

Additional file 2: Assessment of methodical quality, risk of bias and sources of clinical heterogeneity

Instrument:

For each domain, reviewers independently answered the standardized key questions (yes, no or unclear) and assessed the risk of bias for the respective domain (low, high or unclear). In Domain A reviewers also rated their concern that the selection of patients and/or of GPs may have introduced substantial variation/ clinical heterogeneity (low, high or unclear).

Domain A and B referred to all studies regardless of the respective study outcome. Domain C was only considered if the respective study reported data on the underlying aetiologies of cough patients. Domain D was only considered if the respective study presented prognostic outcomes. In Domain C and D, key questions had to be answered separately for each diagnostic or prognostic category respectively.

Domain A: Selection of patients and GPs (refers to all studies regardless of the review question)	
Item 1	Was the symptom to be investigated clearly described?
Item 2	Were the selection criteria of the patients clearly described?
Item 3	Was a consecutive or random sample of patients enrolled?
Item 4	Was it a multi-centre study?
<i>Judgement: Risk that the selection of patients introduced bias: low, unclear, high</i>	
Item 5	Did the selection criteria of the patients permit the study population to represent the full spectrum of those presenting with the symptom in the respective setting/ addressed in the review question?
Item 6	Were the participating health care professionals/ institutions representative for the setting to be investigated in the review.
<i>Judgement: Concern that the selection of patients and GPs introduced substantial variation or clinical heterogeneity: low, unclear, high</i>	
Domain B: Data collection and patient flow (refers to all studies regardless of the review question)	
Item 7	Were data about the symptom und the inclusion criteria collected directly from the patients (as opposed to a proxy like a register, routine documentation)
Item 8	Was the same mode of data collection used for all patients?
Item 9	Was the number of non-responders/ dropouts unlikely to affect the results?
<i>Judgement: Risk that the mode of data collection and/ or patient flow introduced bias: low, unclear, high</i>	
Domain C: Determination of the underlying aetiology/ diagnostic work-up (refers only to review question "What are the underlying conditions and their respective frequencies (differential diagnosis)?"). Had to be answered for each diagnostic category separately.	
Item 10	Was the aetiologic category clearly defined?
Item 11	Was the diagnostic work up likely to correctly classify the respective aetiology?
Item 12	Did every patient receive the same diagnostic work up to detect the respective aetiology?
<i>Judgement: Risk that the diagnostic work up introduced bias: low, unclear, high</i>	
Domain D: Determination of the prognosis/ prognostic work-up (refers only to review question "What is the prognosis of patients with the respective symptom presenting in the respective setting?") Had to be answered for each prognostic category separately.	
Item 13	Was the prognostic outcome clearly defined?
Item 14	Did the study design include a comparison group without the symptom?
Item 15	Was the work up/ measurement likely to correctly classify the respective prognostic outcome?
Item 16	Did every patient receive the same work up/ mode of data collection to verify the respective prognostic outcome?
<i>Judgement: Risk that the prognostic work up introduced bias: low, unclear, high</i>	

Detailed results:

Domain A (Selection of patients and GPs) and domain B (Data collection and patient flow)

Study	Domain A								Domain B			
	Item 1	Item 2	Item 3	Item 4	Risk of bias in selection of patients and GPs	Item 5	Item 6	Substantial variation in selection of patients and GPs	Item 7	Item 8	Item 9	Risk of bias in data collection and patient flow
Ajmi 2011	-	-	?	+	?	+	+	low	?	+	+	low
Albert 2011	-	-	+	-	high	-	-	high	+	+	-	?
BEACH	-	?	+	+	low	+	+	low	+	+	+	low
Ben Abdelaziz 2004	-	+	+	-	?	+	+	low	+	+	+	low
Coenen 2004	+	+	+	+	low	-	+	?	+	+	-	?
CONTENT Laux 2007	-	-	?	+	?	+	+	low	-	+	+	?
CONTENT Leutgeb 2014	-	?	?	-	?	+	-	?	-	+	+	?
French 2005	+	+	+	-	high	+	+	low	+	+	+	low
GRACE Butler 2009; Godycki-Cwirko 2011; Stanton 2010; Van Vugt, Butler 2012	+	+	+	+	low	?	+	?	+	+	-	?
GRACE Francis 2012; Hordijk 2014; Van Vugt 2015; Wood 2011	+	+	+	+	low	?	+	?	+	+	+	low
GRACE Teepe 2015	+	+	+	+	low	?	+	?	+	+	?	low
GRACE Van Vugt, Broekhuizen 2012; Van Vugt, Broekhuizen 2013	+	+	+	+	low	-	+	high	+	+	+	low
Hamre 2005	+	+	+	+	low	?	?	?	+	+	+	low
Harding 1980	-	+	+	+	low	+	?	?	+	+	+	low
Hofmans-Okkes 1993 International Study	-	-	+	+	low	?	?	?	+	+	+	low
Hofmans-Okkes 1993 Dutch Study	-	-	?	?	?	?	?	?	+	+	+	low
Hull 1969	+	+	+	-	high	?	+	?	+	+	+	low
Liu 2017	-	?	+	-	high	+	+	low	+	+	+	low
Martin 1984	-	+	?	-	high	?	-	high	+	+	+	low
Mash 2012	-	?	+	+	low	+	-	high	+	+	+	low
Molony 2016	-	+	+	-	high	+	+	low	-	+	+	?
Morrell 1971/1972	-	+	?	-	high	-	?	high	+	+	?	low
Munyati 2005	+	+	+	-	high	-	+	high	+	+	+	low
NAMCS Metlay 1998	-	-	?	+	?	+	+	low	+	+	?	?
NAMCS Schappert 1999	-	?	+	+	low	+	+	low	+	+	+	low
Nantha 2014	+	-	?	-	high	+	+	low	+	+	-	?
Njalsson 1992	-	-	?	+	low	+	+	low	-	+	+	?
Robertson 1981	-	-	+	-	high	+	+	low	+	+	+	low
SESAM 2 Frese 2008	-	+	+	+	low	+	+	low	+	+	+	low
SESAM 2 Frese 2016	-	+	+	+	low	-	+	high	+	+	+	low
Silva 1998	-	+	+	+	low	+	+	low	+	+	+	low
Stefanoff 2014	+	?	?	+	?	?	?	?	+	+	-	?
TRANSITION Hofmans-Okkes 1993	-	-	+	+	low	+	+	low	+	+	+	low
TRANSITION Okkes 2002	-	?	+	+	low	+	+	low	+	+	?	low
Verzantvoort 2018	-	?	+	+	low	?	-	high	+	+	+	low
Wong 2016	+	+	+	+	low	?	+	?	+	+	-	?
Woolnough 1985	-	-	+	-	high	?	+	?	+	+	?	?
Worrall 2008	+	-	+	-	high	+	+	low	+	+	+	low

Legend: + Yes, - No, ? Unclear

Domain C (Determination of the underlying aetiology of cough / diagnostic work-up)

		Domain C			
Study	Aetiologic category	Item 10	Item 11	Item 12	Risk of bias in diagnostic work-up
CONTENT Laux 2007	R78 acute bronchitis / bronchiolitis, R96 asthma, R79 chronic bronchitis, R95 COPD, R80 influenza, R77 laryngitis / tracheitis acute, R71 pertussis, R81 pneumonia, R75 sinusitis acute / chronic, R84 malignant neoplasm bronchus/lung, R76 tonsillitis acute, R74 Upper respiratory infection acute (ICPC process codes)	-	?	-	high
French 2005	asthma, GERD, URTI	-	?	?	?
GRACE Francis 2012	LRTI, URTI, viral / other RTI, pneumonia	-	?	-	high
GRACE Stanton 2010	chronic bronchitis / bronchiectasis	-	?	-	high
GRACE Teepe 2015	pertussis	-	+	+	low
GRACE Van Vugt, Broekhuizen 2012	acute bronchitis / bronchiolitis	-	-	+	high
	suspected malignancy	+	?	+	?
GRACE Van Vugt 2015	influenza	-	+	+	low
GRACE Wood 2011	asthma, COPD	-	?	-	high
Morrell 1972	acute bronchitis, chronic bronchitis, common cold, influenza, laryngitis / tracheitis, pertussis, pneumonia	-	?	-	high
Munyati 2005	asthma, cryptococcosis, fibrotic lung disease (post-tuberculous disease, idiopathic diffuse fibrosis), heart failure, HIV-associated, LRTI, pneumocystis pneumonia, bacterial pneumonia, tuberculosis, cancer (pulmonary / cutaneous Kaposi sarcoma)	+	+	+	low
NAMCS Metlay 1998	acute bronchitis / bronchitis not specified as acute or chronic 466/490, URTI 465, asthma 493, acute / chronic rhinosinusitis 461/473, pneumonia 481-483/485-486, influenza 487, pharyngitis 462, nasopharyngitis / common cold 460 (ICD-9-CM process codes)	-	?	-	high
Nantha 2014	ACE-inhibitor induced, bronchial asthma, acute bronchitis, COPD, GERD, heart failure, pneumonia, post infectious cough, lung cancer, pulmonary tuberculosis, upper airway cough syndrome	+	+	?	?
SESAM 2 Frese 2008	acute laryngitis / tracheitis, exacerbation chronic bronchitis / COPD, influenza, pneumonia, asthma	-	?	-	high
Stefanoff 2014	pertussis	+	+	-	high
TRANSITION Okkes 2002	R74 upper respiratory infection (head cold), R78 acute bronchitis / bronchiolitis, R77 acute laryngitis / tracheitis, R75 sinusitis acute / chronic, R80 influenza (proven), R96 asthma, R81 pneumonia, R76 tonsillitis acute, R91 chronic bronchitis / bronchiectasis, R95 emphysema /COPD, R71 whooping cough, K77 heart failure (ICPC process codes)	-	?	-	high
Woolnough 1985	bronchospasm	+	+	+	low
Worrall 2008	asthma, croup, influenza, pneumonia, viral RTI	-	?	-	high
<i>Legend: + Yes, - No, ? Unclear, ACE = Angiotensin-converting-enzyme, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, ICD-9-CM = The International Classification of Diseases 9th revision Clinical Modification, ICPC = International Classification of Primary Care, LRTI = lower respiratory tract infection, RTI = respiratory tract infection, URTI = upper respiratory tract infection</i>					

Domain D (Determination of the prognosis / prognostic work-up)

		Domaine D				
Study	Prognostic category	Item 13	Item 14	Item 15	Item 16	Risk of bias in prognostic work-up
Coenen 2004	reconsultation, hospitalization	+	-	?	?	?
GRACE Butler 2009	median time to patients reporting feeling recovered, median time for patients' symptom severity scores to drop to 0	+	-	+	+	low
	admitted to hospital	+	-	?	+	?
GRACE Coenen 2013	median time for patients' symptom severity scores to drop to 0	+	-	+	+	low
GRACE Godycki-Cwirko 2011	reported recovery, median duration of cough after presentation	+	-	+	+	low
	admitted to hospital, reconsultation	+	-	?	?	?
GRACE Hordijk 2014	hospitalized for this illness episode during the 28 day follow up period, reconsulted their GP for this LRTI episode, absent of work/school for a mean of	+	-	?	?	?
	mean symptom severity score at day 1, mean symptom severity score at day 28, steepest decline in symptom scores, felt recovered after 4 weeks, not feeling recovered at 28 days, total illness duration, mean	+	-	+	+	low
GRACE Van Vugt, Butler 2012	hospitalized, died, re-consultation rate	+	-	?	?	?
	stated they felt recovered at 14 days, prolonged illness (>3 weeks)	+	-	+	+	low
GRACE Van Vugt, Broekhuizen 2013	mortality, admitted to hospital	+	-	?	?	?
Hamre 2005	at day 1: first improvement, at day 3: first improvement, at day 7: major improvement + complete recovery, at day 7: complete recovery, at day 14: major improvement + complete recovery, at day 14: complete recovery	+	-	+	+	low
Harnden 2006	total duration of cough, 2 months after the start of their symptoms still coughing	+	-	+	+	low
Wong 2016	mean time for cough recovery	+	-	+	+	low
	hospitalisation since first consult, average days of hospitalisation, re-consultation to health professional	+	-	?	?	?
<i>Legend: + Yes, - No, ? Unclear</i>						