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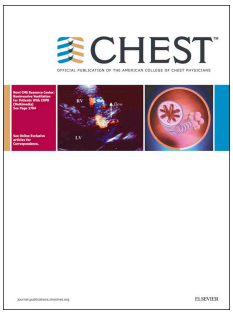

Clinical characteristics of pertussis-associated cough in adults and children: a diagnostic systematic review and meta-analysis

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Abigail Moore takes responsibility for the content of the manuscript, including the data and analysis.

Author contributions:
All authors contributed substantially to the study design, data interpretation, and the writing of the manuscript.
NR designed the search strategy and ran and updated the searches.
AM and HFA screened the abstracts, completed full text reviews, data extraction and assessments of quality and bias. AH acted as an independent adjudicator for any discrepancies in this process.
BS completed the statistical analysis.

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Abstract

Background

Pertussis (whooping cough) is a highly infective cause of cough that causes significant morbidity and mortality. Existing case definitions include paroxysmal cough, whooping and post-tussive vomiting but diagnosis can be difficult. We determined the diagnostic accuracy of clinical characteristics of pertussis-associated cough.

Methods

We systematically searched CINAHL, Embase, Medline and SCI-EXPANDED/CPCI-S up to June 2016. Eligible studies compared clinical characteristics in those positive and negative for *Bordetella pertussis* infection, confirmed by laboratory investigations. Two authors independently completed screening, data extraction and quality and bias assessments. For each characteristic RevMan was used to produce descriptive forest plots. We used the bivariate meta-analysis method to generate pooled estimates of sensitivity and specificity.

Results

Of 1969 identified papers, 53 were included. Forty-one clinical characteristics were assessed for diagnostic accuracy. In adult patients, paroxysmal cough and absence of fever had a 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 respectively), whereas post-tussive vomiting and whooping had low sensitivity (32.5%, CI 24.5-41.6 and 29.8%, CI 8.0-45.2 respectively) and high specificity (77.7%, CI 73.1-81.7 and 79.5%, CI 69.4-86.9 respectively). Post-tussive vomiting in children is moderately sensitive (60.0%, CI 40.3-77.0) and specific 66.0%, CI 52.5-77.3).

Conclusions

In adult patients the presence of whooping or post-tussive 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, post-tussive vomiting is much less helpful as a clinical diagnostic test.

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Introduction

Pertussis (whooping cough), caused by *Bordetella pertussis* infection, is a prevalent cause of acute cough that can often become persistent in both children and adults presenting to primary care and other health care settings.[1,2] Pertussis remains an important cause of child mortality, with an estimated 195,000 deaths reported globally in 2008.[3] In older age groups pertussis causes significant morbidity and generates substantial costs and work absence.[4] Neither natural infection nor immunisation result in life-long immunity.[5]

The symptom triad of paroxysmal cough, whooping and post-tussive vomiting are classically considered essential clinical characteristics, and the Center for Disease Control (CDC) and World Health Organization (WHO) clinical case definitions reflect this.[6,7] However, in clinical practice pertussis-associated cough can occur anywhere along a clinical severity spectrum from minor cough to repeated severe paroxysms.[8,9] Previous immunisation or infection can attenuate the symptoms, especially cough, that occur with a subsequent *B. pertussis* infection.[10] The disease frequently also presents atypically in young infants.[11,12]

Laboratory confirmation of *B. pertussis* infection can be performed using culture (100% specific), polymerase chain reaction (PCR) (88-100% specific), or serology (72-100% specific).[13,14] However, a practising clinician who needs to make an urgent patient management decision frequently has to do this without laboratory data. Identifying pertussis as the cause of a clinical presentation of cough illness is important because of the high infectivity of *B. pertussis*,[8] its significant morbidity and the potential for complications and death, particularly in young infants.[15] Offering a secure clinical diagnosis also helps prevent unnecessary investigations, inappropriate antibiotics and offers patients a more accurate cough prognosis. Early recognition and treatment may also prevent spread of the disease.

Although the diagnostic accuracy for pertussis of different symptoms and signs has been tested in multiple clinical studies, they have not previously been combined in a comprehensive systematic review. A better understanding of the clinical characteristics of pertussis-associated cough, and other clinical features could help clinicians differentiate pertussis cough from other causes of cough.

We therefore aimed to conduct a systematic review and meta-analysis to determine the diagnostic accuracy of clinical characteristics of pertussis-associated cough.

Materials and methods

Study selection and data extraction

A diagnostic test accuracy protocol was developed using the relevant Cochrane handbook[16] but not formally registered (available on request). We considered as eligible studies which included patients of any age attending any health care setting, including pertussis outbreaks, with any clinical characteristic (index test) which might be associated with pertussis, compared to laboratory confirmation of *B. pertussis* (reference standard). We included all studies with sufficient published or unpublished data to construct 2x2 tables for each clinical characteristic(s). Studies were excluded if pertussis diagnosis was not confirmed with recognised laboratory methods (culture, PCR or serology) or there was no suitable comparison group. Studies looking at *B. parapertussis* only were also excluded. By design our inclusion criteria were broad in order to capture the full spectrum of pertussis presentation.

We systematically searched databases CINAHL(EBSCOHost, 1982-present], Embase (OvidSP, 1974-2016 June 02), Medline & Medline In-Process (OvidSP, 1946-present) and SCI-EXPANDED/CPCI-S(Web of Science Core Collection, 1945-present) from inception to November 2014, and this was then updated in June 2016. The search strategy combined MeSH headings with free text search terms for whooping cough and clinical symptoms. English language restrictions were applied. Results were supplemented by review of reference lists of included articles and relevant review articles. e-Appendix 1 gives the full search strategy used for CINAHL as an example.

Titles and abstracts were screened to exclude any obviously irrelevant articles. Full texts of potentially relevant articles were then assessed for eligibility. All steps were completed in tandem by two authors (HFA and AM), with any discrepancies discussed and, if necessary, resolved by adjudication with a third author (AH). We contacted authors of studies to request additional data relevant to this review where it was apparent that it was likely to have been collected but not published. Authors were contacted by email, with a reminder sent at 2 weeks and 4 weeks if no response. We developed and piloted a standardised data extraction form, which was revised until it captured all relevant information. This data extraction form was sent to facilitate return of data in a useable format.

Data extraction and risk of bias assessment were subsequently carried out in duplicate and independently by HFA and AM. Risk of bias was assessed using the QUADAS-2 tool in the domains of patient selection, index tests, reference standard and flow and timing.[17] Completed data extraction forms were compared and any discrepancies checked and resolved. We extracted information on study characteristics, design, details of the reference test used for pertussis detection, the characteristics of included patients and information on

missing data. For each clinical characteristic described, data for a 2x2 table were extracted or calculated from the data presented. Data were entered into a Microsoft Excel spreadsheet by one author (AM) and checked by a second (HFA). Terms used to describe clinical characteristics varied slightly across studies. Similar characteristics were grouped together using clinical judgement by one author (HFA) and checked by a second (AM).

Statistical analysis

Statistical analysis was completed by BS. Binary diagnostic accuracy data were extracted from all included studies as 2x2 tables. For each clinical characteristic, RevMan was used to produce descriptive forest plots to explore the between-study variability in sensitivity and specificity across the included studies. ROC plots were produced, sub-grouped by age of included participants (children, adults or both). The size of each study point is scaled to be proportional to the inverse standard error of the study sensitivity and specificity.

Where sufficient data were available (minimum of four studies), we used the bivariate meta-analysis method to generate pooled estimates of sensitivity and specificity, along with 95% confidence and prediction regions. Results were only pooled within each age-range of patient, categorised as either children or adults. Studies with both adults and children were not included as the presentation of the disease in the age groups are not the same.[11] Due to high heterogeneity, we excluded from meta-analyses studies at high risk of bias on any of the four QUADAS-2 domains, which was a pre-specified sensitivity analysis. In cases where notable heterogeneity remained, meta-analysis was deemed inappropriate.

We planned additional sub-group analyses to explore other possible causes of heterogeneity (co-morbidity, immunisation status, setting) however there were insufficient study data available. We had also planned to adjust for possible sources of heterogeneity by adding them as covariates to the bivariate model. However, we could not do the meta-regression as we did not have enough studies to warrant the addition of variables. Assessment of reporting bias was not included in this review, as funnel plots have been shown to be misleading for reviews of diagnostic test accuracy.[18,19]

Results

Figure 1 shows the flowchart of study selection. We identified 1969 unique papers, of which 422 had a full text review. Forty-seven studies met inclusion criteria for this review and contained sufficient data in the published article for complete data extraction. Fourteen further papers were identified with potential unpublished data. The authors of these papers were contacted, of which 6 provided the necessary information. Overall 53 papers were included in descriptive analysis and meta-analysis (where possible).

Table 1[20-72] summarises characteristics of included studies. The 53 studies included 23796 participants, of whom 4149 (17.4%) had a laboratory diagnosis of pertussis. The proportion of study cohorts with laboratory-confirmed pertussis ranged from 0.3-72.5% (mean 24.7%). Thirty-seven studies had a prospective design, 12 were retrospective and 4 were case-control. Inclusion criteria and reference standard varied widely across studies. Ten studies took place during a pertussis outbreak but the majority of papers did not report this. Those with at least one vaccination dose (recorded in 36 studies) ranged from 0 to 100% (mean 54.3%).

Risk of bias assessment with QUADAS-2 is summarised in Figure 2. Nineteen studies had low risk of bias/low applicability concerns throughout all 7 domains. Twenty-two studies were assessed at high risk of bias in at least one of the 4 domains.

Across the 53 included studies, 41 index tests were assessed for diagnostic accuracy, including 9 cough characteristics as well as other clinical and demographic features (Table 2). Forest plots were generated for each index test, which demonstrate the heterogeneity between studies. These are presented in e-Appendix 2.

After pre-specified meta-analysis exclusions (see methods), pooled estimates of sensitivity and specificity were generated (Table 3). Meta-analysis is not presented for immunisation due to wide heterogeneity in immunisations at different ages and different countries. Figure 3 shows Receiver Operating Characteristic (ROC) plots of the meta-analyses.

Discussion

Summary of evidence

Our meta-analysis demonstrates four key characteristics that are important in ruling in or out a clinical diagnosis of pertussis: paroxysmal cough, post-tussive vomiting, inspiratory whoop and absence of fever.

We found paroxysmal cough and absence of fever in adults have high sensitivity and low specificity. The clinical implication is that if an adult patient does not have paroxysmal cough, or does have a fever they are very unlikely to have pertussis - good ‘rule out’ tests.

Both post-tussive vomiting and whooping in adults have a low sensitivity and high specificity. The clinical implication is that if an adult patient has post-tussive vomiting or whooping, it raises suspicion of pertussis as a differential diagnosis – making both these good ‘rule in’ tests. Post-tussive vomiting in children, however, is only moderately sensitive and specific. This makes it much less helpful as a clinical diagnostic test than in adults.

The forest plots and summary ROC plots demonstrate large statistical heterogeneity within the data synthesised across the other index tests and interpretation of these data should be approached with caution. Index tests with a trend suggesting better sensitivity for diagnosis of pertussis include cough worse at night (sensitive but not specific in adults) and apnoea and cyanosis (moderately sensitive and specific in children). Lymphocytosis may be a relatively sensitive marker for pertussis infection in children, but only 3 studies assessed this and all used different thresholds.[58,62,72] This finding would fit with what is already known about the effect of pertussis toxin in increasing the number of circulating white blood cells in infants with whooping cough.[73]

Comparison with existing literature

There are a number of different clinical case definitions currently in use globally including those created by the United States Centers for Disease Control,[6] Public Health England (PHE) [74] and World Health Organization.[7] In common across all three sets of criteria is the cough lasting at least 14 days - an inclusion criterion of some of studies included in this review.[27,33,38,41-43,51,56,59,69,71] Unfortunately, cough or symptom duration was used as an index test by some included studies, but often without indicating whether this was at presentation or overall. It could not be evaluated diagnostically. The presence of whooping or post-tussive vomiting is also common to the CDC, PHE and WHO clinical criteria, whilst paroxysms of coughing is included by CDC and WHO. This classical triad of symptoms are the index tests that our meta-analysis has shown should raise clinical suspicion of pertussis.

A person suspected by a physician of having pertussis is included in its own right as a criterion in the PHE and WHO criteria. This formed part of the inclusion criteria of a number of studies in this review,[29,35,54] but was only used as an index test in 3 studies,[35,39,44] which may explain the wide-ranging prevalence found across studies.

Apnoea and cyanosis are mentioned in relation to infants aged < 1 year in the CDC criteria, and are shown in our Forest plots (e-Appendix 2) to be moderately sensitive and specific in children.

There is one previous diagnostic accuracy systematic review of these classically described symptoms of pertussis (paroxysmal cough, post-tussive vomiting, and inspiratory whoop).[75] This was completed in 2010 and included three studies with patients over 5 years of age in a non-outbreak setting.[38,49,63] Like our meta-analysis, it showed that paroxysmal cough has low specificity in older patients, and that the presence of whooping and post-tussive vomiting modestly increased the likelihood of pertussis. However, given all three symptoms had only relatively modest positive likelihood ratios between 1.1-1.9 the authors concluded that presence of these symptoms were of limited value in differentiating a pertussis diagnosis from other respiratory illnesses, and that overall clinical judgement was important. Our systematic

review extends this smaller study, by having broader inclusion criteria and considering other clinical symptoms as index tests.

Strengths and limitations

The broad eligibility criteria for this systematic review meant that we collected data from over fifty studies and were therefore able to include information on a large numbers of patients, making this the largest systematic review on this topic to date. However, this has also meant that there is a wide variation in study characteristics, which is likely to have contributed to the heterogeneity of our results.

A number of included studies were classed as high risk of bias for patient selection and were therefore not included in meta-analysis. Some listed features of pertussis as part of their inclusion criteria[26,30,31,53,58,60,63,70] whilst others specifically recruited patients with suspected pertussis[29,35,54] or included all patients who had had a laboratory test for pertussis.[32,37,44,64,68,72]

Misclassification bias is likely to have been influential at both the study and review level as very few papers described the clinical features being assessed. There was also a lack of clarity in some papers as to whether a feature described was from the patient history or examination (e.g. fever). This is likely to have caused inconsistency in study data collection as well as synthesis of data in the systematic review – particularly when grouping similar characteristics together.

Use of single or a combination of reference standards also varied across studies. However, methods for all reference standards were compared to the CDC guidelines,[13] and lack of transparency or deviation from these was reflected in the corresponding domain in the risk of bias assessment. In addition, many papers lacked details in the reporting of design setting (including whether or not there was an outbreak), and patient demographic (age, sex and immunisation status). It was therefore not possible to assess pre-test probability of pertussis is these studies.

For the purposes of systematic review we separated studies looking at adults and children, and excluded those that included patients of all ages. This is because it has been recognised that pertussis in adults and children does not present in the same way. However, an additional limitation is that our 'children' category includes studies with both older children and young infants who may also have very different presentations of pertussis.

Conclusions

There is substantial statistical heterogeneity between all included studies, which reflects heterogeneity in study designs used. As a result, meta-analysis was only possible of a limited number of clinical characteristics – predominantly in adult patients. The results of the meta-

analysis showed that recognising the classical triad of symptoms in adults remains helpful for clinicians. In adult patients the presence of whooping or post-tussive 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, however, presence of post-tussive vomiting is much less helpful as a clinical diagnostic test and pooled estimates of sensitivity and specificity for other characteristics could not be calculated.

Further high quality research is needed to better understand which clinical characteristics can differentiate pertussis associated cough from other causes of cough. Particular consideration should be taken as to the entry criteria/patient population most likely to produce data that can be clinically useful. In addition, clear descriptions of clinical characteristics under testing are important to ensure consistent interpretation and reporting. Future research is likely to involve large prospective studies in primary care, as well as individual patient data analysis to assess the diagnostic utility of different symptoms in combination with the possibility of creating a scoring system to identify patients for definitive testing.

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Figure legends

Figure 1.

Flow of the citations reviewed in the course of this systematic review.

Figure 2.

Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

Figure 3.

Summary Receiver Operating Characteristic plots depicting meta-analysis of various clinical characteristics in adults and children. The summary point represents the summary sensitivity and specificity, the 95% confidence region represents the 95% confidence intervals of the summary sensitivity and specificity and the 95% prediction region represents the 95% confidence interval of sensitivity and specificity of each individual study included in the analysis. Individual study estimates are also plotted indicating individual sensitivity and specificity with the size of the marker scaled according to the total number in each study.

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Table 1. Characteristics of 53 included studies

Overview of all included studies. For more detailed characteristics, see e-Table 1

Study	Country (ies)	Setting	Inclusion criteria	Study type	Laboratory test				Total number of participants	Age category	Number (%) laboratory confirmed pertussis
					Culture	Serology	PCR	DFA			
Abu Raya et al[5]	Israel	Secondary care	<= 4 days of clinically diagnosed acute bronchiolitis	Case control		□	✖		120	Children	23 (19.17)
Bellettini et al[6]	Brazil	Multiple settings	Any patient tested for pertussis during study period	Retrospective			✖		222	Children	161 (72.52)
Bock et al[7]	USA	Multiple settings	Chronic cough (>8 weeks)	Retrospective		✖			48	Adults	19 (39.58)
Bonhoeffer et al[8]	Switzerland	Multiple settings	Acute exacerbation of chronic bronchitis	Prospective	✖	✖	✖		26	Adults	8 (30.77)
Cagney et al[9]	Australia	Vaccine trial cohort	Participants of vaccine trial	Retrospective		✖			346	Children	5 (1.45)
Castagnini et al[10]	USA	Secondary care	Pertussis PCR positive (cases) Alternative diagnosis (controls)	Case control			✖		66	Children	33 (50.00)
Cengiz et al[11]	Turkey	Secondary care	• Cough >= 7 days • Paroxysmal cough • Cough + whoop/vomiting/apnoea	Prospective	✖	✖	✖		35	Children	26 (5.71)
Craig et al[12]	USA	Primary care	Cough > 2 weeks	Prospective	✖	✖	✖	✖	37	Adults	10 (27.03)
Crowcroft[13]	UK	Secondary care	Admitted to PICU with respiratory failure, apnoea +/- bradycardia or acute life threatening episode	Prospective	✖	✖	✖		126	Children	25 (19.84)
Del Valle-Mendoza et al[14]	Peru	Secondary care	Clinically diagnosed with whooping cough	Prospective	✖		✖		133	Children	51 (38.35)
Dinu et al[15]	Romania	Multiple settings	Cough > 1 week plus one of: • Paroxysmal cough • Fever • Nocturnal cough • Apnoea • Post-tussive emesis • Facial cyanosis	Prospective	✖	✖	✖		51	Both	32 (62.75)
Ferronato et al[16]	Brazil	Secondary care	• Dry cough > 2 weeks plus inspiratory stridor • Paroxysmal cough • Vomiting after coughing	Retrospective	✖		✖		34	Children	22 (64.71)
Fine et al[17]	USA	Emergency department	Any patient tested for pertussis during study period	Retrospective	✖				443	Children	38 (8.58)

Ghanaie et al [18]	Iran	Schools	Cough >= 2 weeks	Prospective	✖		✖		328	Children	21 (6.40)
Gilberg et al[19]	France	Primary care	Cough 7-31 days	Prospective	✖	✖	✖		217	Adults	70 (32.26)
Granstrom et al[20]	Sweden	Secondary care	Patients with suspected pertussis	Prospective	✖	✖			285	Both	163 (57.19)
Greenberg et al[21]	Israel	Secondary care	PICU patients with LRTI as their primary or secondary diagnosis on discharge data	Retrospective			✖		74	Children	11 (14.86)
Guinto-Ocampo et al[22]	USA	Not reported	Any patient tested for pertussis during study period	Retrospective	✖		✖	✖	141	Children	18 (12.77)
Harnden et al[23]	UK	Primary care	Cough >= 2 weeks	Prospective		✖			172	Children	64 (37.21)
Heininger et al[24]	Germany	Primary care	Coughing child or household contact	Prospective	✖				3629	Children	601 (16.56)
Jackson et al[25]	USA	Primary care	• Cough >= 5 days • Acute respiratory infection judged to be more severe than common cold	Prospective		✖		□	319	Adults	47 (14.73)
Karagul et al[26]	Turkey	Secondary care	Cough >= 2 weeks	Prospective	✖		✖		214	Adults	15 (7.01)
Kayina et al[27]	Uganda	Multiple settings	Cough >= 2 weeks	Prospective		✖	✖		449	Children	67 (14.92)
Koh et al[28]	Malaysia, Thailand, Taiwan	Multiple settings	Cough >= 2 weeks	Prospective		✖			312	Adults	16 (5.13)
Mitchell et al[29]	UK	Primary care	Any patient tested for pertussis during study period	Retrospective		✖			56	Adults	20 (35.71)
Miyashita et al[30]	Japan	Secondary care	Cough	Prospective		✖	✖		1315	Adults	183 (13.92)
Nicolai et al[31]	Italy	Emergency department	Pertussis PCR positive (cases) RSV positive and pertussis negative (controls)	Case control			✖		38	Children	19 (50.00)
Nieves et al[32]	USA	Secondary care	Pertussis PCR positive (cases) RSV/flu positive (controls)	Case control	✖		✖	✖	126	Children	32 (25.40)
Nuolivirta et al[33]	Finland	Secondary care	Clinical diagnosis of bronchiolitis	Retrospective			✖	✖	142	Children	12 (8.45)
Park et al (2005)[34]	South Korea	Multiple settings	Cough 1-12 weeks	Prospective	✖		✖		102	Adults	3 (2.94)
Park et al (2014)[35]	Korea	Multiple settings	Cough <= 30 days	Prospective	✖		✖		490	Adults	34 (6.94)
Philipson et al[36]	New Zealand	Primary care	Cough > 2 weeks	Prospective		✖			222	Both	23 (10.36)
Piedra et al[37]	USA	Secondary care	Clinical diagnosis of bronchiolitis	Prospective			✖		1405	Children	4 (0.28)
Raymond et al[38]	France	Secondary care	• Hospitalised with apnoea +/- cough • Paroxysmal or vomiting cough	Prospective			✖		41	Children	16 (39.02)
Rosenthal et al[39]	USA	Primary care	Cough > 6 days or suspected pertussis	Prospective	✖	✖			38	Adults	10 (26.32)
Schlapfer et al[40]	Germany	Vaccine trial cohort	Cough >= 1 week	Prospective	✖		✖		546	Both	110 (20.15)
Schmitt-Grohe et al[41]	Germany	Vaccine trial cohort	Cough > 2 weeks	Prospective	✖	✖	✖		203	Adults	64 (31.53)
Senzilet et al[42]	Canada	Multiple settings	Cough 1-8 weeks	Prospective	✖	✖	✖		442	Adults	88 (19.91)

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Shojaei et al[43]	Iran	Secondary care	Cough >= 2 weeks with at least one pertussis associated symptom	Retrospective	✖		✖	118	Children	19 (16.10)
Siriyakorn et al[44]	Thailand	Secondary care	Cough > 2 weeks	Prospective		✖	✖	76	Adults	14 (18.42)
Stefanoff et al[45]	Poland	Primary care	Cough >= 2 weeks At least one of • Paroxysms • Inspiratory whooping • Post-tussive vomiting without any apparent cause	Prospective		✖	✖	1232	Both	288 (23.38)
Steketee et al[46]	USA	Setting of outbreak	Not clear	Prospective	✖	✖		255	Adults	107 (41.96)
Strebel et al (1993)[47]	USA	Multiple settings	Cough	Retrospective	✖			88	Children	33 (37.50)
Strebel et al (2001)[48]	USA	Primary care	Cough 7-34 days or acute paroxysmal cough	Prospective	✖	✖	✖	212	Adults	27 (12.74)
Tarr et al[49]	USA	Multiple settings	Any patient tested for pertussis during study period	Retrospective			✖	250	Children	24 (9.60)
Teepe et al[50]	12 European Countries	Primary care	Cough <= 28 days	Prospective		✖	✖	3074	Adults	93 (3.03)
van den Brink et al[51]	Netherlands	Secondary care	Suspected acute respiratory tract infection	Prospective			✖	306	Children	14 (4.58)
Wirsing von König et al[52]	Germany	Vaccine trial cohort	Cough >=1 week	Prospective	✖	✖		164	Children	112 (68.29)
Waters et al[53]	Canada	Multiple settings	Any patient tested for pertussis during study period	Case control	✖		✖	485	Children	189 (38.97)
Wright et al[54]	USA	Emergency department	Cough >= 2 weeks	Prospective	✖	✖		75	Adults	16 (21.33)
Wymann et al[55]	Switzerland	Primary care	Cough lasting >=2 weeks with either • Epidemiological link to a pertussis case • At least one pertussis associated symptom • Clinical judgement	Prospective			✖	3721	Children	904 (24.29)
Yildirim et al[56]	Turkey	Secondary care	Cough > 2 weeks	Prospective	✖	✖	✖	148	Children	25 (16.89)
Zouari et al[57]	Tunisia	Multiple settings	Any patient tested for pertussis during study period	Prospective	✖	✖	✖	599	Children	120 (20.03)

Table 2. Index tests

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 discolouration	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

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Table 3. Meta-analysis
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	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	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	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	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	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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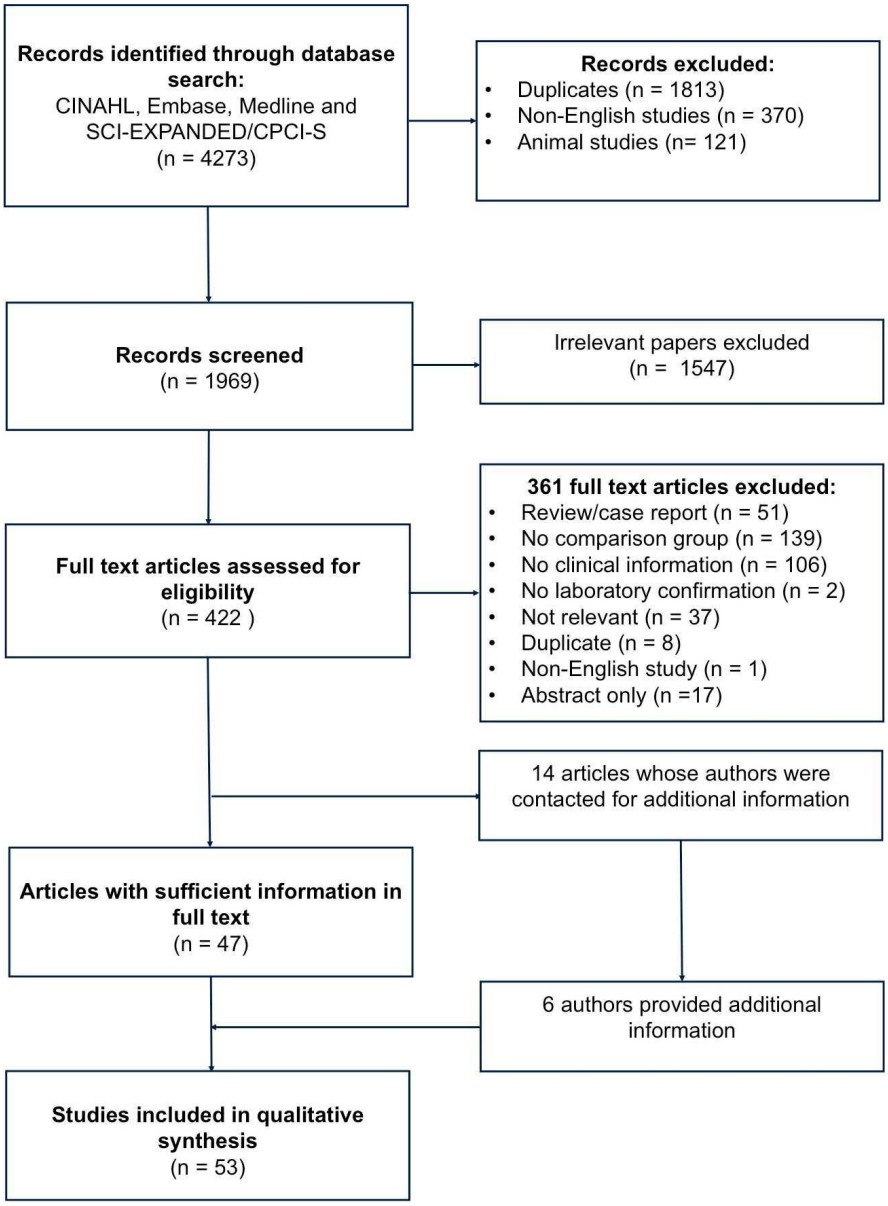
Figure 1.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• Animal studies (n= 121)
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(n = 1969)
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(n = 1547)
Full text articles assessed for eligibility
(n = 422)
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• No comparison group (n = 139)
• No clinical information (n = 106)
• No laboratory confirmation (n = 2)
• Not relevant (n = 37)
• Duplicate (n = 8)
• Non-English study (n = 1)
• Abstract only (n =17)
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Articles with sufficient information in full text
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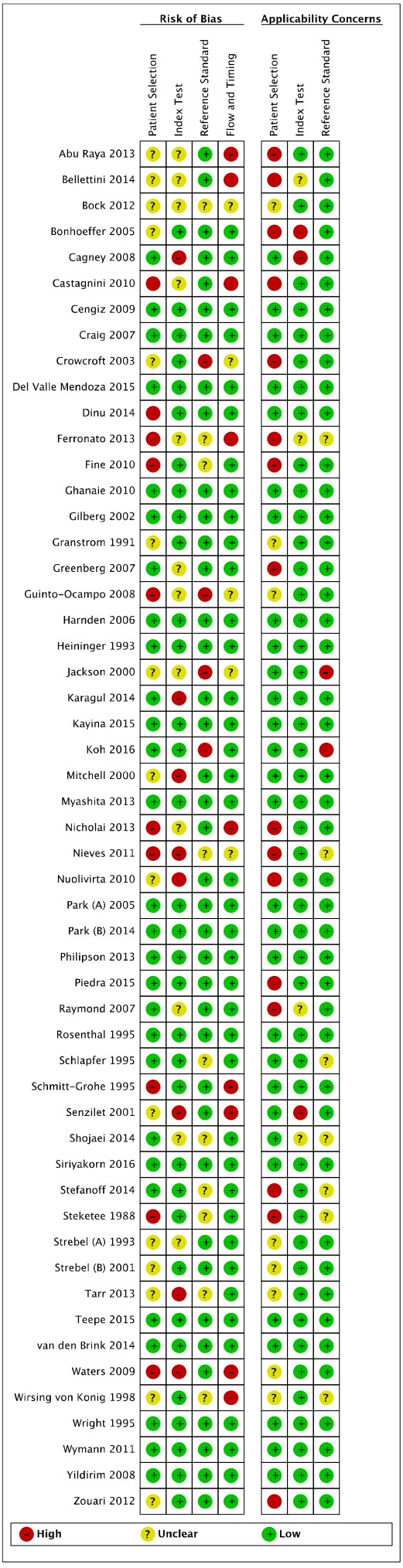
6 authors provided additional information
Studies included in qualitative synthesis
(n = 53)

Figure 2.


Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Patient Selection
Index Test
Reference Standard
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Bellettini 2014
Bock 2012
Bonhoeffer 2005
Cagney 2008
Castagnini 2010
Cengiz 2009
Craig 2007
Crowcroft 2003
Del Valle Mendoza 2015
Dinu 2014
Ferronato 2013
Fine 2010
Ghanaie 2010
Gilberg 2002
Granstrom 1991
Greenberg 2007
Guinto-Ocampo 2008
Harnden 2006
Heininger 1993
Jackson 2000
Karagul 2014
Kayina 2015
Koh 2016
Mitchell 2000
Myashita 2013
Nicholai 2013
Nieves 2011
Nuolivirta 2010
Park (A) 2005
Park (B) 2014
Philipson 2013
Piedra 2015
Raymond 2007
Rosenthal 1995
Schlapfer 1995
Schmitt-Grohe 1995
Senzilet 2001
Shojaei 2014
Siriyakorn 2016
Stefanoff 2014
Steketee 1988
Strebel (A) 1993
Strebel (B) 2001
Tarr 2013
Teepe 2015
van den Brink 2014
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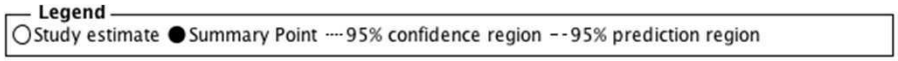
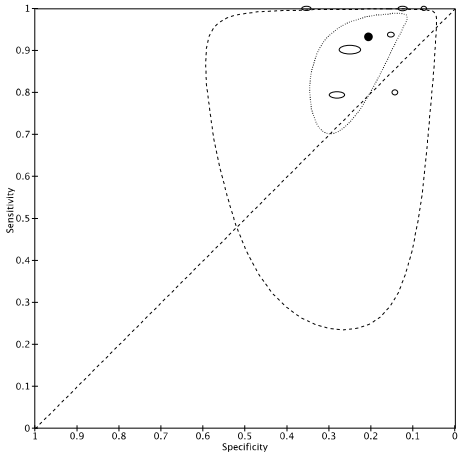
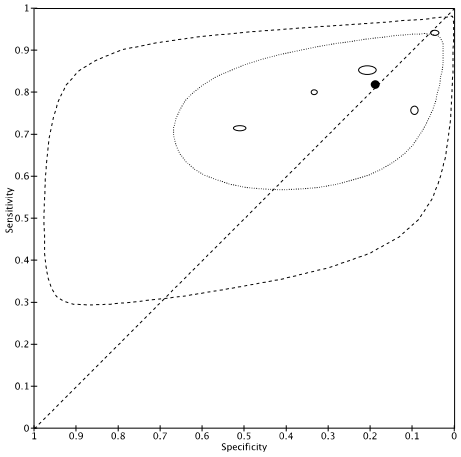
High
Unclear
Low

Figure 3.

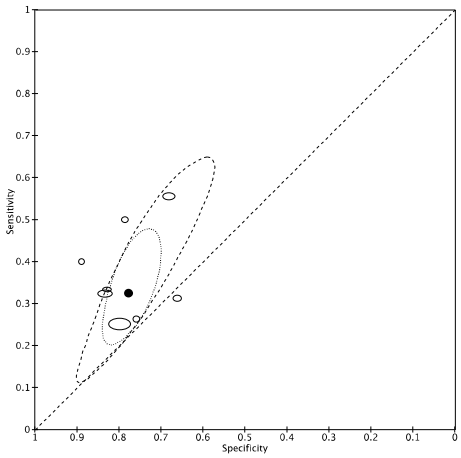




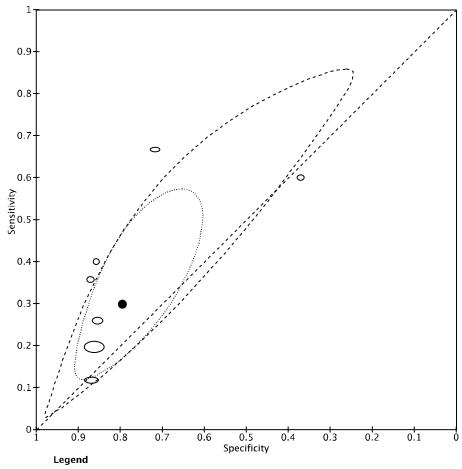
Paroxysmal cough (adults)



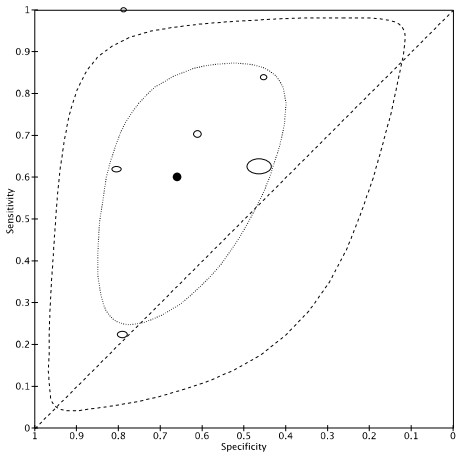
Absence of fever (adults)



Post-tussive vomiting (adults)



Whooping cough (adults)



Post-tussive vomiting (children)

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Abbreviations list

CDC	Center for Disease Control
DFA	direct fluorescent antibody test
PCR	polymerase chain reaction
PHE	Public Health England
ROC	Receiver Operating Characteristic
WHO	World Health Organization

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e-Table 1

Study	Country (ies)	Setting	Inclusion criteria	Study type	Pertussis outbreak	Dates of recruitment	Laboratory test				Total number of participants	Age range	Age category	% Male	Number (%) laboratory confirmed pertussis
							Culture	Serology	PCR	DFA					
Abu Raya et al[8]	Israel	Secondary care	<= 4 days of clinically diagnosed acute bronchiolitis	Case control	Not recorded	2005-2006			×		120	0-52 weeks	Children	64.17%	23 (19.17)
Bellettini et al[6]	Brazil	Multiple settings	Any patient tested for pertussis during study period	Retrospective	Not recorded	2011-2013			×		222	Not recorded	Children	Not recorded	161 (72.52)
Bock et al[7]	USA	Multiple settings	Chronic cough (>8 weeks)	Retrospective	No	2007-2011		×			48	20-88 years	Adults	35.42%	19 (39.58)
Bonhoeffer et al[8]	Switzerland	Multiple settings	Acute exacerbation of chronic bronchitis	Prospective	Not recorded	2000-2002	×	×	×		26	34-86 years	Adults	Not recorded	8 (30.77)
Cagney et al[9]	Australia	Vaccine trial cohort	Participants of vaccine trial	Retrospective	Yes	1999-2000		×			346	Not recorded	Children	67.98%	5 (1.45)
Castagnini et al[10]	USA	Secondary care	Pertussis PCR positive (cases) Alternative diagnosis (controls)	Case control	Not recorded	2000-2007			×		66	12-30 days	Children	48.48%	33 (50.00)
Cengiz et al[11]	Turkey	Secondary care	• Cough >= 7 days • Paroxysmal cough • Cough + whoop/vomiting/apnoea	Prospective	Not recorded	2005-2006	×	×	×		35	2 months - 13 years	Children	65.71%	26 (5.71)
Craig et al[12]	USA	Primary care	Cough > 2 weeks	Prospective	Yes	Not recorded	×	×	×	×	37	18-22 years	Adults	43.24%	10 (27.03)
Crowcroft[13]	UK	Secondary care	Admitted to PICU with respiratory failure, apnoea +/- bradycardia or acute life threatening episode	Prospective	No	1998-1999	×	×	×		126	Not recorded	Children	Not recorded	25 (19.84)
Del Valle-Mendoza et al[14]	Peru	Secondary care	Clinically diagnosed with whooping cough	Prospective	No	2010-2013	×		×		133	<3months - 5 years	Children	54.14%	51 (38.35)
Dinu et al[15]	Romania	Multiple settings	Cough > 1 week plus one of: • Paroxysmal cough • Fever • Nocturnal cough • Apnoea • Post-tussive emesis • Facial cyanosis	Prospective	Not recorded	2012-2013	×	×	×		51	3 months - 75 years	Both	43.14%	32 (62.75)
Ferronato et al[16]	Brazil	Secondary care	• Dry cough > 2 weeks plus inspiratory stridor • Paroxysmal cough • Vomiting after coughing	Retrospective	Not recorded	2009-2012	×		×		34	Not recorded	Children	41.18%	22 (64.71)
Fine et al[17]	USA	Emergency department	Any patient tested for pertussis during study period	Retrospective	Not recorded	2003-2007	×				443	Not recorded	Children	53.05%	38 (8.58)
Ghanaie et al [18]	Iran	Schools	Cough >= 2 weeks	Prospective	Not recorded	2007-2008	×		×		328	6-14 years	Children	54.88%	21 (6.40)
Gilberg et al[19]	France	Primary care	Cough 7-31 days	Prospective	Not recorded	1999	×	×	×		217	18-88 years	Adults	27.19%	70 (32.26)
Granstrom et al[20]	Sweden	Secondary care	Patients with suspected pertussis	Prospective	Not recorded	1986-1987	×	×			285	0.2-63.2 years	Both	50.53%	163 (57.19)
Greenberg et al[21]	Israel	Secondary care	PICU patients with LRTI as their primary or secondary diagnosis on discharge data	Retrospective	Not recorded	1998-2001			×		74	Not recorded	Children	63.51%	11 (14.86)

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Guinto-Ocampo et al[22]	USA	Not reported	Any patient tested for pertussis during study period	Retrospective	Not recorded	2001-2005	×		×	×	141	7-286 days	Children	62.41%	18 (12.77)
Harnden et al[23]	UK	Primary care	Cough >= 2 weeks	Prospective	Not recorded	2001-2005		×			172	5-16.9 years	Children	54.65%	64 (37.21)
Heininger et al[24]	Germany	Primary care	Coughing child or household contact	Prospective	Not recorded	1991-1992	×				3629	Not recorded	Children	Not recorded	601 (16.56)
Jackson et al[25]	USA	Primary care	• Cough >= 5 days • Acute respiratory infection judged to be more severe than common cold	Prospective	Not recorded	Not recorded		×			319	Not recorded	Adults	43.89%	47 (14.73)
Karagul et al[26]	Turkey	Secondary care	Cough >= 2 weeks	Prospective	Not recorded	2010-2011	×		×		214	10- 39 years	Adults	44.86%	15 (7.01)
Kayina et al[27]	Uganda	Multiple settings	Cough >= 2 weeks	Prospective	Not recorded	2013		×	×		449	3 months - 12 years	Children	51.00%	67 (14.92)
Koh et al[28]	Malaysia, Thailand, Taiwan	Multiple settings	Cough >= 2 weeks	Prospective	Not recorded	2012-2013		×			312	19-83 years	Adults	32.69%	16 (5.13)
Mitchell et al[29]	UK	Primary care	Any patient tested for pertussis during study period	Retrospective	No	1995-1996		×			56	16-60 years	Adults	Not recorded	20 (35.71)
Miyashita et al[30]	Japan	Secondary care	Cough	Prospective	No	2005-2012		×	×		1315	16-79 years	Adults	43.65%	183 (13.92)
Nicolai et al[31]	Italy	Emergency department	Pertussis PCR positive (cases) RSV positive and pertussis negative (controls)	Case control	Not recorded	2008-2010			×		38	20-187 days	Children	31.58%	19 (50.00)
Nieves et al[32]	USA	Secondary care	Pertussis PCR positive (cases) RSV/flu positive (controls)	Case control	Not recorded	2009-2010	×		×	×	126	< 3 months	Children	Not recorded	32 (25.40)
Nuolivirta et al[33]	Finland	Secondary care	Clinical diagnosis of bronchiolitis	Retrospective	Not recorded	2001-2004			×	×	142	<4 weeks - 6 months	Children	50.00%	12 (8.45)
Park et al (2005)[34]	South Korea	Multiple settings	Cough 1-12 weeks	Prospective	Not recorded	2002-2003	×		×		102	19-83 years	Adults	52.94%	3 (2.94)
Park et al (2014)[35]	Korea	Multiple settings	Cough <= 30 days	Prospective	No	2011-2012	×		×		490	Not recorded	Adults	27.35%	34 (6.94)
Philipson et al[36]	New Zealand	Primary care	Cough > 2 weeks	Prospective	Not recorded	2011		×			222	5 - 49 years	Both	36.73%	23 (10.36)
Piedra et al[37]	USA	Secondary care	Clinical diagnosis of bronchiolitis	Prospective	No	2007-2010			×		1405	< 6 months	Children	58.29%	4 (0.28)
Raymond et al[38]	France	Secondary care	• Hospitalised with apnoea +/- cough • Paroxysmal or vomiting cough	Prospective	Yes	2004-2005			×		41	< 4 months	Children	Not recorded	16 (39.02)
Rosenthal et al[39]	USA	Primary care	Cough > 6 days or suspected pertussis	Prospective	Yes	1993-1994	×	×			38	13-81 years	Adults	Not recorded	10 (26.32)
Schlapfer et al[40]	Germany	Vaccine trial cohort	Cough >= 1 week	Prospective	Not recorded	1993-1994	×		×		546	Not recorded	Both	Not recorded	110 (20.15)
Schmitt-Grohe et al[41]	Germany	Vaccine trial cohort	Cough > 2 weeks	Prospective	Not recorded	1991-1994	×	×	×		203	18-79 years	Adults	31.53%	64 (31.53)
Senzilet et al[42]	Canada	Multiple settings	Cough 1-8 weeks	Prospective	Not recorded	1996-1997	×	×	×		442	12.3-88.4 years	Adults	30.54%	88 (19.91)
Shojaei et al[43]	Iran	Secondary care	Cough >= 2 weeks with at least one pertussis associated symptom	Retrospective	Yes	2008-2012	×		×		118	Not recorded	Children	49.15%	19 (16.10)
Siriyakorn et al[44]	Thailand	Secondary care	Cough > 2 weeks	Prospective	Not recorded	2010-2011		×	×		76	15-87 years	Adults	36.84%	14 (18.42)
Stefanoff et al[45]	Poland	Primary care	Cough >= 2 weeks At least one of • Paroxysms • Inspiratory whooping • Post-tussive vomiting without any apparent cause	Prospective	Not recorded	2009-2011		×	×		1232	Not recorded	Both	37.42%	288 (23.38)
Steketee et al[46]	USA	Setting of outbreak	Not clear	Prospective	Yes	1984 -?	×	×			255	Not recorded	Adults	Not recorded	107 (41.96)

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Strebel et al (1993)[47]	USA	Multiple settings	Cough	Retrospective	Yes	1989	×			88	Not recorded	Children	Not recorded	33 (37.50)
Strebel et al (2001)[48]	USA	Primary care	Cough 7-34 days or acute paroxysmal cough	Prospective	Not recorded	1995-1996	×	×	×	212	10-49 years	Adults	33.96%	27 (12.74)
Tarr et al[49]	USA	Multiple settings	Any patient tested for pertussis during study period	Retrospective	Yes	2010			×	250	Not recorded	Children	47.60%	24 (9.60)
Teepe et al[50]	12 European Countries	Primary care	Cough <= 28 days	Prospective	No	2007-2010		×	×	3074	NR	Adults	40.11%	93 (3.03)
van den Brink et al[51]	Netherlands	Secondary care	Suspected acute respiratory tract infection	Prospective	Not recorded	2007-2009			×	306	0.1-89.4 months	Children	Not recorded	14 (4.58)
Wirsing von König et al[52]	Germany	Vaccine trial cohort	Cough >=1 week	Prospective	Not recorded	Not recorded	×	×		164	0-18	Children	Not recorded	112 (68.29)
Waters et al[53]	Canada	Multiple settings	Any patient tested for pertussis during study period	Case control	Yes	2005-2006	×		×	485	5 months - 14.9 years	Children	52.58%	189 (38.97)
Wright et al[54]	USA	Emergency department	Cough >= 2 weeks	Prospective	No	1992-1994	×	×		75	NR	Adults	34.67%	16 (21.33)
Wymann et al[55]	Switzerland	Primary care	Cough lasting >=2 weeks with either • Epidemiological link to a pertussis case • At least one pertussis associated symptom • Clinical judgement	Prospective	Yes	1991-2006			×	3721	NR	Children	Not recorded	904 (24.29)
Yildirim et al[56]	Turkey	Secondary care	Cough > 2 weeks	Prospective	No	2005-2006	×	×	×	148	<1-16	Children	56.76%	25 (16.89)
Zouari et al[57]	Tunisia	Multiple settings	Any patient tested for pertussis during study period	Prospective	Not recorded	2007-2011	×	×	×	599	1 day-11months	Children	55.43%	120 (20.03)

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e-Appendix 1. Search strategy for CINAHL

CINAHL

#	Query	Result
1	(MH "Whooping Cough")	1,067
2	(MH "Bordetella Pertussis")	81
3	TI (whooping cough or pertussis) AND AB (whooping cough or pertussis)	311
4	1 OR 2 OR 3	1,158
5	(MH "Cough")	2,455
6	(MH "Symptoms")	3,974
7	(MH "Respiratory Sounds")	1,249
8	TI ((cough* N5 (onset or time or duration or lasting or onset or hour? or day? or week? or length or long* or prolong* or persisten*))) OR AB ((cough* N5 (onset or time or duration or lasting or onset or hour? or day? or week? or length or long* or prolong* or persisten*)))	521
9	TI ((cough* N5 (rapid* or fast or speed or spell? or bout? or period? or frequen* or sound?))) OR AB ((cough* N5 (rapid* or fast or speed or spell? or bout? or period? or frequen* or sound?)))	231
10	TI ((cough* N5 (character* or feature? or presentation? or descri* or document*))) OR AB ((cough* N5 (character* or feature? or presentation? or descri* or document*)))	138
11	TI ((cough* N5 (sever* or intens* or type?))) OR AB ((cough* N5 (sever* or intens* or type?)))	162
12	TI ((cough N5 (productive or nonproductive or dry or explosive or reflex* or refractory or chronic* or vomit*))) OR AB ((cough N5 (productive or nonproductive or dry or explosive or reflex* or refractory or chronic* or vomit*)))	917
13	TI paroxysm* OR AB paroxysm*	2,208
14	TI whoop? OR AB whoop?	17
15	TI wheez* OR AB wheez*	1,521
16	TI gasp* OR AB gasp*	112
17	TI (((chest or respirat*) N2 sound*)) OR AB (((chest or respirat*) N2 sound*)) OR TI (stridor?) OR AB (stridor?)	48
18	TI ((posttussive or post-tussive or tussive)) OR AB ((posttussive or post-tussive or tussive)) OR TI (sputum) OR AB (sputum)	1,631
19	TI ((clinical exam* or physical exam* or chart review)) OR AB ((clinical exam* or physical exam* or chart review))	24,236
20	TI ((clinical N5 (sign? or symptom? or feature? or presentation or characteristic?))) OR AB ((clinical N5 (sign? or symptom? or feature? or presentation or characteristic?)))	22,820
21	TI ((physical N5 (sign? or symptom? or feature? or presentation or characteristic?))) OR AB ((physical N5 (sign? or symptom? or feature? or presentation or characteristic?)))	5,540
22	TI ((present* N5 (sign? or symptom? or feature? or characteristic?))) OR AB ((present* N5 (sign? or symptom? or feature? or characteristic?)))	7,447
23	TI ((symptom* N5 (time or duration or lasting or onset or hour? or day? or week? or length or long* or prolong* or persisten* or presentation))) OR AB ((symptom* N5 (time or duration or lasting or onset or hour? or day? or week? or length or long* or prolong* or persisten* or presentation)))	11,889
24	TI (sign? or symptom? or feature? or presentation or characteristic?)	38,216
25	TI (((household* OR house-hold*) N5 contact*)) OR AB (((household* OR house-hold*) N5 contact*))	252
26	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25	104,390
27	4 AND 26	150

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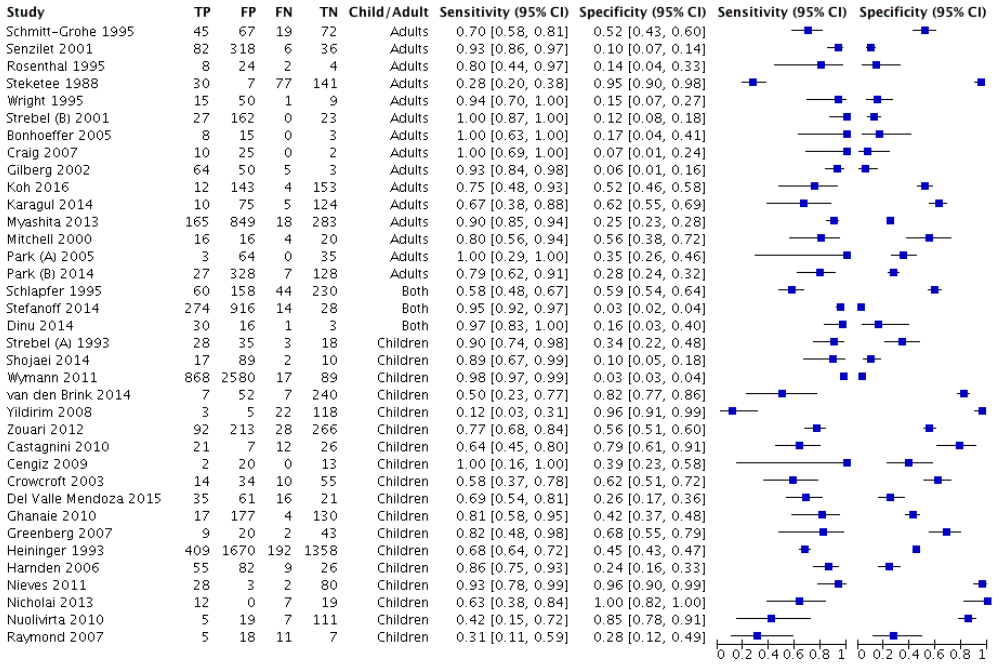
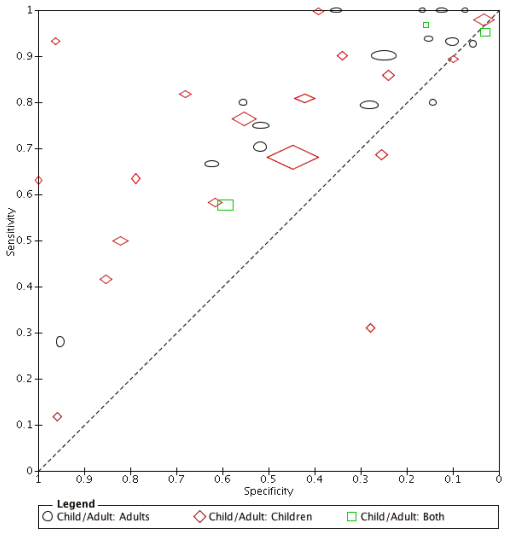
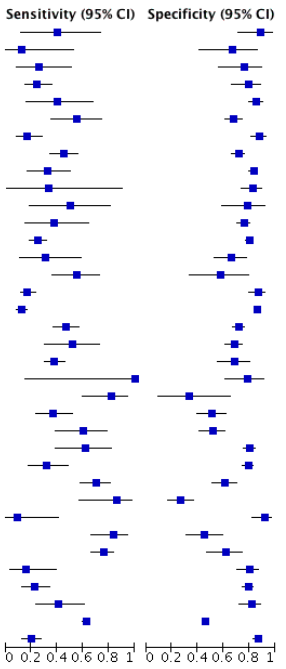
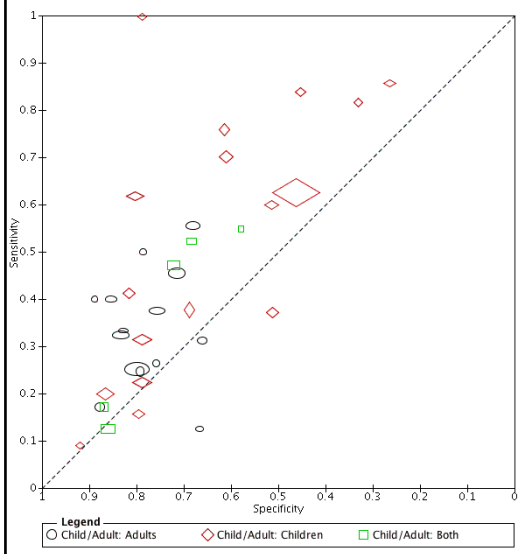
COUGH CHARACTERISTIC			
Clinical characteristic	**Described as**	**Forest plot**	**SROC plot**
Paroxysmal cough	Paroxysmal cough Coughing paroxysms Paroxysms Coughing spells Spasmodic cough		

Clinical characteristic	Described as	Forest plot	SROC plot
Post-tussive vomiting	Post-tussive vomiting Post-tussive emesis Cough with vomiting Accompanied by vomiting Vomit (s) (ing)		
Whooping cough	Whooping cough Whoop Presence of whoops Cough with whooping Inspiratory whoop		

Post-tussive vomiting

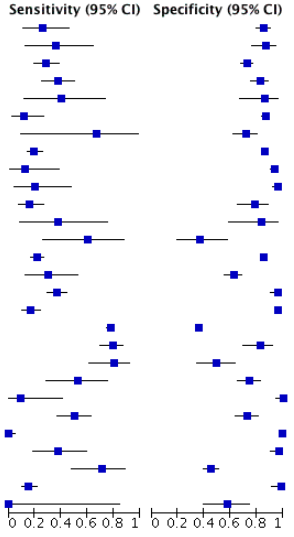
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Craig 2007	4	3	6	24	Adults	0.40 [0.12, 0.74]	0.89 [0.71, 0.98]
Bonhoeffer 2005	1	6	7	12	Adults	0.13 [0.00, 0.53]	0.67 [0.41, 0.87]
Bock 2012	5	7	14	22	Adults	0.26 [0.09, 0.51]	0.76 [0.56, 0.90]
Gilberg 2002	17	11	52	42	Adults	0.25 [0.15, 0.36]	0.79 [0.66, 0.89]
Karagul 2014	6	29	9	170	Adults	0.40 [0.16, 0.68]	0.85 [0.80, 0.90]
Strebel (B) 2001	15	59	12	126	Adults	0.56 [0.35, 0.75]	0.68 [0.61, 0.75]
Schmitt-Grohe 1995	11	17	53	122	Adults	0.17 [0.09, 0.29]	0.88 [0.81, 0.93]
Senzilet 2001	40	101	48	253	Adults	0.45 [0.35, 0.56]	0.71 [0.66, 0.76]
Park (B) 2014	11	76	23	380	Adults	0.32 [0.17, 0.51]	0.83 [0.80, 0.87]
Park (A) 2005	1	17	2	82	Adults	0.33 [0.01, 0.91]	0.83 [0.74, 0.90]
Rosenthal 1995	5	6	5	22	Adults	0.50 [0.19, 0.81]	0.79 [0.59, 0.92]
Koh 2016	6	72	10	224	Adults	0.38 [0.15, 0.65]	0.76 [0.70, 0.80]
Myashita 2013	46	228	137	904	Adults	0.25 [0.19, 0.32]	0.80 [0.77, 0.82]
Wright 1995	5	20	11	39	Adults	0.31 [0.11, 0.59]	0.66 [0.53, 0.78]
Dinu 2014	17	8	14	11	Both	0.55 [0.36, 0.73]	0.58 [0.33, 0.80]
Granstrom 1991	28	16	135	106	Both	0.17 [0.12, 0.24]	0.87 [0.80, 0.92]
Stefanoff 2014	36	132	252	812	Both	0.13 [0.09, 0.17]	0.86 [0.84, 0.88]
Schlapfer 1995	49	108	55	280	Both	0.47 [0.37, 0.57]	0.72 [0.67, 0.77]
Philipson 2013	12	63	11	136	Both	0.52 [0.31, 0.73]	0.68 [0.61, 0.75]
Bellettini 2014	61	19	100	42	Children	0.38 [0.30, 0.46]	0.69 [0.56, 0.80]
Cengiz 2009	2	7	0	26	Children	1.00 [0.16, 1.00]	0.79 [0.61, 0.91]
Ferronato 2013	18	8	4	4	Children	0.82 [0.60, 0.95]	0.33 [0.10, 0.65]
Del Valle Mendoza 2015	19	40	32	42	Children	0.37 [0.24, 0.52]	0.51 [0.40, 0.62]
Crowcroft 2003	15	49	10	52	Children	0.60 [0.39, 0.79]	0.51 [0.41, 0.62]
Ghanaie 2010	13	60	8	247	Children	0.62 [0.38, 0.82]	0.80 [0.76, 0.85]
Fine 2010	12	85	26	320	Children	0.32 [0.18, 0.49]	0.79 [0.75, 0.83]
Harnden 2006	45	42	19	66	Children	0.70 [0.58, 0.81]	0.61 [0.51, 0.70]
Guinto-Ocampo 2008	12	61	2	22	Children	0.86 [0.57, 0.98]	0.27 [0.17, 0.37]
Greenberg 2007	1	5	10	58	Children	0.09 [0.00, 0.41]	0.92 [0.82, 0.97]
Strebel (A) 1993	26	29	5	24	Children	0.84 [0.66, 0.95]	0.45 [0.32, 0.60]
Wirsing von Konig 1998	73	20	23	32	Children	0.76 [0.66, 0.84]	0.62 [0.47, 0.75]
Shojaei 2014	3	20	16	79	Children	0.16 [0.03, 0.40]	0.80 [0.71, 0.87]
Kayina 2015	15	80	52	302	Children	0.22 [0.13, 0.34]	0.79 [0.75, 0.83]
Nieves 2011	12	17	17	76	Children	0.41 [0.24, 0.61]	0.82 [0.72, 0.89]
Wymann 2011	540	1401	323	1212	Children	0.63 [0.59, 0.66]	0.46 [0.44, 0.48]
Zouari 2012	24	64	96	415	Children	0.20 [0.13, 0.28]	0.87 [0.83, 0.90]

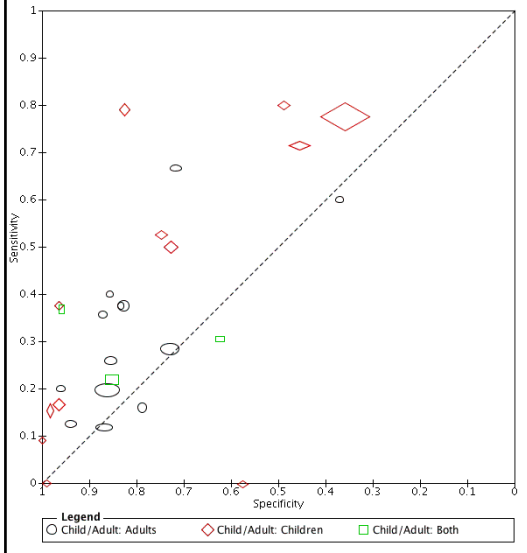


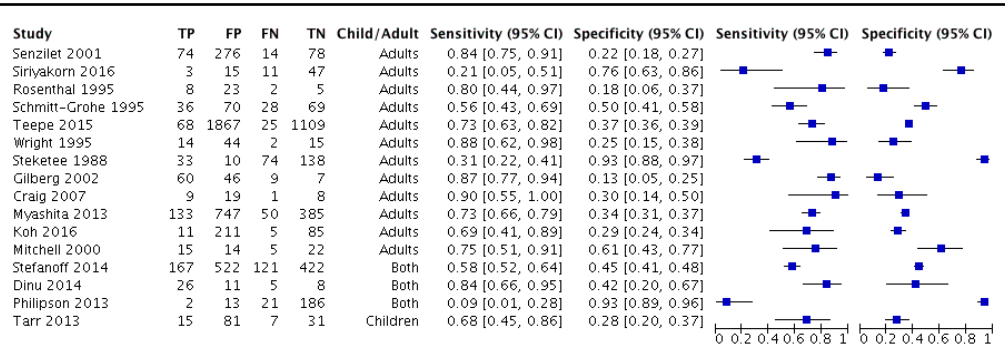
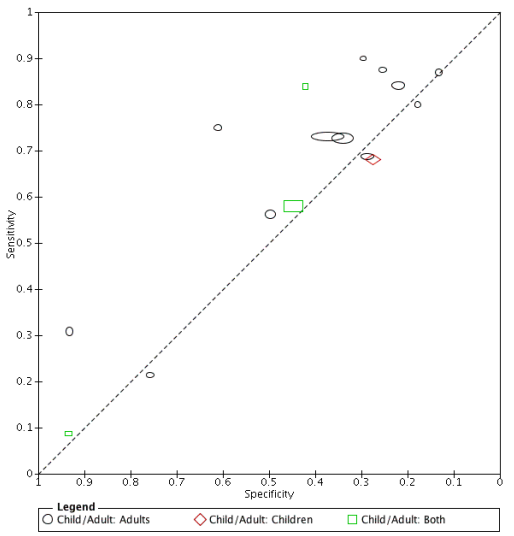
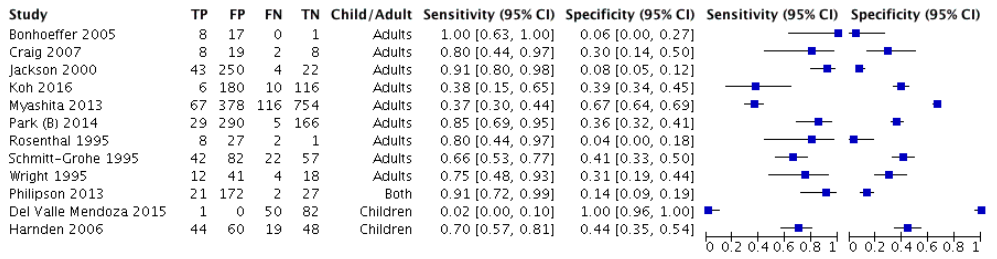
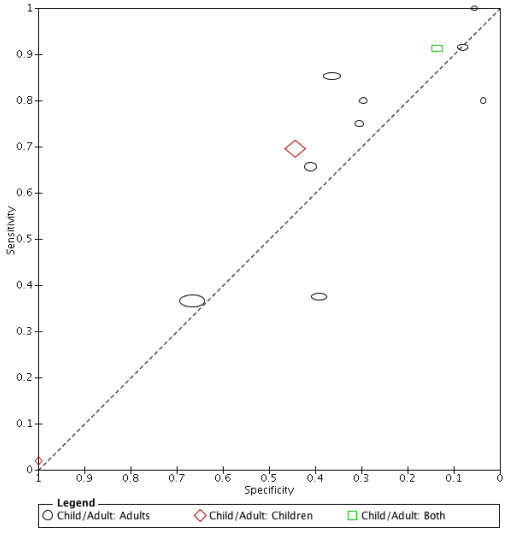


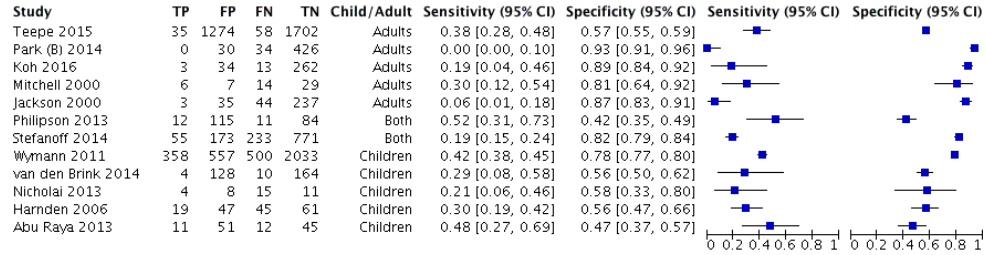
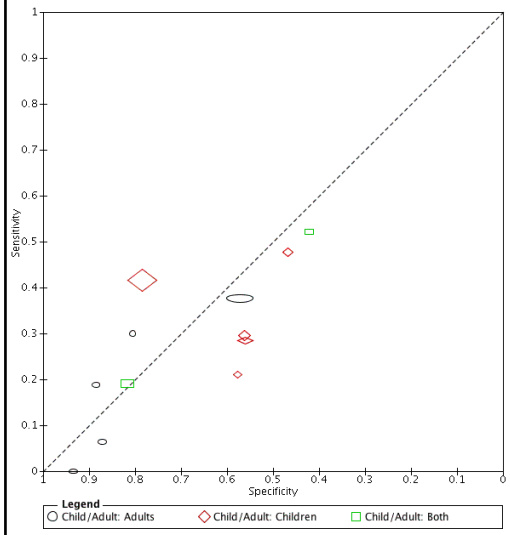
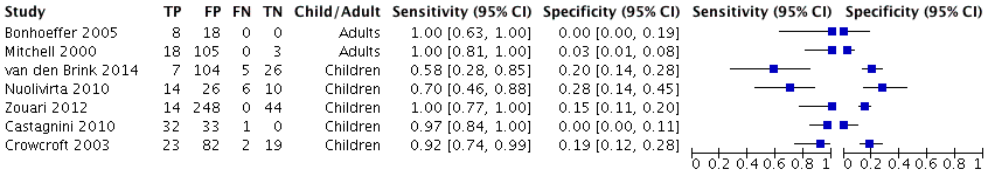
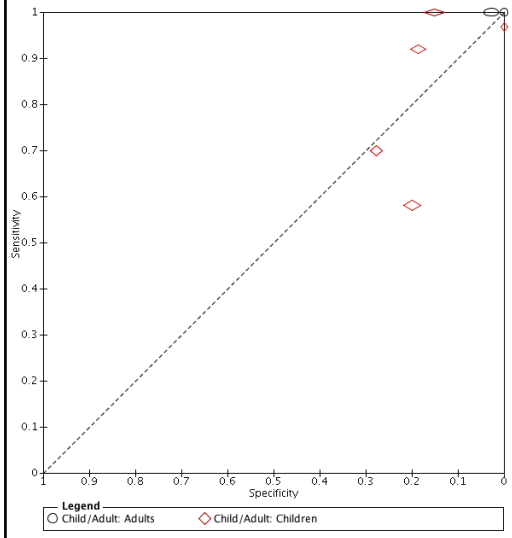
Whooping cough

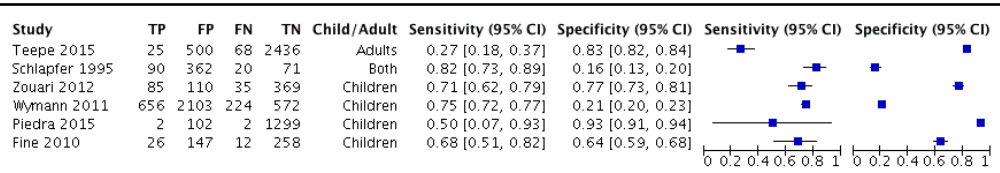
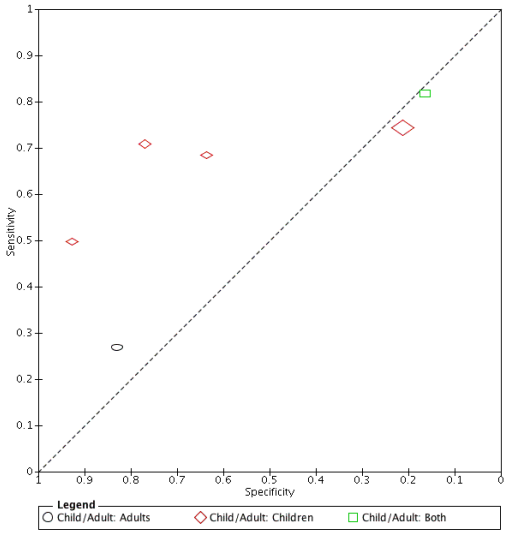
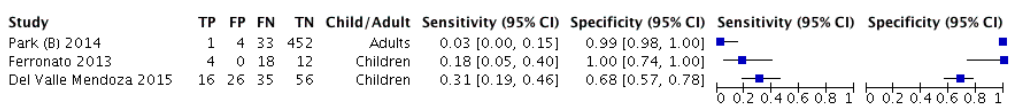
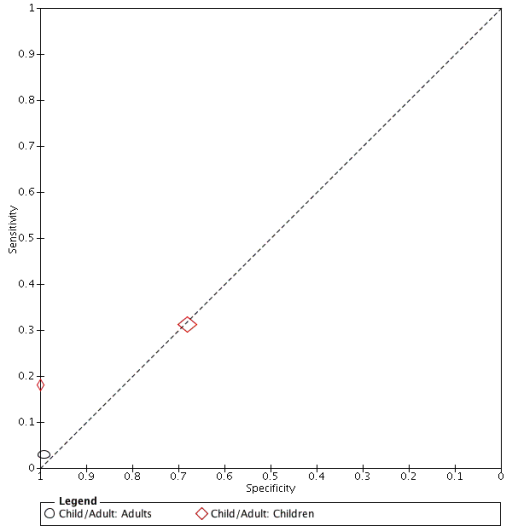
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Strebel (B) 2001	7	27	20	158	Adults	0.26 [0.11, 0.46]	0.85 [0.79, 0.90]
Siriyakorn 2016	5	8	9	54	Adults	0.36 [0.13, 0.65]	0.87 [0.76, 0.94]
Senzilet 2001	25	96	63	258	Adults	0.28 [0.19, 0.39]	0.73 [0.68, 0.77]
Schmitt-Grohe 1995	24	24	40	115	Adults	0.38 [0.26, 0.50]	0.83 [0.75, 0.89]
Rosenthal 1995	4	4	6	24	Adults	0.40 [0.12, 0.74]	0.86 [0.67, 0.96]
Park (B) 2014	4	60	30	396	Adults	0.12 [0.03, 0.27]	0.87 [0.83, 0.90]
Park (A) 2005	2	28	1	71	Adults	0.67 [0.09, 0.99]	0.72 [0.62, 0.80]
Myashita 2013	36	156	147	976	Adults	0.20 [0.14, 0.26]	0.86 [0.84, 0.88]
Koh 2016	2	18	14	278	Adults	0.13 [0.02, 0.38]	0.94 [0.91, 0.96]
Karagul 2014	3	8	12	191	Adults	0.20 [0.04, 0.48]	0.96 [0.92, 0.98]
Gilberg 2002	11	11	58	41	Adults	0.16 [0.08, 0.27]	0.79 [0.65, 0.89]
Bonhoeffer 2005	3	3	5	15	Adults	0.38 [0.09, 0.76]	0.83 [0.59, 0.96]
Craig 2007	6	17	4	10	Adults	0.60 [0.26, 0.88]	0.37 [0.19, 0.58]
Stefanoff 2014	63	140	225	804	Both	0.22 [0.17, 0.27]	0.85 [0.83, 0.87]
Philipson 2013	7	75	16	124	Both	0.30 [0.13, 0.53]	0.62 [0.55, 0.69]
Granstrom 1991	60	5	103	117	Both	0.37 [0.29, 0.45]	0.96 [0.91, 0.99]
Zouari 2012	20	17	100	462	Children	0.17 [0.10, 0.25]	0.96 [0.94, 0.98]
Wymann 2011	668	1669	192	937	Children	0.78 [0.75, 0.80]	0.36 [0.34, 0.38]
Wirsing von Konig 1998	76	9	20	43	Children	0.79 [0.70, 0.87]	0.83 [0.70, 0.92]
Strebel (A) 1993	24	26	6	25	Children	0.80 [0.61, 0.92]	0.49 [0.35, 0.63]
Shojaei 2014	10	25	9	74	Children	0.53 [0.29, 0.76]	0.75 [0.65, 0.83]
Greenberg 2007	1	0	10	63	Children	0.09 [0.00, 0.41]	1.00 [0.94, 1.00]
Harnden 2006	32	29	32	78	Children	0.50 [0.37, 0.63]	0.73 [0.63, 0.81]
Kayina 2015	0	3	67	379	Children	0.00 [0.00, 0.05]	0.99 [0.98, 1.00]
Crowcroft 2003	9	3	15	84	Children	0.38 [0.19, 0.59]	0.97 [0.90, 0.99]
Ghanaie 2010	15	167	6	140	Children	0.71 [0.48, 0.89]	0.46 [0.40, 0.51]
Bellettini 2014	25	1	136	60	Children	0.16 [0.10, 0.22]	0.98 [0.91, 1.00]
Cengiz 2009	0	14	2	19	Children	0.00 [0.00, 0.84]	0.58 [0.39, 0.75]





Clinical characteristic	Described as	Forest plot	SROC plot
Worse at night	Worse at night Nocturnal cough Night cough Mainly at night Disturbed sleep Awakened by cough		
Productive cough	Productive cough Sputum (production) Coughing up phlegm		

Clinical characteristic	Described as	Forest plot	SROC plot
Wheeze	Wheeze (ing) Wheezing on auscultation Wheezing inspiration		
Any cough	Cough Increased cough Persistent cough Coughing without spells		

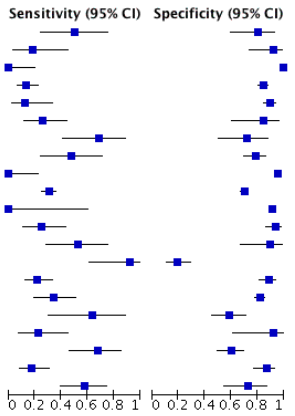
Clinical characteristic	Described as	Forest plot	SROC plot
Cough duration	Cough > 2 weeks		
Stridor	Stridor Cough with stridor		

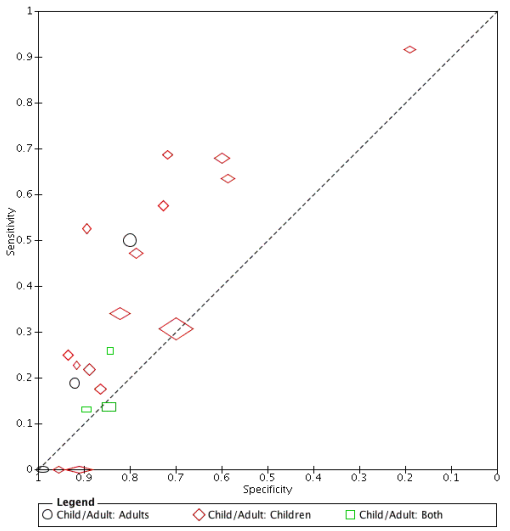
OTHER RESPIRATORY SYMPTOMS/FINDINGS

Clinical characteristic	Described as	Forest plot	SROC plot
Apnoea	Apnoea Cough with apnoea Stopped breathing Apparent life threatening event Apnoea for 30 seconds after cough		
Cyanosis	Cyanosis Cyanotic spell Cough with cyanosis Facial cyanosis Turned blue/purple		

Apnoea

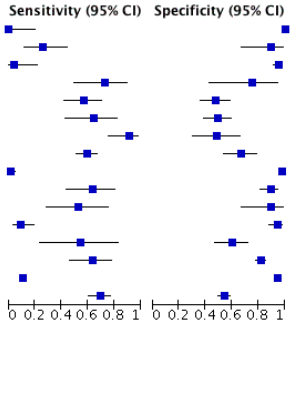
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Senzilet 2001	8	5	8	20	Adults	0.50 [0.25, 0.75]	0.80 [0.59, 0.93]
Rosenthal 1995	3	2	13	23	Adults	0.19 [0.04, 0.46]	0.92 [0.74, 0.99]
Koh 2016	0	3	16	293	Adults	0.00 [0.00, 0.21]	0.99 [0.97, 1.00]
Stefanoff 2014	12	55	76	299	Both	0.14 [0.07, 0.23]	0.84 [0.80, 0.88]
Philipson 2013	3	21	20	178	Both	0.13 [0.03, 0.34]	0.89 [0.84, 0.93]
Dinu 2014	8	3	23	16	Both	0.26 [0.12, 0.45]	0.84 [0.60, 0.97]
Shojaei 2014	11	7	5	18	Children	0.69 [0.41, 0.89]	0.72 [0.51, 0.88]
van den Brink 2014	9	21	10	78	Children	0.47 [0.24, 0.71]	0.79 [0.69, 0.86]
Zouari 2012	0	13	14	279	Children	0.00 [0.00, 0.23]	0.96 [0.93, 0.98]
Waters 2009	89	283	199	661	Children	0.31 [0.26, 0.37]	0.70 [0.67, 0.73]
Piedra 2015	0	125	4	1276	Children	0.00 [0.00, 0.60]	0.91 [0.89, 0.93]
Nieves 2011	8	6	24	87	Children	0.25 [0.11, 0.43]	0.94 [0.86, 0.98]
Nicholai 2013	10	2	9	17	Children	0.53 [0.29, 0.76]	0.89 [0.67, 0.99]
Guinto-Ocampo 2008	11	64	1	15	Children	0.92 [0.62, 1.00]	0.19 [0.11, 0.29]
Harnden 2006	14	12	50	96	Children	0.22 [0.13, 0.34]	0.89 [0.81, 0.94]
Fine 2010	13	72	25	333	Children	0.34 [0.20, 0.51]	0.82 [0.78, 0.86]
Greenberg 2007	7	26	4	37	Children	0.64 [0.31, 0.89]	0.59 [0.46, 0.71]
Ferronato 2013	5	1	17	11	Children	0.23 [0.08, 0.45]	0.92 [0.62, 1.00]
Crowcroft 2003	17	40	8	60	Children	0.68 [0.46, 0.85]	0.60 [0.50, 0.70]
Del Valle Mendoza 2015	9	11	42	71	Children	0.18 [0.08, 0.31]	0.87 [0.77, 0.93]
Castagnini 2010	19	9	14	24	Children	0.58 [0.39, 0.75]	0.73 [0.54, 0.87]

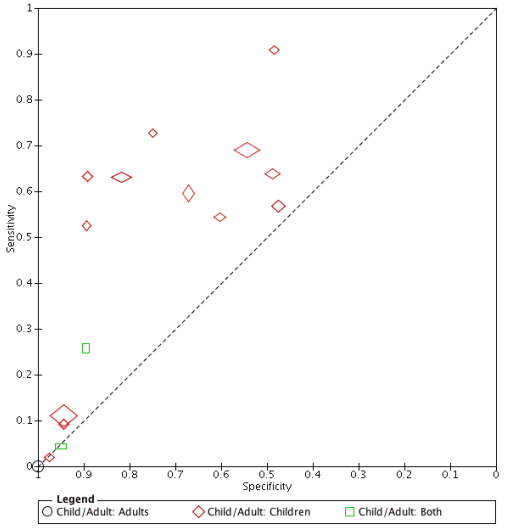


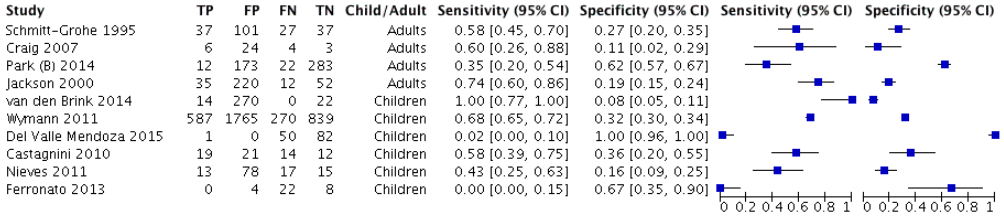
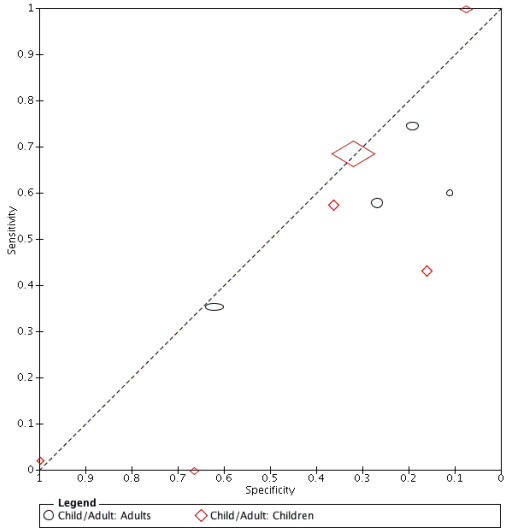
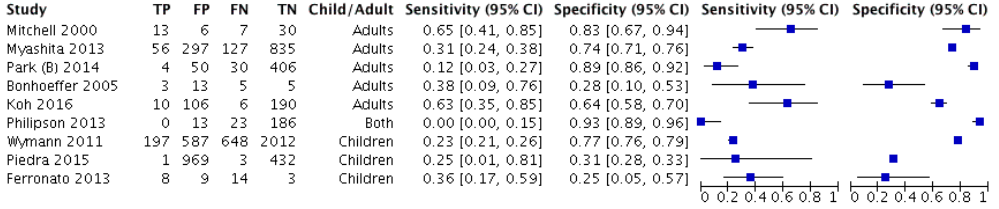
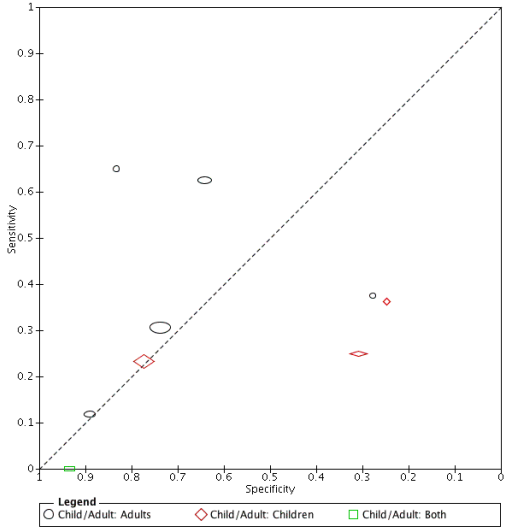


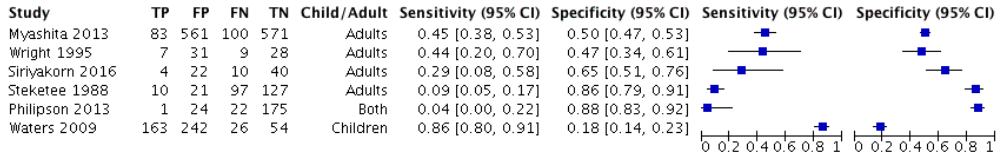
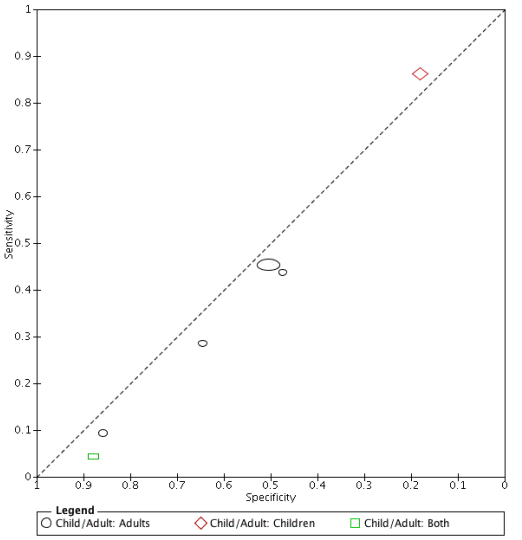
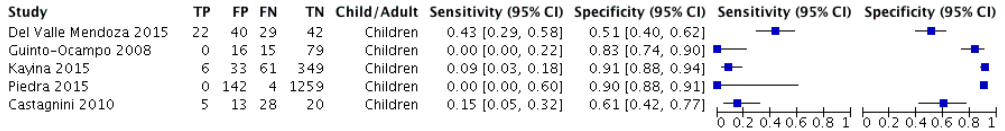
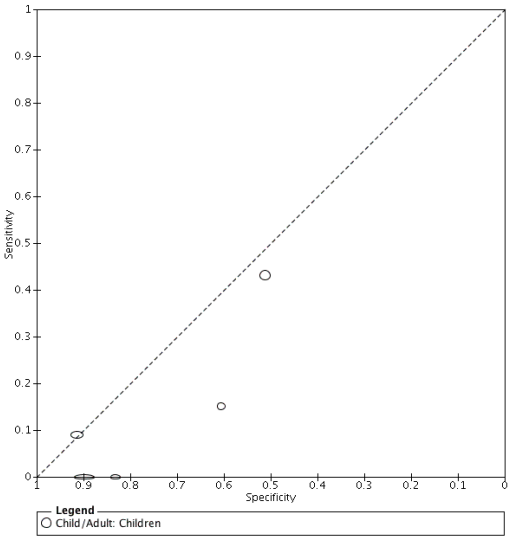
Cyanosis

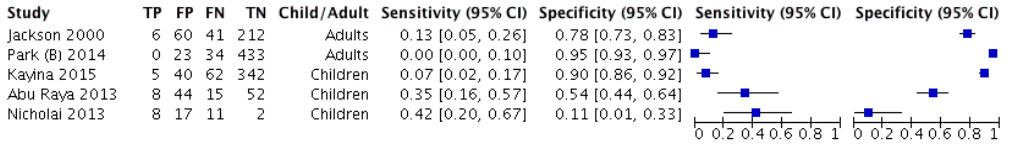
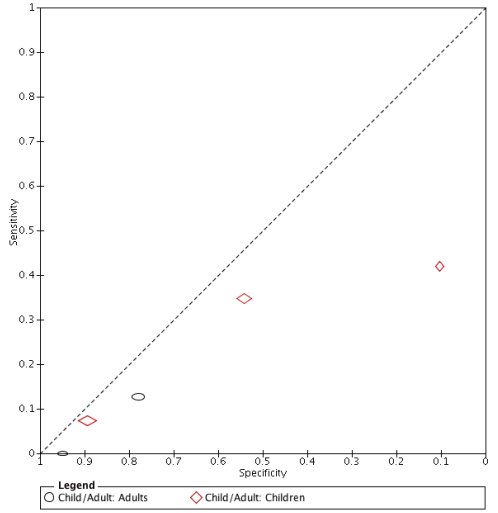
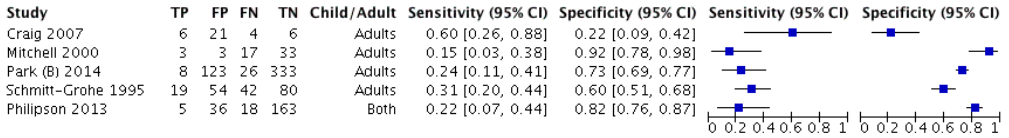
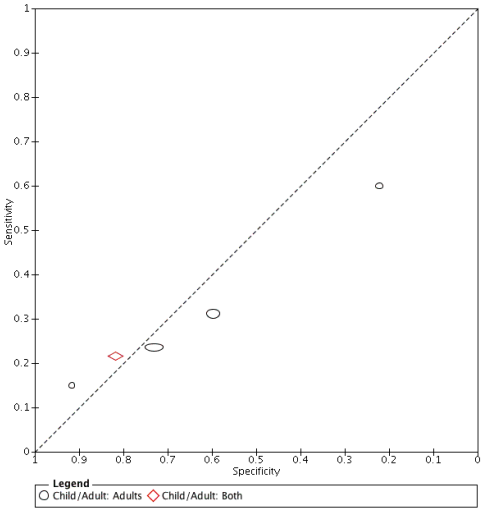
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Koh 2016	0	0	16	296	Adults	0.00 [0.00, 0.21]	1.00 [0.99, 1.00]
Dinu 2014	8	2	23	17	Both	0.26 [0.12, 0.45]	0.89 [0.67, 0.99]
Philipson 2013	1	10	22	189	Both	0.04 [0.00, 0.22]	0.95 [0.91, 0.98]
Ferronato 2013	16	3	6	9	Children	0.73 [0.50, 0.89]	0.75 [0.43, 0.95]
Del Valle Mendoza 2015	29	43	22	39	Children	0.57 [0.42, 0.71]	0.48 [0.36, 0.59]
Crowcroft 2003	16	51	9	49	Children	0.64 [0.43, 0.82]	0.49 [0.39, 0.59]
Castagnini 2010	30	17	3	16	Children	0.91 [0.76, 0.98]	0.48 [0.31, 0.66]
Bellettini 2014	96	20	65	41	Children	0.60 [0.52, 0.67]	0.67 [0.54, 0.79]
Waters 2009	4	7	185	289	Children	0.02 [0.01, 0.05]	0.98 [0.95, 0.99]
Nieves 2011	19	10	11	83	Children	0.63 [0.44, 0.80]	0.89 [0.81, 0.95]
Nicholai 2013	10	2	9	17	Children	0.53 [0.29, 0.76]	0.89 [0.67, 0.99]
Harnden 2006	6	6	58	102	Children	0.09 [0.04, 0.19]	0.94 [0.88, 0.98]
Greenberg 2007	6	25	5	38	Children	0.55 [0.23, 0.83]	0.60 [0.47, 0.72]
Fine 2010	24	73	14	332	Children	0.63 [0.46, 0.78]	0.82 [0.78, 0.86]
Wymann 2011	95	141	759	2439	Children	0.11 [0.09, 0.13]	0.95 [0.94, 0.95]
Zouari 2012	83	218	37	261	Children	0.69 [0.60, 0.77]	0.54 [0.50, 0.59]

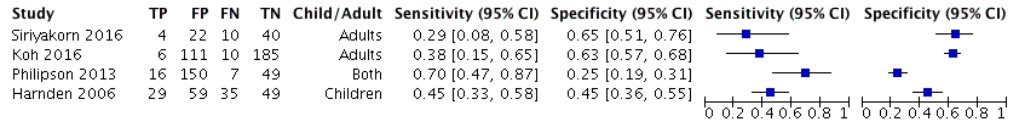
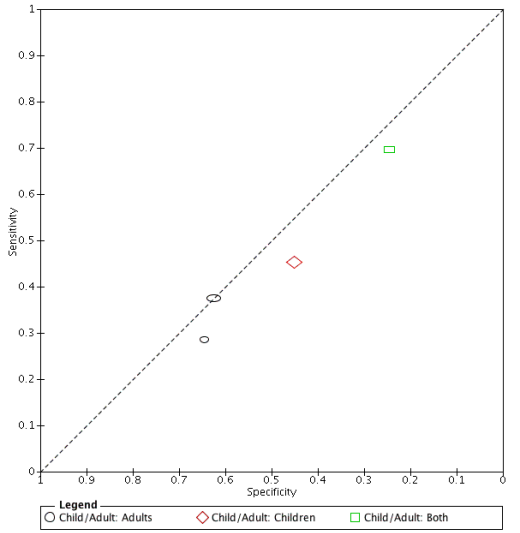
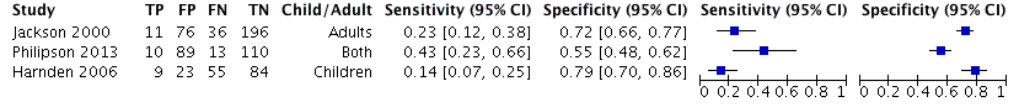
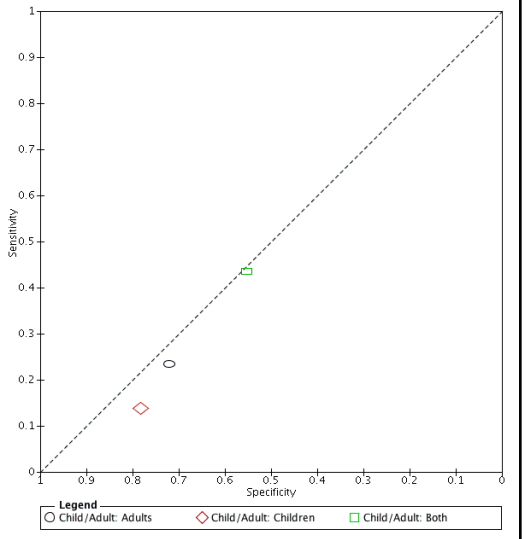


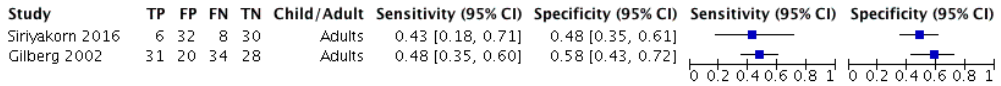
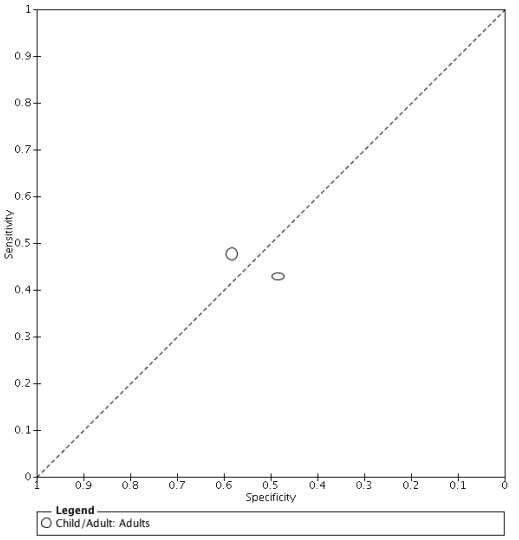
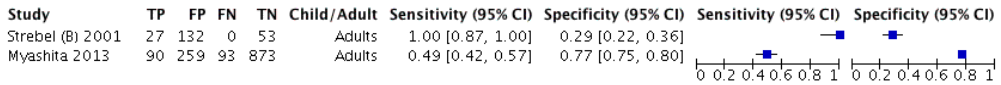
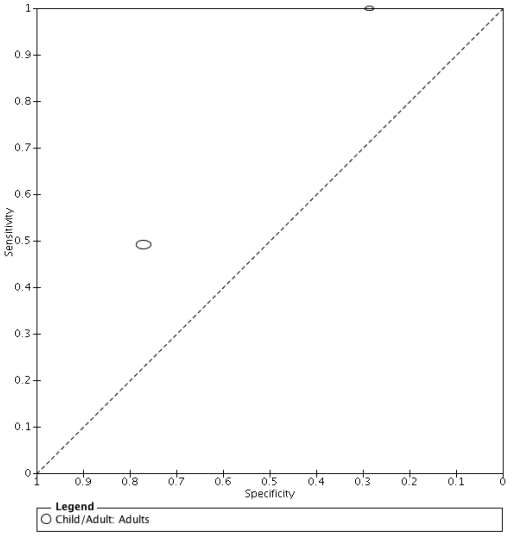


Clinical characteristic	Described as	Forest plot	SROC plot
Rhinorrhoea	Rhinorrhoea Congestion Coryza Rhinitis		
Shortness of breath	Shortness of breath Dyspnoea Breathlessness/chest pain SOB Difficulty breathing		

Clinical characteristic	Described as	Forest plot	SROC plot
URTI symptoms	URTI symptoms URI symptoms only (no cough) Influenza-like symptoms >1 cold-like symptoms: water or red eyes, runny nose, fever, sore throat, vomiting and/or diarrhoea		
Respiratory distress /hypoxia	Respiratory distress Tachypnoea Fast breathing Respiratory rate >= 70 Oxygen saturations < = 94%		

Clinical characteristic	Described as	Forest plot	SROC plot
Chest crackles	(Chest) crackle(s) Crackles on auscultation Chest sounds (rales) Rales		
Sore throat	Sore throat Pharyngitis		

Clinical characteristic	Described as	Forest plot	SROC plot
Sneezing	Sneezing Sneezes Sneezing attack		
Sinus pain	Sinus pain Sinus tenderness to percussion		

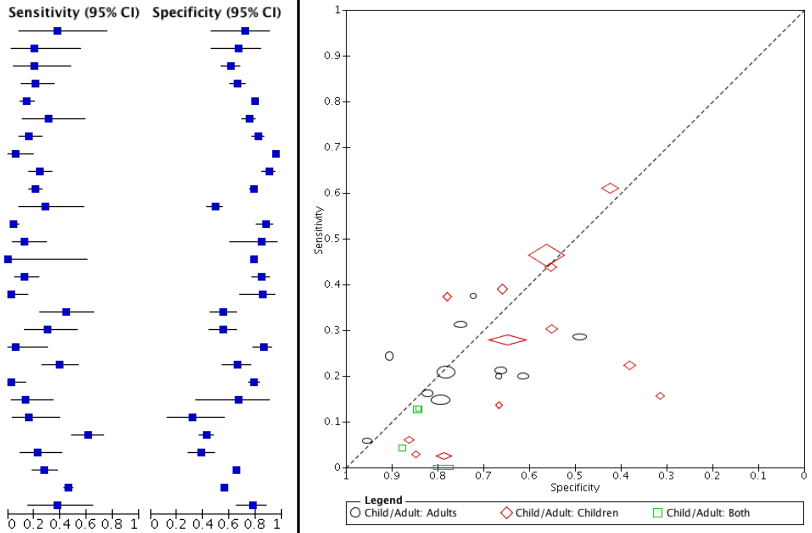
Clinical characteristic	Described as	Forest plot	SROC plot
Hoarseness	Hoarseness		
Post-tussive gagging	Post-tussive gagging		

OTHER CLINICAL FEATURES

Clinical characteristic	Described as	Forest plot	SROC plot
Fever	Fever Fever with cutoff (37/37.2/38 C, 100.4 F variously) Temperature elevation History of fever Fever since onset of cough		
Headache	Headache(s)		

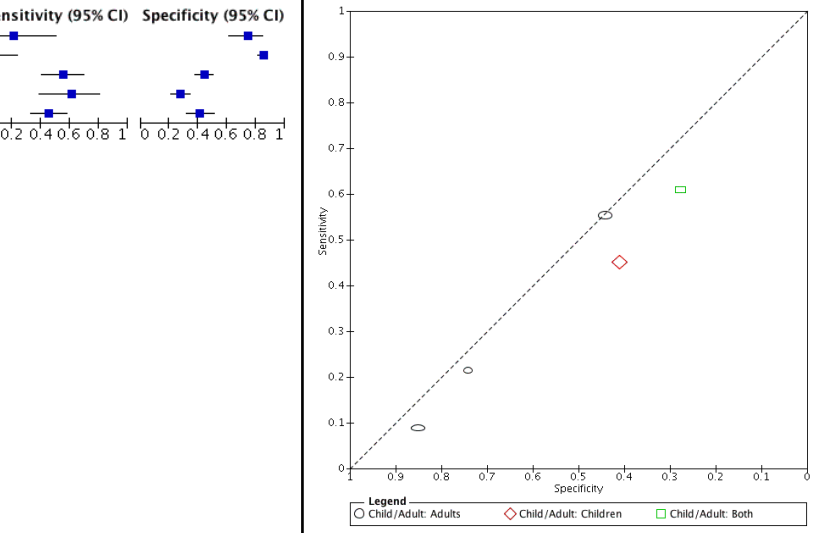
Fever

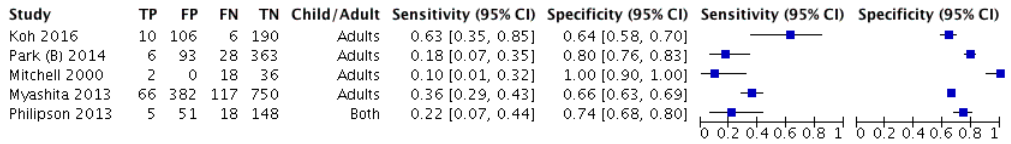
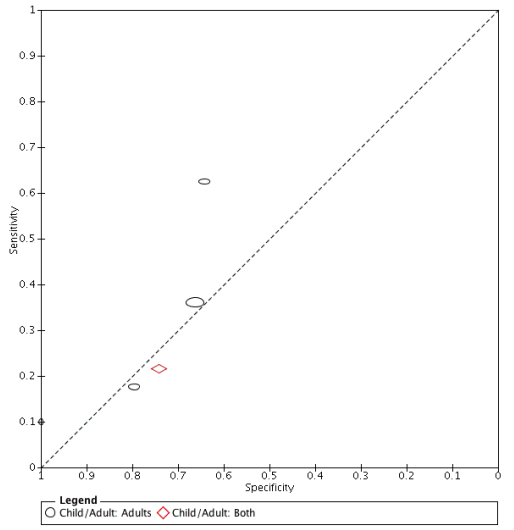
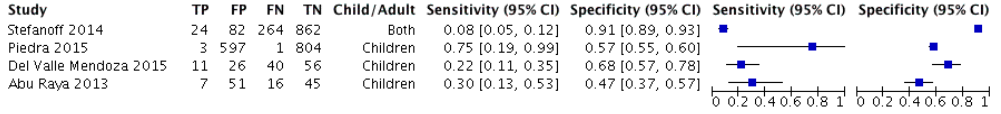
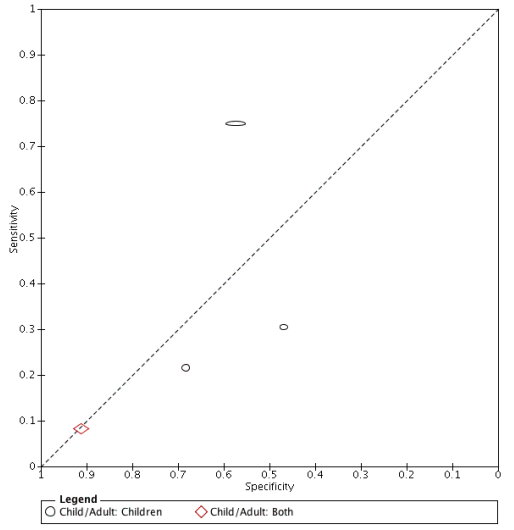
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Bonhoeffer 2005	3	5	5	13	Adults	0.38 [0.09, 0.76]	0.72 [0.47, 0.90]
Craig 2007	2	9	8	18	Adults	0.20 [0.03, 0.56]	0.67 [0.46, 0.83]
Karagul 2014	3	77	12	122	Adults	0.20 [0.04, 0.48]	0.61 [0.54, 0.68]
Jackson 2000	10	92	37	180	Adults	0.21 [0.11, 0.36]	0.66 [0.60, 0.72]
Myashita 2013	27	234	156	898	Adults	0.15 [0.10, 0.21]	0.79 [0.77, 0.82]
Koh 2016	5	74	11	222	Adults	0.31 [0.11, 0.59]	0.75 [0.70, 0.80]
Schmitt-Grohe 1995	12	53	62	244	Adults	0.16 [0.09, 0.27]	0.82 [0.77, 0.86]
Park (B) 2014	2	21	32	435	Adults	0.06 [0.01, 0.20]	0.95 [0.93, 0.97]
Teepe 2015	26	14	81	134	Adults	0.24 [0.17, 0.34]	0.91 [0.85, 0.95]
Steketee 1988	60	206	228	738	Adults	0.21 [0.16, 0.26]	0.78 [0.75, 0.81]
Wright 1995	4	149	10	143	Adults	0.29 [0.08, 0.58]	0.49 [0.43, 0.55]
Granstrom 1991	7	15	156	107	Both	0.04 [0.02, 0.09]	0.88 [0.81, 0.93]
Dinu 2014	4	3	27	16	Both	0.13 [0.04, 0.30]	0.84 [0.60, 0.97]
Schlapfer 1995	0	298	4	1103	Both	0.00 [0.00, 0.60]	0.79 [0.76, 0.81]
Stefanoff 2014	8	21	55	113	Both	0.13 [0.06, 0.23]	0.84 [0.77, 0.90]
Castagnini 2010	1	5	32	28	Children	0.03 [0.00, 0.16]	0.85 [0.68, 0.95]
Crowcroft 2003	11	45	14	56	Children	0.44 [0.24, 0.65]	0.55 [0.45, 0.65]
Abu Raya 2013	7	43	16	53	Children	0.30 [0.13, 0.53]	0.55 [0.45, 0.65]
Guinto-Ocampo 2008	1	14	15	89	Children	0.06 [0.00, 0.30]	0.86 [0.78, 0.92]
Del Valle Mendoza 2015	20	28	31	54	Children	0.39 [0.26, 0.54]	0.66 [0.55, 0.76]
Fine 2010	1	86	37	319	Children	0.03 [0.00, 0.14]	0.79 [0.74, 0.83]
Ferronato 2013	3	4	19	8	Children	0.14 [0.03, 0.35]	0.67 [0.35, 0.90]
Nicholai 2013	3	13	16	6	Children	0.16 [0.03, 0.40]	0.32 [0.13, 0.57]
Kayina 2015	41	220	26	162	Children	0.61 [0.49, 0.73]	0.42 [0.37, 0.48]
Nieves 2011	7	58	24	36	Children	0.23 [0.10, 0.41]	0.38 [0.28, 0.49]
van den Brink 2014	26	1045	67	1931	Children	0.28 [0.19, 0.38]	0.65 [0.63, 0.67]
Zouari 2012	361	1059	417	1365	Children	0.46 [0.43, 0.50]	0.56 [0.54, 0.58]
Wymann 2011	6	13	10	46	Children	0.38 [0.15, 0.65]	0.78 [0.65, 0.88]

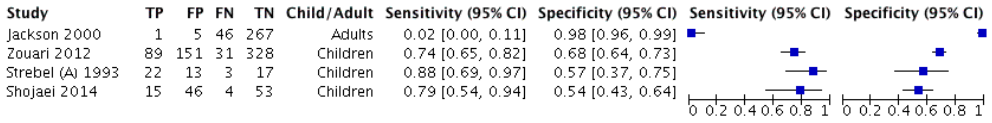
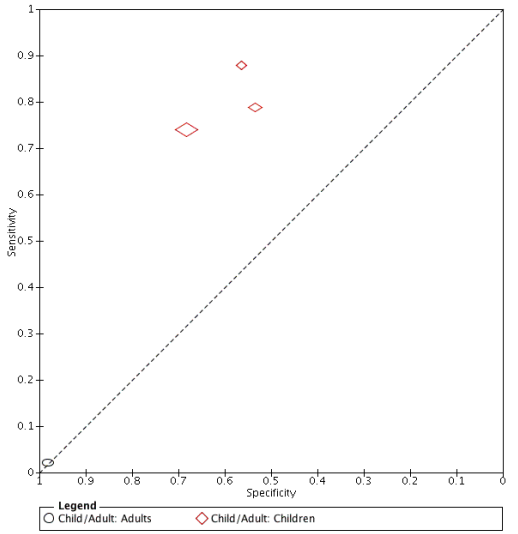
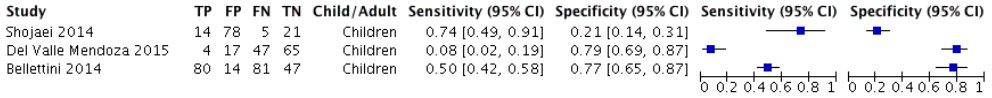
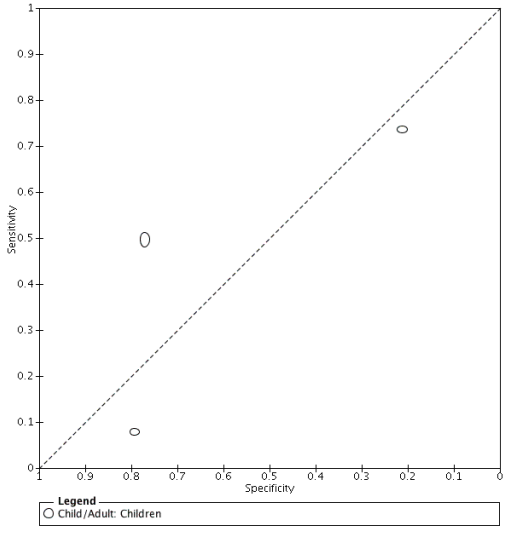


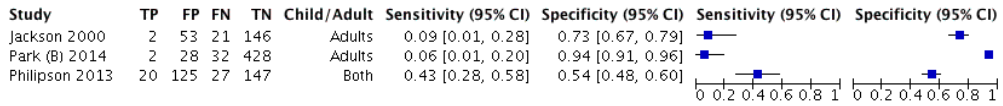
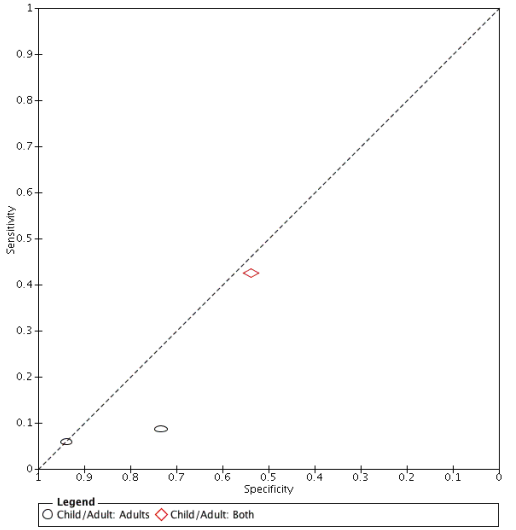
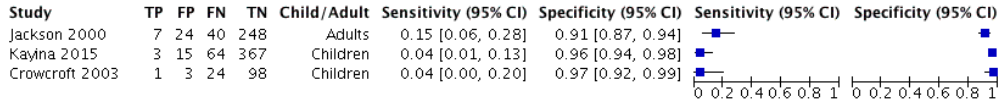
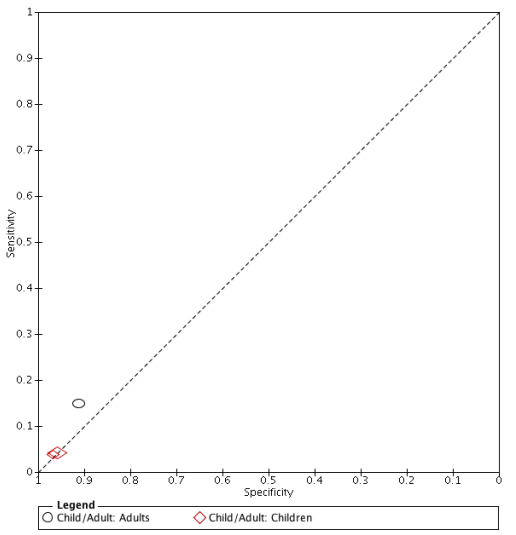
Headache

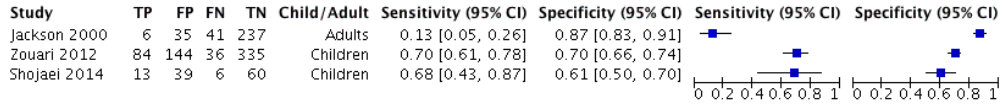
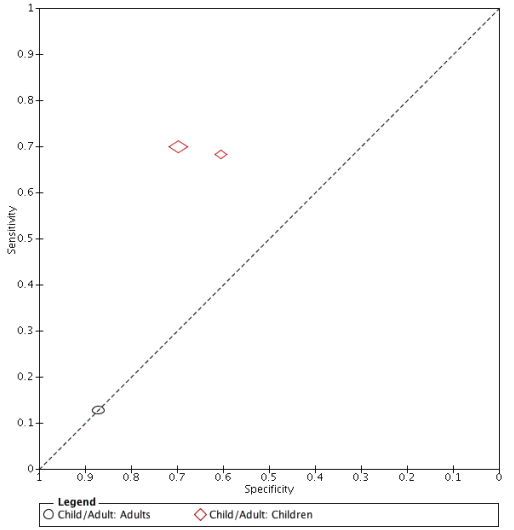
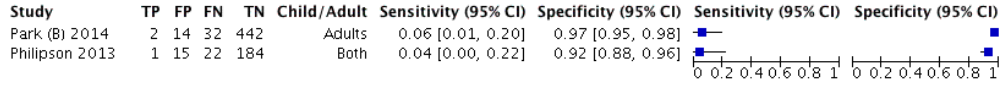
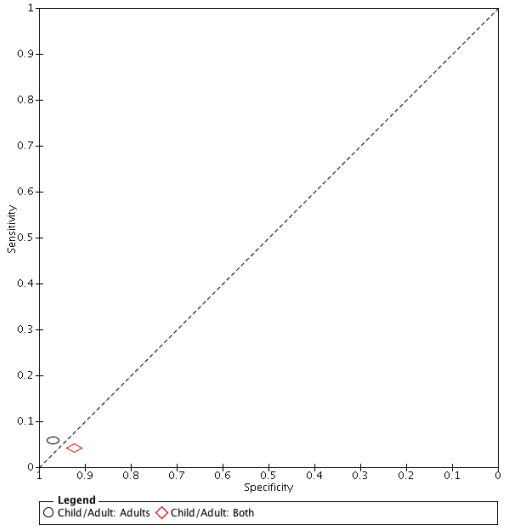
Study	TP	FP	FN	TN	Child/Adult	Sensitivity (95% CI)	Specificity (95% CI)
Siriyakorn 2016	3	16	11	46	Adults	0.21 [0.05, 0.51]	0.74 [0.62, 0.84]
Park (B) 2014	3	68	31	388	Adults	0.09 [0.02, 0.24]	0.85 [0.81, 0.88]
Jackson 2000	26	152	21	120	Adults	0.55 [0.40, 0.70]	0.44 [0.38, 0.50]
Philipson 2013	14	144	9	55	Both	0.61 [0.39, 0.80]	0.28 [0.22, 0.34]
Harnden 2006	29	63	35	44	Children	0.45 [0.33, 0.58]	0.41 [0.32, 0.51]

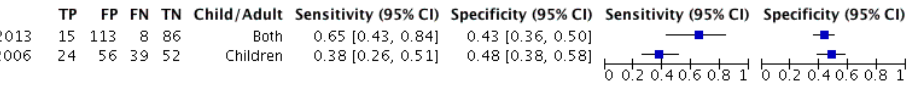
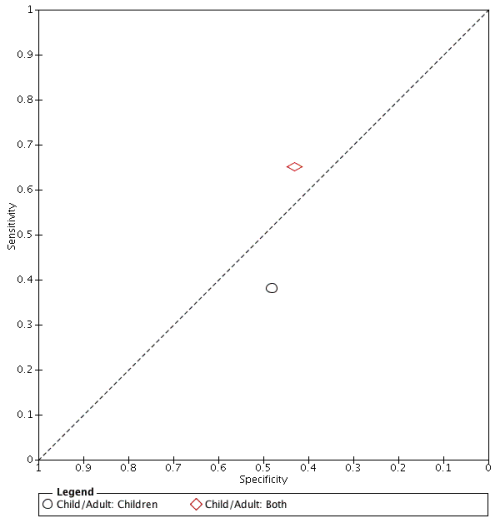
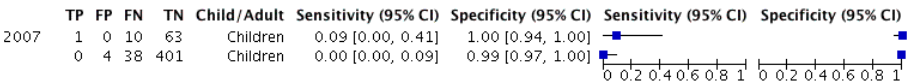
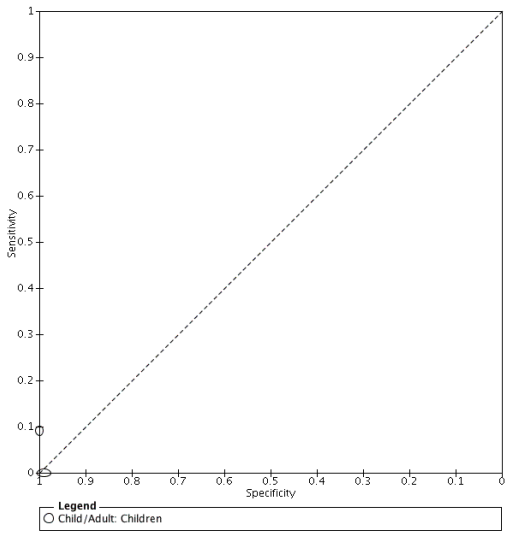


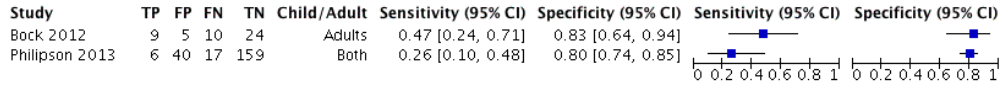
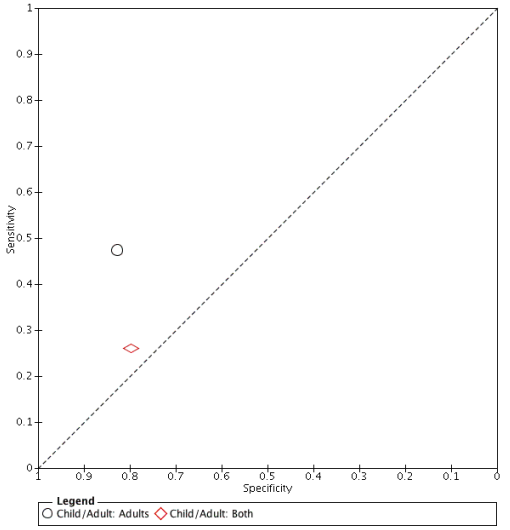
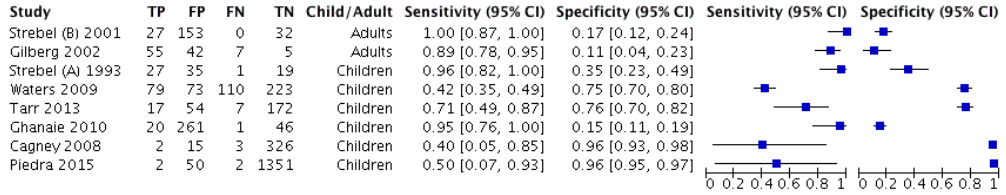
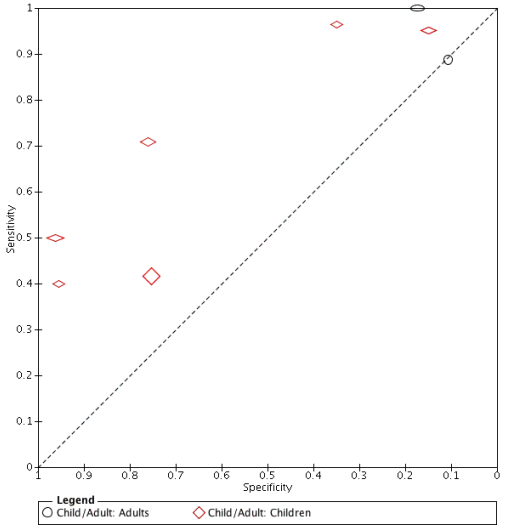
Clinical characteristic	Described as	Forest plot	SROC plot
Chest pain	Chest pain Chest/rib pain Pleuritic pain Breathlessness/chest pain		
Feeding difficulties	Feeding difficulties before admission Breast feeding problems Inadequate oral intake Aphagia		

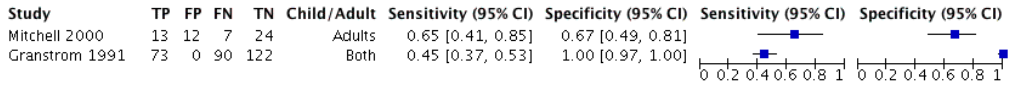
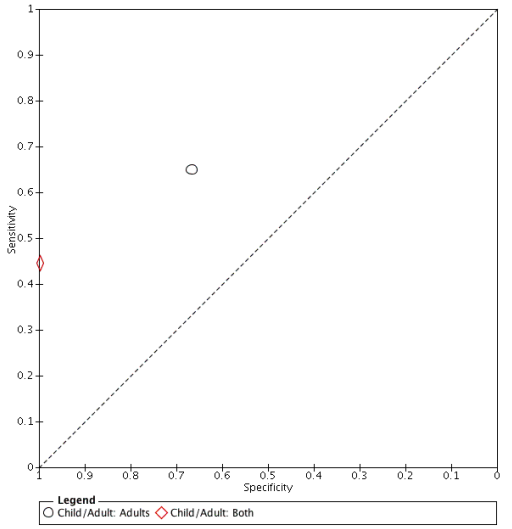
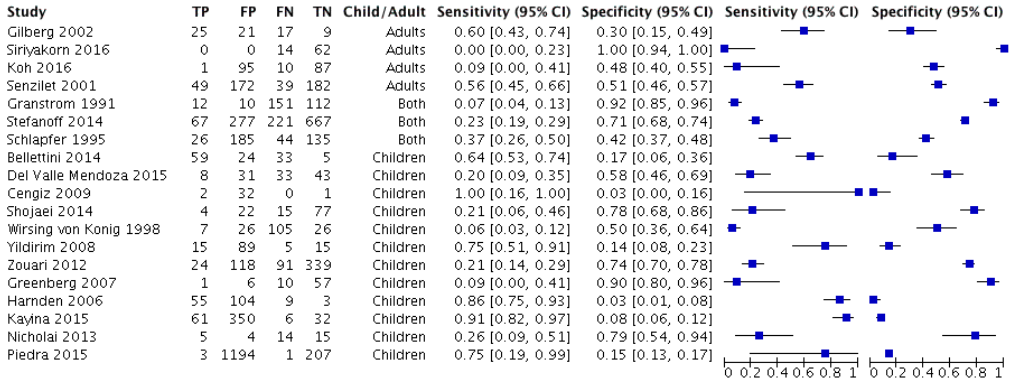
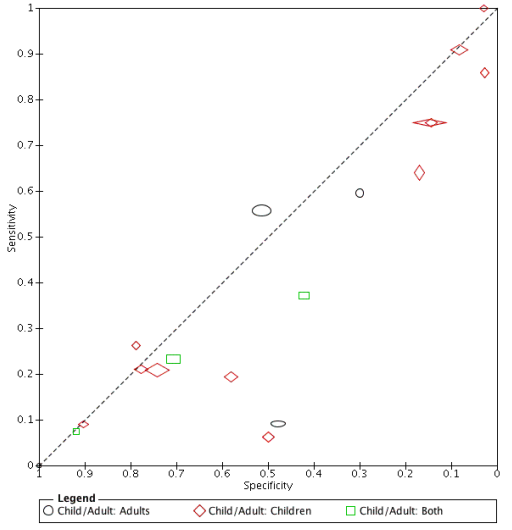
Clinical characteristic	Described as	Forest plot	SROC plot
Lymphocytosis	Lymphocytes > =50% Lymphocytes >= 11,000 cell/ml Lymphocytosis > 10000/mm3 Lymphocytosis (>=10000/ul)		
Facial discolouration	Facial discolouration Plethora Redness		

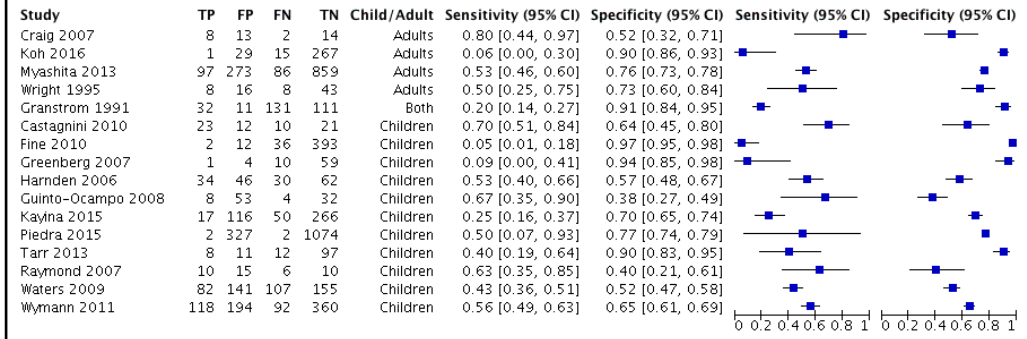
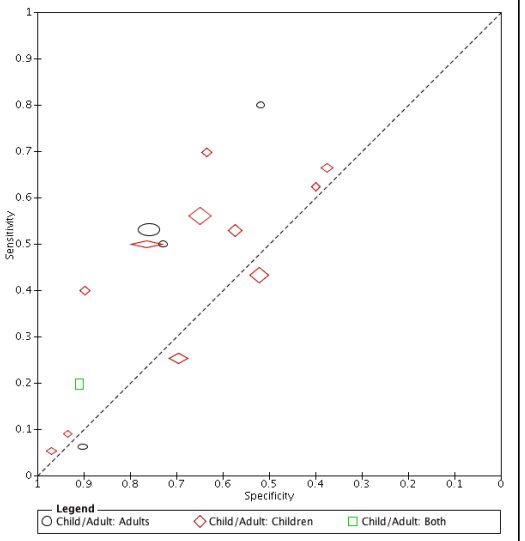
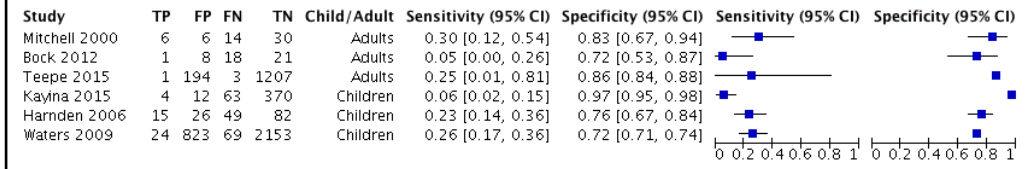
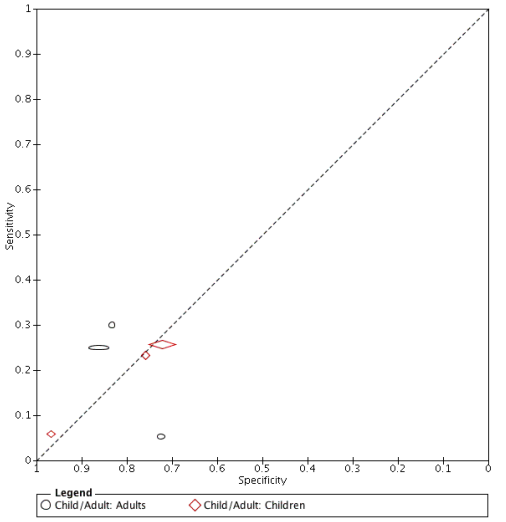
Clinical characteristic	Described as	Forest plot	SROC plot
Myalgia	Myalgia Other muscle pain		
Conjunctival changes	Conjunctival haemorrhage Conjunctival injection Conjunctivitis		

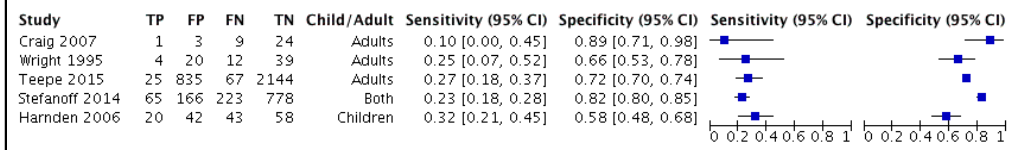
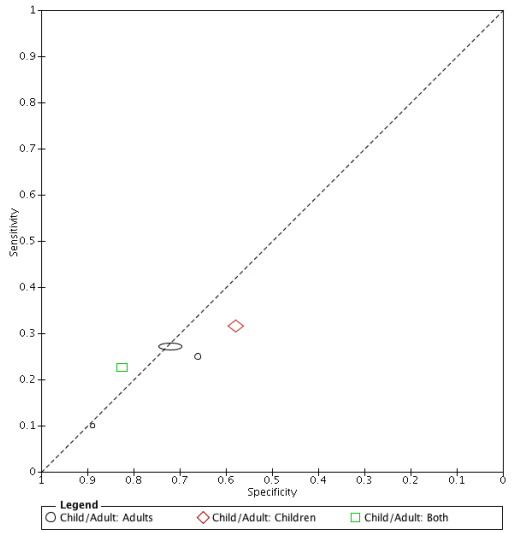
Clinical characteristic	Described as	Forest plot	SROC plot
White blood cell count	WCC > 10000 cells/ml Leukocytosis (>=15000/uL WBC >= 16,000 cell/ml		
Fatigue	Malaise Tiredness		

Clinical characteristic	Described as	Forest plot	SROC plot
Sweating	Sweating		
Seizure	History of seizure Convulsions		

Clinical characteristic	Described as	Forest plot	SROC plot
Post-tussive syncope	Post-tussive syncope Dizziness		
CLINICAL JUDGEMENT			
Meets CDC/WHO clinical definition	Clinical diagnosis – CDC Clinical diagnosis – WHO		

Clinical characteristic	Described as	Forest plot	SROC plot
Clinical suspicion	Physician/clinical diagnosis of pertussis Initial clinical diagnosis		
PATIENT DEMOGRAPHICS			
Vaccinated	At least one vaccination		

Clinical characteristic	Described as	Forest plot	SROC plot
Exposure to contact	Sick household member Exposed to persistent cough (Household) exposure to pertussis Cough in family member Contact with cough Contact with known/suspected whooping cough Known exposure to pertussis Reported contact with pertussis		
Co-morbidity	Major co-morbid condition Comorbidity Pre-existing medical conditiosn History of COPD History of asthma HIV status Pre-existing chest diseases		

Clinical characteristic	Described as	Forest plot	SROC plot
Smoking	Current smoker Smoker in household		
Previous whooping cough	Whooping cough history Previous similar cough Previous (diagnosis of) pertussis