute (< 4 weeks) cough, posttussive vomiting is suggestive of pertussis but is much less helpful as a clinical diagnostic test. Guideline suggestions are made based upon these findings and conclusions.

ABBREVIATIONS:

CDC = Centers for Disease Control

PCR = polymerase chain reaction

PHE = Public Health England

PIRT = population, index test, reference test, target condition

WHO = World Health Organization

SUMMARY OF RECOMMENDATIONS:

1. For adult patients complaining of acute cough (< 3 weeks in duration) or subacute cough (3-8 weeks), we suggest that clinicians should specifically assess for the 4 key characteristics of paroxysmal cough, post-tussive vomiting, inspiratory whooping, and absence of fever in ruling in or out a clinical diagnosis of pertussis. (Grade 2C)

Remark: Paroxysmal cough is defined as recurrent prolonged coughing episodes (i.e., an expiratory phase with multiple burst of outflow) with an inability to breathe during spells. Post-tussive vomiting is defined as vomiting induced by coughing. Inspiratory whooping is defined as a continuous inspiratory airway sound with a whooping quality to it. Fever is defined as any body temperature above the normal of 98.6 º F (37 º C).

2. For adult patients complaining of acute or sub-acute cough, we suggest that clinicians consider that the cough is unlikely to be due to pertussis if the patient has a fever or the cough is not paroxysmal in nature. (Grade 2C)

3. For adult patients complaining of acute or subacute cough, we suggest that clinicians consider that the cough is likely to be caused by pertussis if there is post-tussive vomiting or is associated with an inspiratory whooping sound. (Grade 2C)

4. For children complaining of acute cough (< 4 weeks duration), we suggest that clinicians should specifically assess for the 3 classical characteristics of paroxysmal cough, post-tussive vomiting, inspiratory whooping. (Ungraded consensus-based statement)

5. For children complaining of acute cough, we suggest that clinicians consider that the cough could be caused by pertussis if there is post-tussive vomiting. (Grade 2C)

6. For children complaining of acute cough, we suggest that clinicians consider that the cough could be caused by pertussis if there is paroxysmal cough or inspiratory whooping. (Ungraded consensus-based statement)

INTRODUCTION:

Pertussis (whooping cough), caused by *Bordetella pertussis,* is a highly contagious respiratory tract infection that can be associated with significant morbidity and mortality, particularly in young infants.

Pertussis causes an acute cough that can often become persistent and is classically associated with paroxysms of coughing, inspiratory whooping and post-tussive vomiting. However, clinical judgement also plays an important role in diagnosis. This is reflected in the clinical definitions used by the World Health Organization[1], Centers for Disease Control (CDC)[2] and Public Health England (PHE)[3] (Table 1).

There are several recognized laboratory methods to confirm a diagnosis of pertussis; culture (100% specific), polymerase chain reaction (PCR) (88-100% specific), serology (72-100% specific)[4,5] and oral fluid testing (91-99% specific)[6]. These are used variously by the different health organizations (Table 2)[1-3].

The treatment of pertussis has been the subject of a recent Cochrane systematic review[7]. There are several effective antibiotics; these eliminate B. pertussis but do not alter the clinical course of the illness. However, treatment should be initiated as soon as possible after onset of illness to prevent spread of the disease.[3] The decision to treat with antibiotics is therefore frequently based on a clinical diagnosis rather than waiting for laboratory confirmation.

Because reviews of laboratory diagnosis and treatment have recently been published[7] and diagnosis is usually made clinically, the current guideline focuses on making the clinical diagnosis of pertussis-associated cough in adults and children.

MATERIALS AND METHODS:

The methodology of the CHEST Guideline Oversight Committee[8,9] was used to select the Expert Cough Panel Chair and the international panel of experts to synthesize the evidence and to develop the recommendations and suggestions that are contained within this article. In addition to the quality of the evidence, the recommendation/suggestion grading also includes a strength of recommendation dimension, used for all CHEST Guidelines[8,9]. In the context of practice recommendations, a grade 1 recommendation is a strong recommendation and applies to almost all patients whereas a grade 2 recommendation is weak and conditional and only applies to some patients. The strength of recommendation here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Harms incorporate risks and burdens to the patients that can include convenience or lack of convenience, difficulty of administration, and invasiveness. These, in turn, impact patient preferences. The resource considerations go beyond economics and should also factor in time and other indirect costs. The authors of these recommendations

or suggestions have considered these parameters in determining the strength of the recommendations or suggestions and associated grades.

The findings of a systematic review and meta-analysis that was carried out to be the basis of this guideline and has recently been published[10] were used to support the evidence graded recommendations or suggestions. The first, second, and third authors of this current guideline article were among the authors of the systematic review and meta-analysis. The process of review of previous studies identified in the systematic review included assessment using the QUADAS-2 tool in the domains of patient selection, index tests, reference standard, and flow and timing.[11] When the quality of studies included in the systematic review[10] were checked using the DART tool[12], similar quality results were found. A highly structured consensus-based Delphi approach was employed to provide expert advice on all guidance statements. The total number of eligible voters for each guidance statement did not vary because none were recused from voting on any particular statements because of any potential conflicts of interest. A lay person representing the interests of patients participated in the process and voting. Transparency of process was documented. Further details of the methods related to conflicts of interests and transparency for all CHEST guidelines have been published elsewhere [8,9].

Based on the systematic review and meta-analysis[10] and the Delphi methodology described, the writing group developed guideline recommendations or suggestions. These then underwent review and consensus agreement through an online anonymous voting survey by the full cough panel. For a recommendation or suggestion to be accepted, it had to be voted upon by 75% of the eligible Cough Panelists and achieve ratings of strongly agree or agree by 80% of the voting panelists. Agreement was achieved by 87.24 to 95.75% of those voting on the current recommendations or suggestions. No panelist was excluded from voting.

Because a paroxysmal cough figures heavily in making a clinical diagnosis of a pertussis-associated cough, we have defined it as recurrent prolonged coughing episodes (i.e., an expiratory phase with multiple burst of outflow) with an inability to breathe during spells.

RESULTS:

The recommendations that follow are based upon the recently published high quality systematic review[10] that included a comprehensive search of multiple databases restricted to the English language. The systematic review followed all the standards of the National Academy of Medicine (previously referred to as the Institute of Medicine)[13]. After generating the key clinical question for the systematic review, population, index test, reference test, target condition (PIRT) elements were derived to inform the literature review (Table 3).[10] The authors of the review systematically searched the following databases:

CINAHL (EBSCHost from 1982 to 2016, Embase (OvidSP from 1974 to 2016, Medline & Medline In-Process (OvidSP from 1946 to 2016, and SCI-EXPANDED/CPCI-S (Web of Science Core Collection from 1945 to 2016. The search strategy combined MeSH headings with free text search terms for whooping cough and clinical symptoms. The search was supplemented by review of reference lists of included articles and relevant review articles as well as by contacting authors of studies to request additional relevant data where it was apparent that it was likely to have been collected but not published. The full search strategy can be found in e-Appendix 1 of the systematic review.[10]

After the initial screening of articles, full text review, data extraction and quality assessment, 53 articles were identified for descriptive analysis and meta-analysis[10]. These articles included 23,796 subjects, of whom 4,149 (17.4%) had a laboratory diagnosis of pertussis. Thirty-six of the 53 articles had a prospective design, 12 were retrospective, and 5 were case-control. From these 53 studies, 41 clinical characteristics (i.e., index tests) were assessed for diagnostic accuracy including 9 cough characteristics as well as other clinical and demographic features (Table 4).[10] After excluding from the meta-analysis studies at high risk of bias (28 studies), pooled estimates of sensitivity and specificity were generated by meta-analysis (Table 5).[10]

Evidence and Recommendations.

Key clinical question: In patients presenting with cough, how can we most accurately diagnose from clinical features alone those who have pertussis-associated cough as opposed to other causes of cough?

Summary of the Evidence in Adults and Interpretation: After pre-specified meta-analysis exclusions, pooled estimates of sensitivity and specificity were generated for only 4 clinical features in adult patients: paroxysmal cough, post-tussive vomiting, inspiratory whoop and absence of fever. Both paroxysmal cough and absence of fever had high sensitivity and low specificity (Table 5, e-Table 2).[10] This means that a patient without these features is unlikely to have a diagnosis of pertussis (few false negatives). Inspiratory whoop and post-tussive vomiting had a low sensitivity but high specificity (Table 5, e-Table 2).[10] This means that a diagnosis of pertussis should be considered in a patient with these features (few false positives).

1. For adult patients complaining of acute cough (< 3 weeks in duration) or subacute cough (3-8 weeks), we suggest that clinicians should specifically assess for the 4 key characteristics of paroxysmal cough, post-tussive vomiting, inspiratory whooping, and absence of fever in ruling in or out a clinical diagnosis of pertussis. (Grade 2C)

Remark: Paroxysmal cough is defined as recurrent prolonged coughing episodes (i.e., an expiratory phase with multiple burst of outflow) with an inability to breathe during spells. Post-tussive vomiting is defined as vomiting induced by coughing. Inspiratory whooping is defined as a continuous inspiratory airway sound with a whooping quality to it. Fever is defined as any body temperature above the normal of 98.6 º F (37 º C).

2. For adult patients complaining of acute or sub-acute cough, we suggest that clinicians consider that the cough is unlikely to be due to pertussis if the patient has a fever or the cough is not paroxysmal in nature. (Grade 2C)

3. For adult patients complaining of acute or subacute cough, we suggest that clinicians consider that the cough is likely to be caused by pertussis if there is post-tussive vomiting or is associated with an inspiratory whooping sound. (Grade 2C)

Summary of the Evidence in Children and Interpretation: After pre-specified meta-analysis exclusions, pooled estimates of sensitivity and specificity were generated for only one clinical feature in children: post-tussive vomiting. Post-tussive vomiting in children (ages 0 - 18) was only moderately sensitive and specific (Table 5, e-Table 2).[10]

4. For children complaining of acute cough (< 4 weeks in duration), we suggest that clinicians should specifically assess for the 3 classical characteristics of paroxysmal cough, post-tussive vomiting, inspiratory whooping. (Ungraded consensus-based statement)

5. For children complaining of acute cough, we suggest that clinicians consider that the cough could be caused by pertussis if there is post-tussive vomiting. (Grade 2C)

6. For children complaining of acute cough, we suggest that clinicians consider that the cough could be caused by pertussis if there is paroxysmal cough or inspiratory whooping. (Ungraded consensus-based statement)

DISCUSSION:

The systematic review used to form the basis of this guideline is the largest on this topic to date. The broad inclusion criteria were designed to capture the full spectrum of pertussis presentation, but meant that there was significant variation in included study characteristics – including different study designs (case-control and retrospective/prospective cohort), those in specialist populations (e.g., outbreaks) and used different reference standards. While the systematic review was done according to rigorous methods, it did have limitations. For example, while assessment of quality meant that those at resultant high risk of bias were excluded from meta-analysis, heterogeneity in the remaining studies meant that only 4 characteristics could be analyzed in this way. Because the review excluded non-English studies, potentially relevant studies may have been missed. In addition, the systematic review was published in 2017 and it was based upon a literature search that was last updated in June of 2016, and studies published since this time have not been taken into account. Although data were analyzed separately for adults and children, it is important to note that the "children" category includes studies with both older children (up to 18) and young infants who may also have very different presentations of pertussis.

A second systematic review has been written on this topic within the last year.[14] Compared to the systematic review used to compile this guideline, Ebell et al used a more restrictive search strategy in Medline only and included only prospective cohort studies. Eight unique references were included compared to the systematic review used for this guideline. However, these references were excluded from our systematic review for the following reasons: 4 had no comparison group, 2 compared pertussis to parapertussis, 1 had no clinical information and 1 was not in English. In Ebell et al, meta-analysis was done for all index tests with no comment on heterogeneity, and index tests were only analyzed separately in adults and children for paroxysmal cough, whooping cough and post-tussive vomiting. For these reasons, it was felt that the findings of Ebell, et al should not be taken into account in compiling this guideline.

The existing clinical criteria in use by multiple health agencies (Table 1)[1-3], contain the index tests shown in the meta-analysis to be useful in the diagnosis of pertussis and recommended/suggested by this guideline. The presence of whooping or posttussive vomiting is common to the CDC, PHE, and WHO clinical criteria, whereas paroxysms of coughing is included by just the CDC and WHO. Apnea and cyanosis are mentioned in relation to infants aged < 1 year in the CDC criteria and were shown in forest plots in the systematic review (e-Appendix 2)[10] to be moderately sensitive and specific in children.

AREAS FOR FUTURE RESEARCH:

To advance the field, a number of research endeavors to address the gaps in knowledge should be undertaken. These include conducting further large prospective studies in primary care of patients presenting with acute or subacute cough – particularly in infants and children. To improve on the problems in study design identified by the systematic review, the following would be needed: detailed

epidemiological/baseline characteristics of included patients, time since symptom onset recorded rather than acting as inclusion criteria, clear definitions of clinical characteristics recorded, characteristics recorded at presentation and ideally subsequently in a symptom diary. It would also be helpful to assess clinical judgement as part of this. Individual patient analysis would help assess the diagnostic utility of different symptoms in combination.

CONCLUSIONS:

Cough due to pertussis in adults and children has been the sole focus in this update, compared with one of many causes of postinfectious cough in the 2006 CHEST Cough Guidelines.[15] This guideline focuses on how to make the clinical diagnosis of pertussis because this is how the decision to treat with antibiotics is usually made. This guideline is based upon a high quality systematic review and it identifies gaps in our knowledge and areas for future research; we therefore believe it advances the field.

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Author contributions. AM, AH, and CCG were the authors of the original systematic review and meta-analysis upon which this guideline is based. AM, AH, CCG, SP, and RSI were part of the writing group that developed the key clinical question, wrote and reviewed the manuscript, and take responsibility for the accuracy of the information contained within.

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Table 1. Clinical case criteria:

	Clinical judgement	Cough > 2 weeks	Inspiratory whooping	Post-tussive vomiting	Paroxysms of coughing	Apnoea	Epidemiological contact
WHO[1]	A case diagnosed as pertussis by a physician OR	A person with a cough lasting at least two weeks with at least one of the following symptoms:	Inspiratory whooping OR	Post-tussive vomiting (i.e. vomiting immediately after coughing) without other apparent cause	Paroxysms (i.e. fits) of coughing		
CDC[2]	In the absence of a more likely diagnosis	A cough illness lasting ≥2 weeks with one of the following symptoms:	Inspiratory whooping OR	Post-tussive vomiting OR	Paroxysms of coughing	Apnoea (with or without cyanosis) for infants <1 year only	
PHE[3]	Without an apparent cause	Acute cough lasting for 14 days or more plus one or more of the following:	Inspiratory whooping OR	Post-tussive vomiting OR	Paroxysms of coughing	Undiagnosed apnoeic attacks in young infants OR	Someone with signs and symptoms consistent with pertussis who has been in contact with a confirmed case in the previous 21 days OR someone who is known to be part of any ongoing outbreak investigation in a specific group of people

Table 2. Recognized laboratory methods to confirm a case.

	Culture	Polymerase chain reaction	Serology	Oral fluid testing for anti-pertussis toxin IgG
WHO[1]	X	X	X	
CDC[2]	X	X		
PHE[3]	X	X	X	X

Table 3. Population, index test, reference test, target condition (PIRT) elements derived to inform the literature review.[10]

Population	Index Test	Reference Test	Target Condition
People of any age, gender, ethnicity and nationality attending either primary or secondary care settings with cough	Any presenting clinical characteristic of pertussis-associated cough	Laboratory diagnostic tests for pertussis, including culture, PCR and serology	B. pertussis

Table 4. Index tests[10]

Clinical characteristics, examination findings and patient demographics, and number of studies in which these were recorded

	Index test	Number of studies
Cough characteristic	Paroxysmal cough	36
	Post-tussive vomiting	36
	Whooping cough	28
	Worse at night	16
	Productive cough	12
	Wheeze	12
	Any cough	7
	Cough duration	6
	Stridor	3
Other respiratory symptoms/findings	Apnoea	21
	Cyanosis	16
	Rhinorrhoea	10
	Shortness of breath	9
	URTI symptoms	6
	Respiratory distress/hypoxia	5
	Chest crackles	5
	Sore throat	5
	Sneezing	4
	Sinus pain	3

	Hoarseness	2
	Post-tussive gagging	2
Other clinical features	Fever	28
	Headache	5
	Chest pain	5
	Feeding difficulties	4
	Lymphocytosis	4
	Facial discoloration	3
	Myalgia	3
	Conjunctival changes	3
	White blood cell count	3
	Fatigue	2
	Sweating	2
	Seizure	2
	Post-tussive syncope	2
Clinical judgement	Meets CDC/WHO clinical definition	8
	Clinical suspicion	2
Patient demographics	Vaccinated	19
	Exposure to contact	16
	Co-morbidity	6
	Smoking	5
	Previous whooping cough	4

359
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361

Table 5. Meta-analysis[10]

Pooled estimates of sensitivity and specificity

Clinical feature on which meta- analysis performed	Age category	Number of studies	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Paroxysmal cough[16-22]	Adults	7	93.2 (83.2-97.4)	20.6 (14.7-28.1)	1.17 (1.10-1.25)	0.33 (0.15-0.71)
Post-tussive vomiting[16-23]	Adults	8	32.5 (24.5-41.6)	77.7 (73.1-81.7)	1.45 (1.19-1.79)	0.87 (0.79-0.96)
Inspiratory whoop[16-21,24]	Adults	7	29.8 (18.0-45.2)	79.5 (69.4-86.9)	1.46 (1.07-1.97)	0.88 (0.77-1.00)
Absence of fever[16-18,22,25]	Adults	5	81.8 (72.2-88.7)	18.8 (8.1-37.9)	1.01 (0.86-1.18)	0.97 (0.49-1.90)
Post-tussive vomiting[26-31]	Children	6	60.0 (40.3-77.0)	66.0 (52.5-77.3)	1.76 (1.26-2.48)	0.61 (0.40-0.91)

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