# 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?
Judgeme	ent: Risk that the selection of patients introduced bias: low, unclear, high
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.
	ent: Concern that the selection of patients and GPs introduced substantial variation or clinical neity: low, unclear, high
	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?
Judgeme	ent: Risk that the mode of data collection and/ or patient flow introduced bias: low, unclear, high
"What a answere	C: Determination of the underlying aetiology/ diagnostic work-up (refers only to review question re the underlying conditions and their respective frequencies (differential diagnosis)?"). Had to be d 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?
Judgeme	ent: Risk that the diagnostic work up introduced bias: low, unclear, high
Domain the prog	
Domain the prog	ent: Risk that the diagnostic work up introduced bias: low, unclear, high D: Determination of the prognosis/ prognostic work-up (refers only to review question "What is nosis of patients with the respective symptom presenting in the respective setting?")
Domain the prog Had to b	D: Determination of the prognosis/ prognostic work-up (refers only to review question "What is nosis of patients with the respective symptom presenting in the respective setting?") e answered for each prognostic category separately.
Domain the prog Had to b Item 13	D: Determination of the prognosis/ prognostic work-up (refers only to review question "What is nosis of patients with the respective symptom presenting in the respective setting?")         e answered for each prognostic category separately.         Was the prognostic outcome clearly defined?
Domain the prog Had to b Item 13 Item 14	Determination of the prognosis/ prognostic work-up (refers only to review question "What is nosis of patients with the respective symptom presenting in the respective setting?")         e answered for each prognostic category separately.         Was the prognostic outcome clearly defined?         Did the study design include a comparison group without the symptom?

### **Detailed results:**

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

Study         F         N         F         N         F <th></th> <th colspan="3">Domain A</th> <th colspan="4">Domain B</th>		Domain A			Domain B								
Study         Fig. 6         Fig. 6 </th <th></th>													
Alber 2011       -       -       +       -       -       high       +       +       -       ?         BEACH       -       ?       +       +       low       +       +       +       H       low       +       +       +       H       low         Ben Abdelaziz 2004       -       +       +       +       H       low       -       +       +       H       low         Connem 2004       +       +       +       +       H       low       -       +       +       -       ?         CONTENT Laux 2007       -       ?       +       +       H       low       +       +       +       ?       ?       +       +       +       ?       ?       +       +       +       ?       ?       ?       +       +       +       ?       ?       ?       +       +       +       ?       P       ?       +       +       +       P       P       +       +       P       P       +       +       P       P       P       +       +       P       P       P       P       +       +       P       P	Study	Item 1		Item 3	Item 4		Item 5	Item 6	Substantial vari- ation in selection of patients and GPs	Item 7	Item 8	Item 9	Risk of bias in data collection and patient flow
Alber 2011       -       -       +       -       -       high       +       +       -       ?         BEACH       -       ?       +       +       low       +       +       +       H       low       +       +       +       H       low         Ben Abdelaziz 2004       -       +       +       +       H       low       -       +       +       H       low         Connem 2004       +       +       +       +       H       low       -       +       +       -       ?         CONTENT Laux 2007       -       ?       +       +       H       low       +       +       +       ?       ?       +       +       +       ?       ?       +       +       +       ?       ?       ?       +       +       +       ?       ?       ?       +       +       +       ?       P       ?       +       +       +       P       P       +       +       P       P       +       +       P       P       P       +       +       P       P       P       P       +       +       P       P	Ajmi 2011	-	-	?	+	?	+	+	low	?	+	+	low
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Ben Abdelaziz 2004       -       +		-	?	+	+		+	+		+	+	+	low
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CONTENT Leutgeb 2014       -       ?       ?       +		-	-	?	+		+	+		-	+	+	
French 2005       +       +       +       +       +       Iow       +       +       +       +       Iow         GRACE       Godyck-Cwirko 2011;       +       +       +       +       +       +       ?       +       +       +       +       -       ?         Godyck-Cwirko 2011;       +       +       +       +       +       +       ?       +       +       +       +       +       ?       +<		-	?	?	-	?	+	-		-	+	+	
GRACE       Butler 2009;       Gravicki-Cwirko 2011;       +       +       +       +       +       +       +       ?       +       +       +       ?         Stanton 2010;       Van Vugt, Butler 2012;       +       +       +       +       +       ?       +       +       +       +       ?       ?       +		+	-		_		+	+		+	+	+	
Francis 2012; Hordijk 2014; Woan Vugt 2015; Wood 2011       +	GRACE Butler 2009; Godycki-Cwirko 2011; Stanton 2010; Van Vugt, Butler 2012	+	+	+	+		?	+		+	+	-	
GRACE       Van Vugt, Broekhuizen 2012;       +       +       +       +       high       +       +       +       low         Hamre 2005       +       +       +       +       low       ?       ?       ?       +       +       +       low         Harding 1980       -       +       +       +       low       +       ?       ?       +       +       +       low         Hofmans-Okkes 1993       -       -       +       +       low       ?       ?       ?       +       +       +       low         Hofmans-Okkes 1993       -       -       ?       ?       ?       ?       ?       +       +       +       low         Hull 1969       +       +       +       -       high       +       +       tow       +       +       +       low         Mash 2012       -       ?       +       +       tow       +       +       tow       +       +       tow         Morell 1971/1972       -       +       ?       high       +       +       tow       +       +       ?       low         MAMCS Metlay 198	Francis 2012; Hordijk 2014; Van Vugt 2015; Wood 2011	+	+	+	+	low		+		+	+		
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		+	-	+	-			+	low	+	+	+	low
	Legend: + Yes, - No, ? Unclear												

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

			D	omai	n C
Study	Aetiologic category	Item 10	Item 11	ltem 12	Risk of bias in diagnostic
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,	acute bronchitis / bronchiolitis	-	-	+	high
Broekhuizen 2012	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 bronchits / 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
disease, GERD revision Clinical	<ul> <li>No, ? Unclear, ACE = Angiotensin-converting-enzyme, COPD = chronic o = gastroesophageal reflux disease, ICD-9-CM = The International Classific Modification, ICPC = International Classification of Primary Care, LRTI = lo respiratory tract infection, URTI = upper respiratory tract infection</li> </ul>	cation	of Dis	sease	s 9th

### 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-	reported recovery, median duration of cough after presentation	+	-	+	+	low
Cwirko 2011	admitted to hospital, reconsultation	+	-	?	?	?
	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	+	-	?	?	?
GRACE Hordijk 2014	mean symptom severity score at day 1, mean symptom severity score at day 28, streepest decline in symptom scores, felt recovered after 4 weeks, not feeling recovered at 28 days, total illness duration,mean	+	-	+	+	low
GRACE	hospitalized, died, re-consultation rate	+	-	?	?	?
Van Vugt, Butler 2012	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
	mean time for cough recovery	+	-	+	+	low
Wong 2016	hospitalisation since first consult, average days of hospitalisation, re-consultation to health professional	+	-	?	?	?
Legend: + Yes, ·	- No, ? Unclear					