

**Supplement Table S1.1a**

**Prospective studies on children with chronic wet cough that included management (diagnosis and Rx) outlining the evidence for presence of PBB (part KQ 1)** [modified with permission from Chest 20016;149:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

Abbreviations for all tables are in the footnote of the last table

1 <sup>st</sup> author, publication year; country	Setting ; Study design	Inclusion criteria; Exclusion or definitions	N enrolled, N completed; Follow-up length; Age	Main aim(s) of study	Primary findings relating to KQ	Proportion with PBB <sup>A</sup> in cohort; Definition used; Symptoms and signs	Duration of cough; other comment
Asilsoy,{4030} 2008 Turkey	Single center, Pediatric OPD; cohort	>4 w cough; Exc: NR	N=108, N completed=108 FU:NR Mean age=8.4 y range 6-14	“evaluate children with cough in accordance with the 2006 ACCP guidelines”{4030}	56 had wet cough: BE=3; 36 treated 10 d with clarithromycin =PBB=25. Of 56 post AB Rx, 14 had subsequent dry cough and 10 treated with inhaled corticosteroid	23%; Chronic (>4 w) moist cough and resolution of cough within 2-4 w with clarithromycin, (15 mg/kg/d) for 10 d; Wet cough; signs not described	Not described for PBB grp; mean duration of entire cohort=4.2 mo SD 4.9 Unclear what were outcomes of others with wet cough
Chang{5797} 2015 Australia <sup>@</sup>	Multi-center, Resp OPD; cohort	Aged <18 years >4 w cough newly referred Exc: chronic respiratory illness	N of cohort=346, N completed=326; Follow-up=12 mo for Dx, 6 mo post Dx Mean age=4.5 y, SD 3	In children newly referred for chronic cough, to describe data relating specific cough pointers of the 3 most common etiologies	In those with wet cough, OR of 73.7 (95%CI 10, 544.2) for finding an etiology where ABs was effective	42%; Resolution of wet cough resolved with 2 w of amox-clav; Of 138 with PBB, wet cough=100%, exertional dyspnea=3.5%; creps=1.4%; hyperinflation=1.4%	Median=20 w (IQR 10-40)  Likelihood ratios, sensitivity, specificity of the different symptoms/signs presented
Darelid{2263} 1993 Sweden	3 centers Pediatric	Aged 0.5-6 y, persistent cough >10 d.	N cohort=88; N completed=87# FU=3 mo;	Whether 7 d of erythromycin clinically	88% cured (d 7) in erythromycin group vs. 36% in controls	Cohort was not called PBB; All with cough,	Study included as 50% had a cough

	c OPD; open RCT	Exc: acute otitis media, pneumonia, allergy, tonsillitis, cardiac dis, suspected pertussis	Median age group=13-24 mo (IQR NR)	improves children 0.5-6y of age with a cough <sup>+</sup> >10 d	(p<0.006)	<sup>+</sup> vomiting or cough night attacks=34%, not eating or playing as usual=61%, <sup>+</sup> bronchial secretions noises=20%, wheeze=5% ( <sup>+</sup> as described by authors)	>21 d. Authors confirmed that the cough was wet (as in Cochrane review{2752}).
Gedik{606 2}, 2015, Turkey	Single center, pediatric or Allergy dept; Cohort	Aged < 17 y, persistent cough >4 w. Exc: known chronic resp, neuromuscul ar, growth, or cardiac problems, syndromes, or prematurity	N=563, N completed=563 FU:NR Mean age=5.4 SD 3.8	The evaluation of children with chronic cough and aged-based etiological factors	85 children had wet cough and all underwent FB. Amox- clav (2-4 w) given to 81. Cough resolved in 67 (78.8%), and changed from wet to dry in remaining 14 who were then Rx with ICS with resolution of the cough. Remaining children: vascular ring (n=1) and TBM (n=3)	11.9% of cohort; Chronic wet cough, with and resolution of the cough to ABs within 2–4 w; By definition, no other symptoms or signs present	Not described for PBB grp; mean duration of entire cohort 2.8 ± 2.7 mo; Other aetiology found in those with cough pointers{5954} based on clinical findings and CXR changes.
Gottfard{ 1877} 1994 Sweden	3 centers Pediatric OPD; DB RCT	Lower resp tract infection with cough >10 d, >11 coughing attacks in 24 hours. Exc: pneumonia, acute otitis media,	N cohort=52; N completed=52# FU=14 d; Median age=2.6-2.7 y (IQR NR)	“To investigate the nasopharyngeal flora of children with persistent cough and the effects of Rx with amoxil- clavulanate” <sup>+</sup> {1877}	“AB treated group had significantly better recovery in both in both the pediatricians estimation (p=0.02) and independent parental judgement (p=0.002)”{1877}	Cohort was not called PBB; A composite score that included post- tussive vomiting, crepitations and rales was used but proportion with other symptoms and signs were not reported	Mean duration of cough was 3-4 weeks (spread NR). Authors confirmed that the cough was wet (as in Cochrane review{2752}).

		clinical suspicion of pertussis					
<b>Karabel{5644} 2014 Turkey</b>	Single center, Resp OPD; cohort	>4 w cough Exc: Nuromuscular, cardiac, syndromes, Resp infection in last 4 w	N cohort=270, N completed=270, FU=12 mo Mean age=6.5 y range 7 mo-17 y	To determine the etiology of chronic cough in children using the ACCP guidelines	Children Dx with PBB when cough resolved with 2 w of clarithromycin	6%; “regression of sputum cough after 15 mg/kg/d clarithromycin”{5444} for 10 d; other symptoms and signs not mentioned	Duration of cough in cohort was not reported
<b>Marchant {3095} 2006 Australia</b>	Single center, Resp OPD, cohort	>3 w cough, age <18 y and newly referred Exc: known chronic dis	N cohort=108; N completed=103 FU=12 mo; Median age=2.6 yr (IQR 1.2-6.9)	In children with chronic cough, to; (a) evaluate the use of an adult-based algorithmic approach in the management, (b) describe the etiology	Cough resolved in 43 in cohort with chronic wet cough treated with 2 w of amox-clav (termed protracted bacterial bronchitis)	42%; PBB=chronic moist cough, positive BAL culture ( $10^5$ cfu/ml), and resolution to ABs within 2 w; Probable PBB=chronic moist cough and either positive BAL culture ( $10^3$ or $4$ cfu/ml) or response to ABs (cough resolution within 2 w); Wet cough only (no other symptoms), none had abnormal signs	Not described for PBB grp; median duration of entire cohort=6 mo (IQR 3 to 12)
<b>Marchant {5280} 2012 Australia</b>	Single center, Pediatric and resp OPD;	Aged 0.5-18 y, doctor observed wet cough >3 w; Exc: chronic lung, cardiac	N cohort=50, N completed=47 FU=2 w Mean=1.8-2.8 y IQR=0.9-5.3	Efficacy of 2 w of oral amoxil-clav (compared with placebo) in achieving cough resolution in	Amoxil-clav effective for wet cough: Cough resolution rates (48%) in amox-clav group vs placebo (16%), $p=0.016$	Of the 50 children, FB performed in 37 and all BAL consistent with PBB; Wet cough only (no other symptoms),	Median cough duration in amox-clav arm=15 (IQR 8.5-59) w, placebo=11 (4-28); BAL in subgroup

	DB RCT	neuro- development dis, ABs in last 2 w, acutely unwell		children with chronic wet cough		none had abnormal signs	(n=37) indicate PBB
Usta,{5929 } 2014 Turkey	Single center, pediatric allergy OPD; cohort	Inclusion: NR Exc: cardiac or chronic dis, prematurity, neuro- development, , chest wall deformity, smoking, clubbing, unable to perform spirometry	N cohort=156, N completed=156, FU=max 18 mo for Dx, NR post Dx; Mean age=8.4 y SD 2.6	“Evaluate assessment and Mx of chronic cough in children according to the British Thoracic Society guidelines”	Most common diagnosis was “post nasal drip” and asthma	12% of cohort; 19 of the 23 (82.6%) of those with wet cough had PBB; Isolated chronic productive cough that resolves within 2 w of clarithromycin (15 mg/kg/d); Other symptoms and signs not mentioned	Not described for PBB grp; mean duration of entire cohort=4mo SD 3.2; British Thoracic Society guidelines{3882} recommends 4-6 w of ABs; Authors wrote PBB Dx after other underlying conditions excluded but results suggest otherwise

**Supplementary Table S1.1b**

**Retrospective studies on children with chronic wet cough that included management (diagnosis and Rx) outlining the evidence for presence of PBB (part KQ 1)** [modified with permission from Chest 20016;149:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

First author, publication yr, country	Setting	Inclusion criteria; Exclusion	N; Age; FU length	Main aim(s)	Primary finding relating to KQ	Proportion with PBB <sup>A</sup> in cohort; Definition used; Symptoms and signs	Duration of cough; other comment
Donnelly{3644} 2007, England	Single center, Resp OPD; review of clinic letters (random)	“Persistent, wet cough present for 1 mo that resolves with appropriate AB Rx”	81; Median age=3.8 y (range 0.4, 14.8); FU=NR	To present “results of a retrospective review of outcomes in 81 randomly selected patients diagnosed with PBB”	95% cured with AB use; 48% reported ‘wheeze’ but had ‘rattle’	95%; Def: wet cough $\geq$ 1 mo that resolves with AB Symptoms: wheeze=48%, dyspnea=43%, Signs: rattle~48% (article reported almost all with wheeze), coarse inspiratory and expiratory noises=“a minority”	59% coughing for >1 yr; BE in 4 of 14 who had chest CT; 31% with concomitant ‘asthma’
Kompare{5095} 2011, USA	Single center, Resp & allergy OPD	Cough, wheeze or noisy breathing of >1 mo without other diagnoses, infected BAL ( $\geq 10^4$ cfu/ml) and response to $\geq 2$ w ABs	70 in cohort (cough=51) Summary age NR; FU=NR	Review of all infected BAL of children aged <5y with cough, wheeze or noisy breathing of >1 mo without other diagnoses, to determine if PBB was present	Outcome data (available in 87%): symptoms resolved with AB Rx in all but one child. Length of AB was $\geq 2$ w	73% with cough; PBB not defined in paper but implied def=BAL with $10^4$ cfu/ml Of those with cough, wheeze present=31%, “noisy breathing”=18% Wheeze + noisy breathing=6%	Median=5 mo (range 1-60 ); Tracheo- or broncho-malacia=74%; Asthma=2.9%

Pritchard{5767} 2014, England	Single center, Pediatric or Resp OPD	AB responsive wet cough confirmed by a positive BAL culture (undefined)	43 (+1 lost to FU); Median age=2.7y (IQR 1.5, 4); FU=11.3 mo (IQR 8.3-14.7)	Review of outcomes for children with AB responsive wet cough with positive BAL culture	Cough resolved in 77% after initial AB course (6-8 w) but only 24% remained cough free i.e high relapse rate	100% Def=AB responsive wet cough; Other symptoms and signs not described	Median=11 mo (IQR 9-14.7); Of the 10 whose cough did not resolve after 2 w ABs, 6 required prolonged AB course, 3 had other conditions
Smith{5958} 1985, USA	Resp OPD, Chart review	Presence of chronic bronchitis by FB evaluation. Exc: CF or other abnormality that could contribute to chronic bronchitis	20, FU=NR; Mean age=5.7y (range 0.5-15)	To investigate clinical, allergic, immunologic and physiological characteristics of children with chronic bronchitis	Existence of chronic bronchitis, 9 of the 11 treated with AB clinically improved; 6 of the 26 with chronic bronchitis had other causes (tracheostomy, BPD, BE, emphysema, lung abscess, foreign body)	PBB not used in paper; Def=Not applicable; “All judged to have experienced benefit from bronchodilator therapy”, the symptoms and signs not described	Authors concluded that chronic bronchitis in children is distinct from adults  None had CT scan; thus likely some had BE as length of symptoms were 1 w to 15 y
Wang,{6061} 2015; China	Single centre, Hospitalised in children's hosp, unclear how children were identified	Chronic cough (>4 w) without acute lower resp infection and no response to conventional Rx. Excl: heart dis, immune-deficiency, pulmonary dysplasia, neuromuscular dis, foreign body	66 with wet cough of which 50 had PBB; median age=10 mo (5.8-14 <sup>3</sup> )	To describe the clinical characteristics children aged < 3 y with PBB	Cough resolved in 76% of PBB group, children treated with amox-clav for 17.4 ± 9.0 d (max 22 d)	75.8%; Def: (a) isolated chronic wet cough; (b) positive BAL culture or neutrophilia (> 3.5%); and (c) resolution of cough with ABs within 2 w; (d) absence of alternative etiology. Wheeze=90%, stridor=4%	Mean cough 10.0 (± 1.6 <sup>3</sup> ) weeks; Although this was a retrospective study, parents completed a daily cough diary for 28 d post enrolment and all Rx with amox-clav, airway malacia in 44%.

**Supplement Table S1.2: Current national pediatric chronic cough guidelines [from Pediatric Pulmonology 2016{5970}]**

First author, publication year	Country	Society	PBB mentioned or specified	Definition used*
Chang{3101} 2006	Australia	Thoracic Society of Australia and New Zealand	Yes	PBB-clinical $\pm$ PBB-micro
Chang{3114} 2006	USA	American College of Chest Physicians	Yes	Chronic wet cough and response to 2-4 w of ABs
Gibson{4718} 2008	Australia	Australian Lung Foundation	Yes (pediatric section)	PBB-clinical $\pm$ BAL
Kohno{3700} 2006	Japan	Japanese Respiratory Society	No	Not applicable
Leconte{4575} 2008	Belgium	Primary care	Yes	Not defined
Lu{5927} 2014	China	Multiple societies	Yes (based on translated article)	PBB-clinical $\pm$ BAL
Shields{3882} 2008	England	British Thoracic Society	Yes	Chronic wet cough and response to 4-6 w of ABs
Zacharasiewicz{5928} 2014	Austria	Austrian Society of Pediatrics, Austrian Society of Pneumology	Yes	PBB-clinical $\pm$ BAL

\*Original microbiologic-based case definition{3095}(also termed PBB-micro). (i) Presence of chronic wet cough (>4-weeks), (ii) Lower airway infection (recognized respiratory bacterial pathogens growing in sputum or at BAL at density of a single bacterial species  $\geq 10^4$  colony-forming units/mL); and (iii) Cough resolved following a 2-week course of an appropriate oral AB (usually amoxicillin-clavulanate)

PBB-clinical (modified clinical-based case definition{3101, 5970}) = (i) Presence of chronic wet cough (>4-weeks); (ii) Absence of symptoms or signs of other causes of wet or productive cough<sup>^</sup>; and (iii) Cough resolved following a 2-week course of an appropriate oral AB (usually amoxicillin-clavulanate). [<sup>^</sup>Specific cough pointers{3114, 3101, 1192} are: chest pain, history suggestive of inhaled foreign body, dyspnea, exertional dyspnea, hemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sino-pulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis, signs of respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles, chest radiographic changes (other than perihilar changes), lung function abnormalities].



**Supplement Table S1.3a: Prospective studies involving children with protracted bacterial bronchitis [modified with permission from Chest 2006;134:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]**

1 <sup>st</sup> author, publication yr; country	Setting ; Study design	Inclusion criteria; Exc or definitions	No. enrolled, No. completed; Age	Main aim(s)	Key findings of the PBB component	Specimen; microbiology results	Other main findings
Marchant, {3095} 2006; Australia	Single center, Resp OPD	>3 w cough, age <18 y and newly referred Exc: NR	No. with PBB=43; Median age of whole cohort=2.6 y (IQR 1.2-6.9)	In children with chronic cough, to; (a) evaluate the use of an adult-based algorithmic approach in the management, (b) describe the etiology	BAL median total cell count and neutrophil% in PBB ( $350 \times 10^6/L$ , 40%) was significantly higher than 'natural resolution' group (228, 4%)	BAL; Hi=47%, Spn=35%; Mcat=26%	
Marchant, {4395} 2008; Australia	Single center, Resp OPD; cross-sectional	PBB=chronic wet cough (>3 w), BAL bacterial culture ( $\geq 10^5$ CFU/mL) & response to Abs (cough resolved 2 w); Other etiologies =other chronic cough aetiologies in cohort,{3095} Controls=children with stridor, but without chronic cough	PBB=38, other Dx=25, SR=22, controls=15; Respective median age (IQR): 2.4 y (0.9-4.2), 2.6 y (1.1, 9.6), 3.8 y (0.9, 6.8), 2.8 y (0.6, 9.8)	To: (a) describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL of children with PBB compared to children with other etiologies and controls without cough , (b) explore selected innate immunity signaling receptors, specifically TLR-2,-4	BAL in PBB group had significantly elevated total cell counts, airway neutrophilia, IL-8, and active MMP-9 compared to other groups  TLR-2 and -4 mRNA relative expression ratio in BAL of PBB group was significantly higher than controls	BAL; Hi=45%, Spn=32%; Mcat=24%	IL-8 levels significantly correlated with BAL neutrophil% and MMP-9
Chang,{5188} 2012; Australia	Single center, Resp	PBB=chronic wet cough, response to ABs with	Current PBB=61, PBB well=20,	To determine whether BAL levels of hBD2, SP-A, and MBL: (a)	hBD2 and MBL levels in BAL were significantly higher in children with	BAL; microbiology NR	SP-A levels in the BAL and cytokine production of



	OPD; cross-sectional	resolution of cough within 2 w & absence of signs/symptoms of other dis; PBB well = previous PBB, but no cough when FB done	Controls=21; Respective mean age (SD) =2.5 y (2.3), 4.2 y (3.0), 2.2 y (2.8)	differed between children with current PBB, PBB well, and controls; and (b) related with airway neutrophilia and endobronchial infection	PBB compared with PBB well group and controls. hBD2 levels were associated with airway infection and are related to airway neutrophilia and MBL		stimulated BAL cells similar between groups.
Marchant, {5280} 2012; Australia	Single center, Pediatric and resp OPD; RCT	Aged 0.5-18 y, doctor observed wet cough >3 w; Exc: chronic lung, cardiac or neuro-developmental disorders, ABs in last 2 w or if acutely unwell	50, 3 lost to FU that were analyzed as failures. Mean=1.8 y for Rx gp and 2.8 y for placebo group	Efficacy of 2 w of oral amox-clav (compared with placebo) in achieving cough resolution in children with chronic wet cough	Amox-clav effective for wet cough- cough resolution rates (48%) in amox-clav group vs placebo (16%), p=0.016	BAL; Hi=38%, Spn=24%; Mcat=19% All amox-clav sensitive	BAL in subgroup (n=37): Results consistent with PBB
Wurzel{5646} 2014; Australia	Single center, Resp OPD; cross-sectional	PBB=clinical def; Controls=chronic resp symptoms, but no PBB, CSLD	PBB=104, Controls=21; Respective median age (IQR)=19mo (12-30), and 20mo (8-63)	To provide extensive clinical, laboratory, and BAL characterization of PBB	Previous parent-reported wheeze (81%), but no increased propensity to atopy (IgE and RAST normal). Normal immunoglobulin levels and antibody responses (Hib and tetanus vaccines)	BAL; In PBB grp; Hi=72%, Spn=39%; Mcat=43%; AdV=23%; Any virus=38%	PBB and childcare attendance elevated serum NK-cell levels; Tracheo-broncho-malacia common, but similar rates in controls
Baines,{5693} 2014; Australia	Single center, Resp OPD; exp & validation cohorts	PBB=clinical definition; Resolved PBB =previous PBB, but no cough at FB	Exp: PBB=21; Controls=33; Respective mean ages= 2.3 and 9.7 y; Validation: PBB=36; Controls=11;	To evaluate the IL-1 and TNF- $\alpha$ /NF- $\kappa$ B pathways and mediators in 2 cohorts of PBB and control children	Increased expression of neutrophil-related mediators in PBB, including IL-1 pathway members, neutrophil $\alpha$ -defensins, and the chemokine receptor CXCR2	BAL: Microbiology NR	IL-1 $\beta$ protein levels correlated with BAL neutrophilia & duration and severity of cough symptoms

			Respective mean ages=2.0 and 0.7 y				
Wurzel,{5712} 2014; Australia	Single center, Resp OPD; cross-sectional	PBB=clinical def; BE=Dx on CT scan	PBB=159, BE=112; Median (IQR) age: PBB with AdV=17mo (12-22), PBB without AdV=26mo (15-56)	To identify: (a) the prevalence of AdV; (b) diversity of genotypes and species (c) whether presence of AdV increased the odds of bacterial coinfection	AdV-C (genotypes 1, 2) was the major AdV species in BAL; lower airway bacterial infection, (with Hi, Mcat and Spn, but not Sa) increased in those with AdV	BAL; In AdV+ grp; Hi=68%, Spn=39%; Mcat=35%. In AdV- grp; Hi=47%, Spn=22%; Mcat=19%	Younger age independent predictor of AdV with respiratory bacteria co-infection
Van der Gast,{5715} 2014; USA and Australia	Multi-center, Resp OPD; cross-sectional	PBB=clinical def; BE=Dx on CT scan; CF=sweat test	PBB=12, BE=19; CF=25; Respective mean (SD) age: 8.9 y (4.7), 2.3 y (1.7), 12.5 y (3.5)	To compare: (a) the core and satellite microbiota in cohorts of children with different diseases; (b) the respiratory metacommunities in PBB and pediatric and adult CF and BE cases	Similar resp sample core microbiota in the 3 diseases; microbiota from adults with CF and BE differed significantly from each other and from those of children with the same dis	BAL and sputum; traditional and non-traditional organisms described	
Chang,{5797} 2015; Australia	Multi-center, Resp OPD	PBB=clinical definition	PBB=138, asthma=52, BE=20, self-resolved=40 Median age (IQR) PBB=2.4 yr (1.2, 4.8) BE=3.9 (2.2, 6.4) Self resolved=5.2 (2.1, 8.2)	In children newly referred for chronic cough, to describe data relating specific cough pointers of the 3 most common etiologies	At presentation (preDx), cough score,{938} PC-QOL, PedQL scores, number of doctors' visits between groups were similar	Not applicable	Likelihood ratios, sensitivity, specificity of the different symptoms/signs presented

Hodge{59 52} 2016; Australia	Single center, Resp OPD; cross- section al	PBB-micro; Controls=no cough and FB undertaken for other reasons (e.g. stridor); BE=CT defined with clinical symptoms	PBB=13, BE=55, controls=13. Median ages and IQR: PBB=6.5 mo (1.6, 14) BE=22 mo (14, 33) Controls=5.5 (4, 9.9)	(a) Quantify phagocytosis of airway apoptotic cells and NTHi by alveolar macrophages in children with PBB and BE; (b) Determine if phagocytic capacity was associated with clinical or demographic variables, and differing patterns of airway inflammation	Macrophage phagocytic capacity significantly lower in PBB and BE c.f. controls (p=0.003 and <0.001 for efferocytosis and 0.041 and 0.004 for phagocytosis of NTHi; PBB and BE respectively); median phagocytosis of NTHi: BE=13.7% (IQR 11-16%) PBB=16% (11- 16%), controls=19.0% (13-21%); median efferocytosis: BE=14.1% (10-16%), PBB=16.2% (14-17%), controls=18.1% (16-21%)	NR	IL-1 $\beta$ levels significantly correlated BAL %neutrophil (r=0.93 p=0.0001). Negative, but non- significant correlations between IL-1 $\beta$ and phagocytosis of apoptotic cells or NTHi (r= -0.37 p=0.080, -0.43 p=0.099 respectively)
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**Supplementary Table S1.3b: Retrospective studies on children including children with protracted bacterial bronchitis** [modified with permission from Chest 20016;149:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

First author, publication yr; country	Setting; Study design	Definition of PBB used	No. in study; Age	Main aim(s)	Key finding(s)	Specimen; microbiology	Other main findings	Comment
Donnelly, {5644} 2007; England	Resp OPD; review of clinic letters (random)	Persistent, wet cough present for 1mo that resolved with “appropriate” AB Rx	81; Median=3.8 y (range 0.4, 14.8)	Review the outcomes in 81 randomly selected patients diagnosed with PBB	95% cured with AB use; 48% reported ‘wheeze,’ but had a ‘rattle’ instead	BAL (n=19), Cough swab (n=51). Of infected specimens (~50%): Hi=81% Spn=37%	59% symptomatic for >1yr; BE in 4/14 who had chest CT scan; 31% with concomitant ‘asthma’ (BDR demonstrated or responsive to steroids)	Not all children had PBB based on original definition of PBB
Kompare, {5095} 2011; USA	Resp & allergy OPD	Cough, wheeze or noisy breathing for >1 mo without other diagnoses, BAL ( $\geq 10^4$ CFU/mL) and response to $\geq 2$ w AB Rx	70; Summary age NR	Review all BAL ( $\geq 10^4$ CFU/mL) cultures of children aged <5 y with cough, wheeze or noisy breathing for >1 mo without other diagnoses so as to determine if PBB was present	Tracheo- or broncho-malacia present in 74%;	BAL Hi=56%, Spn=37%; Mcat=59%	Outcome data (available in 87%): symptoms resolved with AB Rx in all but one child	Bronchitis itself may cause malacia
Narang,{5776} 2014; England	Pediatric and Resp OPD; 50 consecutive notes	Suspected PBB (ND)	50; Median age=2.9 y (IQR 1.7, 4.4)	Review BAL and chest radiograph results, and assess the bacterial distribution across lung lobes	Bacterial distribution in PBB was heterogeneous	BAL Hi=50%, Spn=16% Mcat=28% Sa=22%	Limiting sampling to 1-2 lobes will underestimate the microbiology of the lung (70% positive versus 82%)	Positive culture undefined as quantitative culture was not done

Priftis,{59 41} 2013; Greece and England	Resp OPD	Children with chronic cough suspected of PBB who had FB to confirm diagnosis	Greece=18 England=39 ; Median age=4.8 y (range 0.9, 14.4)	To (a) determine specific serotypes of Spn and NTHi in BAL samples; (b) compare Spn serotypes between the 2 countries and Spn vaccination	PCV-13 Spn serotypes in all Greek BALs, but only in 72% of English BALs (significantly different b/w countries)	Greek BAL; Hi=61%, Spn=27.6%; Mcat=32% Sa=6%; English BAL restricted to Spn+ specs	Vaccine Spn serotypes rarely found in immunized children (OR=0.02; 95%CI 0.003-0.115); 26 NTHi isolates (English BAL) had unique genotypes	Recent or current AB use NR. Evidence of serotype replacement dis in Spn immunized children
Pritchard, {5767} 2014; England	Pediatric and Resp OPD	AB responsive wet cough and positive BAL culture	43; Median =2.7 y (IQR 1.5, 4)	Review of Rx outcomes for children with PBB	Cough resolved in 77% after initial AB course (6-8 w) but only 24% remained cough free (ie. 76% relapsed)	BAL; Hi=63%, Spn=23%; Mcat=51% Sa=19%	Of the 10 whose cough did not resolve after 6-8 w ABs, 7 required prolonged ABs and 3 had other resp conditions	BE more likely to be present when wet cough unresponsive to 4 w of ABs.{5600} Thus likely some in cohort did not have PBB
Rother{59 73} 2015, Germany	Single centre, tertiary hosp	NA with respect to key question. Children with an established diagnosis of asthma, PCD, PBB, acute bronchitis, CF or pneumonia.	18 children with PBB	“To develop and test a questionnaire- based and data mining-supported tool providing diagnostic support for selected pulmonary diseases”		No data	Def: Chronic cough (>8 w), BAL neutrophilia (>15%), positive BAL culture ( $\geq 10^5$ cfu/ml), no underlying diseases (e.g. CF, PCD, immunodeficiency, UACS) and cough improve/resolved within 6 w ABs (amoxicillin 60-80 mg/kg/d in most)	Information obtained from authors

**Supplement Table S2.1: Studies on children presenting with chronic wet (productive) cough that included investigations (but excludes research mechanistic studies) and diagnoses of the cough (part key question 2)**

[modified with permission from Chest 20016;149:120-142 {6008} and Pediatric Pulmonology 2016{5970}]

First author, pub yr, country	Setting ; Study design	Inclusion criteria; Exclusion (Exc)	N; Age; FU length	Main aim(s)	Primary findings relating to KQ	Specimen type; Bacteriology^	Other major findings or comment
Aluoch{5957} 1984, Kenya	Single center; General OPD, Prosp cross sectional	Aged >6 yr, first attendance with main complaint of cough, sputum (>1 mo) or hemoptysis; Exc: NR	N=601; N with sputum=601; median age NR and study included adults; FU=NR	Yield of tuberculosis from systemic examination of first presentation	Yield of active tuberculosis cases (bacteriology confirmed)=5.5% of cohort; 0% of those aged <15 y; 2.6% in 15-24 y. No difference in yield when cough duration grouped by 1-3 mo vs. 4-12 mo	Sputum; Other than TB, no other pathogens reported	Wet cough was not mentioned but as sputum obtained in all, productive cough present. Results dependent on smear + culture, thus, results would grossly under-estimate pediatric TB prevalence
Asilsoy,{4030} 2008 Turkey	Single center, Pediatric OPD; cohort	Chronic cough (>4 w) Exc: NR	N=108, N completed =108 FU:NR Mean age= 8.4 y range 6-14	“Evaluate children with cough in accordance with the 2006 ACCP guidelines”{4030}	94.5% success of determining etiology. Causes of wet cough found in 40% (PBB, BE, TB, congenital malformation)	NR	ACCP guidelines recommends investigating if the wet cough persists after 4 w ABs or if specific cough pointers present
Chang{2789} 2006 Australia	Single center; Resp OPD, Prosp cross section	Children undergoing FB without a known underlying resp Dx	N=106; Median age=2.6 y, IQR 5.7 FU=NR	Compare (a) cough quality (wet/dry and brassy/non-brassy) to FB findings of secretions and	Parent's assessment of cough quality (wet/dry) agreed with clinicians' (Kappa= 0.75, 95%CI 0.58–0.93). Clinicians marginally better than	NR	BAL total cell count and airway neutrophilia was significantly higher in those with wet cough

	al			tracheomalacia respectively, (b) parent's vs clinician's evaluation of cough quality (wet/dry).	parent's when compared to secretions seen during FB (aROC = 0.85 95%CI 0.77, 0.92)		
Chang{5444} 2013 Australia	Multicenter, Resp OPD, RCT	Aged <18 y, >4 w cough, newly referred; Exc: known chronic resp illness	N enrolled=270, N completed =253 FU=12 mo for Dx, 6 mo post Dx; Mean=4.5 y, SD=3.7	Determine if Mx according to a standardized clinical Mx pathway improves clinical outcomes	Earlier application of the pathway led to earlier cough resolution and improved parental quality of life	NR	Pathway{4921} recommends Ix when cough pointers are present and when wet cough does not resolve after 4 w of ABs
Chang{5797} 2015 Australia	Multi-center, Resp OPD; cohort	Aged <18 years >4 w cough newly referred Exc: chronic respiratory illness	N cohort=346, N completed =326; Follow-up=12 mo for Dx, 6 mo post Dx Mean age=4.5 y, SD 3	In children newly referred for chronic cough, to describe data relating specific cough pointers of the 3 most common etiologies	Children were investigated if wet cough not resolved after 4 w of Rx or if specific cough pointers present	NR	In those with wet cough, OR=73.7 (95%CI 10, 544.2) for finding an etiology where ABs was effective
Coren{2210} 1998 England	Uni-center; General OPD, Prosp cross section	All CT scans undertaken over 12 mo. Exc: NR	102 children had 106 CTs. FU=NR; Median age = 5 y range 7 w-15 y	To determine whether use of pediatric chest CT scans was appropriate (new Dx and how it influenced Mx)	Of the 48 scans done for chronic (>6 mo) productive cough, 38 (79%) abnormal	NR	Abnormalities: BE=21, interstitial lung dis=1, bronchiolitis obliterans=1, congenital lung emphysema=1, minor changes=14



De Baets{5959} 2012 Belgium	Dual-center; Respl OPD, Prosp cross sectional	“Persistent resp symptoms, productive cough, bronchorrhoea and wheezing for $\geq 3$ mo.” Exc: premature, failure to thrive, CF, prolonged intubation, tracheotomy, dysmorphic, neurology or cardiac problems, CXR consolidation	N=124; FU=NR; Median age=10 mo, (IQR 7-14)	Description of results of diagnostic investigations in children with persistent resp symptoms despite regular asthma Rx	Laryngo-tracho-bronchomalacia in 46%; mucosal inflammation in 79%. Those with mucosal inflammation had airway neutrophilia	Non-quantitative BAL; Culture +ve in 56% NTHi=28%, Spn=13%; Mcat=51% Sa=10% <i>E. coli</i> =4%, <i>K. oxytoca</i> =1% <i>Pa</i> =1%	24-h pHmetry positive in 29%
Douros{5027} 2011, Greece	Allergy-Resp OPD, Retros	Chronic (>6 w) wet cough with FB undertaken for criteria++; Exc: CF, immunodeficiency, neuromuscular disorder, aspiration	93; FU=NR Mean age=5.8 y SD 3.6	In children with chronic wet cough: (a) Comparison of chest CT and FB in detecting airway abnormalities and (b) explore radiologic and FB/BAL associations	(a) FB/BAL superior to CT in detecting abnormal changes (b) Bhalla score correlated with cough duration ( $r=0.23$ , $p=0.028$ )	Quantitative BAL ( $\geq 10^4$ cfu/ml) Hi=37%, Spn=27%; Mcat=18% G-bact=12%; Sa=5% Pa=5%	Bhalla score correlated with FB findings of increasing severity and % neutrophils in BAL and worse bronchoscopic classification{1920}; Response to ABs NR
Gedik{6062}, 2015, Turkey	Single center, pediatric or Allergy dept; Cohort	Aged < 17 y, cough >4 w. Exc: known chronic resp, neuromuscular, growth, or cardiac problems,	N=563, N completed=563 FU:NR Mean age=5.4 SD 3.8	The evaluation of children with chronic cough and aged-based etiological factors	85 children had wet cough and all underwent FB. Amox-clav (2-4 w) given to 81. Cough resolved in 67 (78.8%), and changed from wet to	11.9% of cohort; Chronic wet cough, with and resolution of the cough to ABs within 2–4 w; By definition,	

		syndromes, or prematurity			dry in remaining 14 who were then Rx with ICS with resolution of the cough. Remaining children: vascular ring (n=1) and TBM (n=3)	no other symptoms or signs present	
<b>Goyal{5600} 2014 Australia</b>	Single center; Resp OPD, Retrospective	Chronic wet cough (>4 w) and having completed >4 w of oral ABs directed against likely resp bacteria Exc: asthma, CF, known BE or CT scans requested by oncology, surgical, intensive care, trauma teams	N=144 (106 with BE); FU=NR; Median age=4.7 y (range 0.3-17)	“To determine whether a child with chronic wet cough and poor response to at least 4 weeks of oral ABs is more likely to have BE” (radiologically defined)	Non response to 4 weeks of ABs increased risk of having BE (adjusted OR=20.9, 95% CI 5.4, 81.8). Being Indigenous was also independently associated with BE (adjusted OR=5.9, 95% CI 1.2, 28.5)	NR	Median duration of persistent wet cough=12 mo (range 1.5-144). Cough >12 mo was not significantly associated with presence of BE aOR=3 (0.97, 9.3)
<b>Karabel{5644} 2014 Turkey</b>	Single center, Resp OPD, Prospective cohort	>4 w cough Exc: NM, cardiac, syndromes, RTI in last 4 w	N cohort=270, N completed=270, FU=12 mo Mean age=6.5 y range 7 mo-17 y	To determine the etiology of chronic cough in children using the ACCP guidelines	97 (36%) of cohort had wet cough. All had abnormal CXRs. In accordance to ACCP guidelines, Ix were untaken. Dx were BE=22, TB=2, CF=3, foreign body=2, laryngeal web=1, fistula=2, lymphangioma=1, airway abnormality=4	NR	ACCP guidelines recommends investigating if the wet cough persists after 4 w ABs or if specific cough pointers present
<b>Kompare{5095} 2011,</b>	Resp & allergy OPD;	Cough, wheeze or noisy breathing of >1 mo without	70 in cohort (cough=51) FU=NR	Review of all infected BAL of children aged <5	Tracheo- or broncho-malacia present in 74%	Quantitative BAL ( $\geq 10^4$ cfu/ml)	Outcome data (available in 87%): symptoms resolved

USA	Retrospect	other diagnoses, infected BAL ( $\geq 10^4$ cfu/ml) and response to $\geq 2$ weeks AB Rx	Summary age NR	y with cough, wheeze or noisy breathing of $>1$ mo without other diagnoses, to determine if PBB was present	(note only 51 of the cohort had cough)	Hi=55.7%, Spn=37.1%; Mcat=58.6%	with AB Rx in all but one child
Lim{5960} 2012 England	Single center; Resp OPD; Retrospect	Chronic wet cough ( $>8$ w) attending clinic over a 12-mo Exc: CF	96 children with wet cough, 66 tested; All $>2$ y (summary NR); FU=18 mo	“determine the prevalence of specific antibody deficiency in children with chronic wet cough”{5960}	58% failed to mount an adequate antibody response to Spn polysaccharide 23-valent vaccine, consistent with specific antibody deficiency	7 had “positive culture of bacteria pathogens on resp sample” (types NR)	3 of 5 children who subsequently had CT scans had BE; Duration of cough in cohort NR
Marchant {3095} 2006 Australia	Single center, Resp OPD, Prosp	$>3$ w cough, age $<18$ y and newly referred Exc: NR	N cohort=108 N compl=103 N with chronic wet cough=43; FU=12 mo Median age=2.6 y (IQR 1.2-6.9)	In children with chronic cough, to; (a) evaluate the use of an adult-based algorithmic approach in the management, (b) describe the etiology	Airway malacia present in 35% of cohort; BAL median neutrophil in PBB and total cell count was significantly higher than ‘natural resolution’ group	Quantitative BAL; Hi=47%, Spn=35%; Mcat=26%	
Seear{835} 1997 Canada	Single center, Resp OPD, Prosp	Chronic ( $\geq 3$ mo) productive or rattly cough, with or without wheezing. Exc: known causes of productive cough Controls: children with asthma	N=81 N compl=81 FU:NR Mean age=8.4y range 6-14 y N controls=60	In children with chronic productive cough, “(a) do such diagnostic orphans exist? (b) if so, can they be classified in a clinically useful manner”	All subjects were Ix to determine cause. Chronic bronchitis described but no mention of use of ABs. FB done in 6 of the 34 children	NR	No Rx described

Usta,{5929} } 2014 Turkey	Single center, pediatric allergy OPD; Prosp cohort	Inclusion: NR Exc: prematurity, neurodevelopment, cardiac or chronic dis, chest wall deformity, smoking, clubbing, unable to perform spirometry	N cohort=156, N completed=156, FU=max 18 mo for Dx, NR post Dx; Mean age=8.4 y SD 2.6	“Evaluate assessment and Mx of chronic cough in children according to the British Thoracic Society (BTS) guidelines”	Unclear how many had wet cough. Causes of wet cough found in 14.7% (PBB, BE, TB).  Children Dx with PBB when cough resolved with 2 w of clarithromycin	NR	BTS guidelines{3883} recommends Ix in presence of moist cough with irritability and arching after feeds or choking on feeding and specific cough pointers but not adhered to, in paper
Wang,{6061} 2015; China	Single centre, Hospitalised, children's hosp, retro	Chronic cough (>4 w) without acute lower resp infection and no response to conventional Rx. Excl: heart dis, immunodeficiency, pulmonary or bronchus dysplasia, neuromuscular dis, foreign body aspiration	66 with wet cough of which 50 had PBB; median age=10 mo (5.8–14 <sup>3</sup> )	To describe the clinical characteristics children aged < 3 y with PBB	Other causes of wet cough not described (group described had FB not wet cough not described)  Cough resolved in 76% of PBB group, children treated with amox-clav for 17.4 ± 9.0 d (max 22 d)	BAL (≥10 <sup>4</sup> cfu/ml); Hi=47%, Spn=37%, E. Coli=6% Enterobacter=5% Immune function: IgA, IgM, IgG=normal; subtle difference in lymphocyte subsets c.f. diseased controls	Laryngomalacia=32%, tracheomalacia=14%, bronchomalacia=41% Laryngo-bronchomalacia=9%, tracheobronchomalacia=4%  Unclear how children were identified
Wurzel{5458} 2014 Australia	Single center, Resp OPD, Prosp	Children undergoing FB. Children categorized into wet cough, dry cough, no cough groups;	Wet cough n=143 Median age=26 mo (IQR 15, 60) Dry cough n=18	Examine the relationships between cough nature, lower airway infection and severity of neutrophilic	lower airway bacterial infection, viral infection and viral-bacterial co-infection more likely present in wet cough group compared to those	Quantitative BAL; Wet cough group Hi=34%, Spn=18%; Mcat=15%;	No Rx described

		Exc: CF	Median age=66 mo (IQR 31, 159) FU=NR	airway inflammation	without wet cough	Sa=6% Dry or no cough: Hi=12%, Spn=6%; Mcat=8%; Sa=3%	
Zgherea{5 093} 2012, USA	Single center, Resp OPD, Chart review, Retrospect	Primary symptom of chronic (>4-w) wet cough who had FB. Exc: CF, ciliary dyskinesia, immune- deficiency, aspiration, asthma, genetic, known airway or neuro- muscular disorders	197, FU=NR Mean=NR <3y:55%; 3-7y:36%; >7 y: 9%	“Determine the frequency of lower respiratory tract bacterial infections in children with chronic wet cough and to analyze the bronchoscopic findings”	91% of BAL showed positive bacterial culture ( $\geq 10^4$ cfu/ml) in those with purulent bronchitis	Quantitative BAL NTHi=49%, Spn=20%; Mcat=17% Sa=12%	Tracheo- or broncho-malacia present in 24%; positive culture more likely in those with higher bronchoscopic score{3522} (signifying increased secretions)

**Supplement Table S2.2: Studies that reported on duration of wet cough symptoms to outcomes [modified with permission from Chest 20016;149:120-142 {6008} and Pediatric Pulmonology 2016{5970}]**

1st author, publication y, country	Setting ; Study design	Inclusion criteria; Exclusion (Exc)	N; FU length; Age	Main aim(s)	Key finding(s) relating to KQ	Specimen type; Bacteriology^	Other main findings
Baines,{5693} 2014; Australia	Single center, Resp OPD; exp & validation cohorts	Children with PBB= history of chronic (>4 w) wet cough and a response to AB with cough resolution within 2 w in the absence of signs and symptoms of other diseases. Controls: age matched children undergoing gastroscopy or bronchoscopy without chronic cough or resp illness	Exp: PBB=21; Controls=33; Respective mean age=2.3 and 9.7 y; Validation: PBB=36; Controls=11; Respective mean ages=2.0 and 0.7 y	To evaluate the IL-1 and TNF- $\alpha$ /NF- $\kappa$ B pathways and mediators in 2 cohorts of PBB and control children	Activation of IL-1 signaling predicts PBB recurrence, IL-1 $\beta$ levels at correlated to duration of cough (r=0.29, p=0.049)	BAL; Bacteriology NR	IL-1 pathway signaling molecules ( <i>PELII</i> , <i>IRAK2</i> ) significantly higher at baseline in those with recurrent vs non-recurrent PBB
Douros{5027} 2011, Greece	Allergy-Resp OPD; Retrospect	Chronic (>6 w) wet cough with FB undertaken for criteria++ Exc: CF, immune-deficiency, neuromuscular, aspiration	93; FU=NR Mean=5.8 y SD 3.6	In children with chronic wet cough: (a) Comparison of chest CT and FB in detecting airway abnormalities, (b) explore radiologic and FB/BAL associations	Bhalla score correlated with duration of cough (r=0.23, p=0.028)	Quantitative BAL ( $\geq 10^4$ cfu/ml) Hi=37%, Spn=27%; Mcat=18% Gram negative bacteria=12%; Sa=5% Pa=5%	
Goyal{5600} 2014 Australia	Single center; Resp OPD,	Chronic wet cough (>4 w) and having completed >4 w of oral Abs directed against likely resp	N=144 (106 with BE); FU=NR; Median	“To determine whether a child with chronic wet cough and poor	Cough >12 mo was not significantly associated with	NR	Median duration of persistent wet cough=12 mo

	Retrospect	bacteria. Exc: asthma, CF, known BE or CT scans requested by oncology, surgical, intensive care, trauma teams	age=4.7 y (range 0.3-17)	response to at least 4 weeks of oral ABs is more likely to have BE” (radiologically defined)	presence of BE aOR=3 (0.97, 9.3)		(range 1.5-144).
<b>Pritchard{ 5767} 2014, England</b>	Pediatric and Resp OPD; Retrospect	AB responsive wet cough that had been confirmed by a positive BAL culture	43; Median FU=11.3 mo (IQR 8.3–14.7) Median age=2.7y (IQR 1.5, 4)	Review of outcomes for children with AB responsive wet cough with positive BAL culture	Cough resolved in 77% after initial AB course (6-8 w) but only 24% remained cough free i.e high relapse rate	Non quantitative BAL; Hi=62.8%, Spn=23.3%; Mcat=51.2% Sa=18.6%	Of the 10 whose cough did not resolve after 2 w AB, 6 required prolonged AB course, 3 had other conditions



**Supplement Table S2.3: Mechanistic studies that studied children with chronic wet cough (not related to BE or CF) that are not included in any tables above (copied with permission from Pediatric Pulmonology 2016{5970})**

First author, publication y, country	Setting ; Study design	Cohort of children studied	N in study; Age	Main aim(s)	Key finding(s)	Specimen; microbiology <sup>y</sup>	Other main findings and/or comment
<b>Prospective studies</b>							
<b>Heino{442} 1990 Finland</b>	Single center, Resp OPD; cross sectional	Chronic productive cough (>3 mo) unresponsive to oral ABs and oral bronchodilators	N=7; Age range 5-11 y	Describe ultrastructural nature of epithelial damage in respiratory symptoms	Epithelial inflammation (increased proportion of intercellular spaces and inflammatory cells) and a reduction in number of ciliated cells	NR	All children had early lower respiratory infection  CT scan was not performed. Likely these children had BE (5 had obstructive airways on spirometry)
<b>Marchant {4395} 2008 Australia</b>	Single center, Resp OPD; cross sectional	PBB=chronic wet cough, other etiologies =other causes of chronic cough in cohort{3095}, Controls=children with stridor without chronic cough	PBB=38, other Dx=25, SR=22, controls=15 ; Respective median age (IQR): 2.4 y (0.9-4.2), 2.6 (1.1, 9.6), 3.8 (0.9, 6.8), 2.8 (0.6, 9.8)	(a) Describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL of children with PBB c.f. to other etiology & controls, (b) explore selected innate immunity signal receptors	BAL in PBB group had significantly elevated airway neutrophilia, IL-8, active MMP-9, total cell count c.f. other groups.  TLR-2 and -4 mRNA relative expression ratio in BAL of PBB group significantly higher than controls	Quantitative BAL; Hi=45%, Spn=32%; Mcat=24%	IL-8 levels significantly correlated with BAL neutrophil% and MMP-9

Chang{5188} 2012 Australia	Single center, Resp OPD; cross sectional	PBB, PBB-well (resolved PBB) and controls	Current PBB=61, PBB well=20, Controls=21; Respective mean age (SD) =2.5 y (2.3), 4.2 (3), 2.2 (2.8)	Determine whether BAL levels of hBD2, SP-A, and MBL: (a) differed between children with current PBB, PBB-well, and controls; (b) relates with airway neutrophilia and endobronchial infection	hBD2 and MBL levels in BAL were significantly higher in children with PBB compared with PBB well grp and controls. hBD2 levels were associated with airway infection and are related to airway neutrophilia and MBL	Quantitative BAL; Bacteria: NR	SP-A levels in the BAL and cytokine production of stimulated BAL cells similar between groups.
Wurzel{5646} 2014 Australia	Single center, Resp OPD; cross sectional	PBB, 'diseased controls'= chronic resp symptoms but no PBB, CSLD	PBB=104, Controls=21; Respective median age (IQR)=19 mo (12-30), 20 (8-63)	Provide extensive clinical, laboratory, and BAL characterization of children with PBB	Previous parent-reported wheeze (81%) but no increased propensity to atopy (IgE and RAST normal). Normal immunoglobulin levels, antibody responses (Hi type b, tetanus vaccines)	Quantitative BAL; In PBB grp; Hi=72%, Spn=39%; Mcat=43%; Adenovirus =23%; Any virus=38%	PBB group: significantly increased odds of childcare attendance elevated serum NK-cell levels; Tracheobronchomalacia common but similar rates in controls
Baines{5693} 2014 Australia	Single center, Resp OPD; exp & validation cohorts	PBB, resolved PBB and controls	Exp: PBB=21; Controls=33; Respective mean age =9.7, 2.3 y Validation: PBB=36;	To evaluate the IL-1 and TNF- $\alpha$ /NF- $\kappa$ B pathways and mediators in 2 cohorts of PBB and control children	"Increased expression of neutrophil-related mediators in PBB, including IL-1 pathway members, neutrophil $\alpha$ -defensins, and the chemokine receptor CXCR2"	BAL; Microbia not reported	IL-1 $\beta$ protein levels correlated with BAL neutrophilia, duration and severity of cough symptoms

			Controls=1 1; Respective mean 0.7, 2.0				
<b>Van der Gast{5715 } 2014</b>  <b>USA and Australia</b>	Multi-center, Resp OPD; cross sectional	PBB, BE and CF	PBB=12, BE=19; CF=25; Respective mean age (SD): 8.9 y (4.7), 2.3 (1.7), 12.5 (3.5)	Compare (a) the core and satellite microbiota in cohorts of children with different diseases; (b) the respiratory metacommunities pediatric and adult CF and BE	Similar resp sample core microbiota in the 3 diseases; microbiota from adults with CF and BE differed significantly from each other and from those of children with the same dis	BAL and sputum; traditional and non-traditional organisms described	
<b>Retrospective studies</b>							
<b>Priftis{5941} 2013</b> <b>England, Greece</b>	Resp OPD	Children with chronic cough suspected of having PBB who had FB to confirm diagnosis	England=39, Greece=18; Median=4.8 y (range 0.9, 14.4)	(a) “determine specific serotypes of Spn and NTHi in BAL samples”; (b) compare the Spn serotypes between the 2 countries and Spn vaccination	PCV-13 Spn serotypes in all Greek BALs but only in 71.8% of English BALs (significantly different b/w countries)	Greek BAL; Hi=61%, Spn=27.6%; Mcat=32% Sa=6%; English BAL restricted to Spn+ specs	Spn vaccination related with isolation of Spn serotypes not included in the vaccine  Recent or current AB use not reported
<b>Narang{5776} 2014</b> <b>England</b>	Pediatric + Resp OPD; 50 consecutive notes	Suspected PBB (not defined)	50; Median=2.9 y (IQR 1.7, 4.4)	To (a) “review the FB-BAL and CXR results”, (b) “assess the bacteria distribution across lung lobes”	Bacterial distribution in PBB was heterogeneous	BAL Hi=50%, Spn=16% Mcat=28% Sa=22%	Limiting sampling to 1-2 lobes would miss number of organisms (70% positive instead of 82%) but positive culture was undefined

**Supplementary Table S3.1**  
**Summary of bacteriology on children with chronic wet cough**

<b>Ist Author, publication year; country</b>	<b><i>H. influenzae</i> (Hi)%</b>	<b><i>S. pneumoniae</i> (Spn)%</b>	<b><i>M. catarrhalis</i> (Mcat)%</b>	<b>Other</b>	<b>Quantitative or Non-quantitative culture</b>
Gedik{6062} 2015 Turkey	43.3	23.9	23.9	Sa=3%, S.py=6%	NR
De Baets{5959} 2012 Belgium	28	13	51	Sa=10%, <i>E.coli</i> =4%, <i>K.oxytoca</i> =1%, P.a=1%	Non-quantitative
Zgherea{5093} 2012 USA	49	20	17	Sa=12%	Quantitative
Douros{5644} 2011 Greece	37	27	18	Gram neg bact=12% Sa=5%, Pa=5%	Quantitative
Kompare{5095} 2011 USA	56	37	59		Quantitative
Marchant{3095} 2006 Australia	47	35	26		Quantitative
Chang{3522} 2006 Australia	57.8	57.8	15.6		Quantitative

**Supplement Table S3.2**  
**Summary of bacteriology on children with PBB**

<b>Ist Author, publication year; country</b>	<b><i>H. influenzae</i> (Hi)%</b>	<b><i>S. pneumoniae</i> (Spn)%</b>	<b><i>M. catarrhalis</i> (Mcat)%</b>	<b>Other</b>	<b>&gt;=2 organisms</b>	<b>Quantitative or Non-quantitative culture</b>
Wang{6061} 2015 China	47	37	0	E.coli=6%, Enterobacter=5%	NR	NR
Wurzel{5458} 2104 Australia	72	39	43		50%	Quantitative
Pritchard{5767} 2014 England	63	23	51	Sa=19%	48%	NR
Narang{5776} 2014 England	50	16	28	Sa=22%	39%	Non-quantitative
Wurzel{5712} 2014 Australia	Adv+: 68 AdV-:47	35 22	35 19	Sa=10.2%	NR	Quantitative *some cohort had BE
Van de Gast{5715} 2014, Australia	50	NR	NR	Sa=16%	NR	Quantitative *PBB cohort only
Priftis{5941} 2013 Greece and England	Greek grp: 61	27.6	32	Sa=6%	39%	Quantitative
Marchant{5280} 2012 Australia	38	24	19		NR	Quantitative
Marchant{4395} 2008 Australia	45	32	24		NR	Quantitative
Donnelly{3644} 2007 England	81	37	NR		30%	Cough swab n=50 BAL n=19

**Supplement Table S4.1**

**Studies on children with PBB that included viruses present in lower airways** [modified with permission from Chest 20016;149:120-42,{6008}  
Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

First author, publication yr, country	Setting	Inclusion criteria; Exclusion	N; Age;	Main aim(s)	BAL Microbiology	BAL Viruses	Comments
<b>Wurzel{57 12} 2014; Australia</b>	Single center, Resp OPD; cross-sectional	PBB=clinical def; BE=Dx on CT scan	PBB=159, BE=112; Median (IQR) age: PBB with AdV=17mo (12-22), PBB without AdV=26mo (15-56)  ** BE and PBB children in cohort	To identify: (a) the prevalence of AdV; (b) diversity of genotypes and species (c) whether presence of AdV increased the odds of bacterial coinfection	In AdV+ grp Hi=68% Spn=35% Mcat=35%  In AdV- grp Hi=47% Spn=22% Mcat=19% Sa=10.2%	HAdV-C was the major species detected in 96% HAdV+ children  Younger age risk factor for HAdV+ infection	Lower airway bacterial infection, (with Hi, Mcat and Spn, but not Sa) increased in those with AdV This association disappeared with adjustment for age in multiple logistic regression
<b>Wurzel{54 58} 2014; Australia</b>	Single center, Resp OPD; cross-sectional	<b>PBB=clinical def;</b> Controls=chronic resp symptoms, but no PBB, CSLD	<b>PBB=104,</b> Controls=49;  median age (IQR)=19mo (12-30), and 20mo (8-63)	To provide extensive clinical, laboratory, and BAL characterization of PBB	In PBB grp Hi=72% Spn=39% Mcat=43%	HAdV=23%; Any virus=38% Subset had extended viral panel (n=27 PBB) 67% +ve for any virus; rhinovirus (n=11, 41%), human bocavirus (n=1, 4%), HCoV (n=1, 4%)	Children with PBB more likely to have co-infection Hi and HAdV (p=0.001)

**Supplement Table S5.1a**  
**Summary of BAL cellularity on children with PBB\***

Ist Author, publication year; country	Neutrophil % in BAL (IQR)	TCC in BAL X 10 <sup>6</sup> /L	Comment
Hodge{5952} 2016 Australia	25.5 (5,58)	188 (94,411)	E 0%, No diff E and L with control group
Wang{6061} 2015 China	29.2 (+/- 30.2)	NR	No diff E and L with non-PBB grp
Baines{5693} 2014 Australia	34 (10,44)	365 (196,632)	L increased in PBB grp 125 (IQR 7,22)
Wurzel{5458} 2014a Australia	44 (19,66)	NR	No diff E and L with control grp
Marchant{5280} 2012 Australia	38.5 (13,58)	426 (196,632)	Rx grp listed; placebo similar
Chang{5188} 2012 Australia	41.5 (18,7,69)	305 (157,498)	E 0%, No diff E and L with control group
Marchant{4395} 2008 Australia	43 (11, 75.5)	372.5 (199.5, 1050)	
Marchant{3095} 2006 Australia	40 (10,73)	350 (233, 1000)	

\*Donnelly{3644} (England) also found “BAL cellularity dominated by neutrophils” not specified



**Supplement Table S5.1b: Studies involving children with protracted bacterial bronchitis and association with pathobiology: risk factors, underlying mechanisms, immunity and cellular pathways**

[modified with permission from Chest 20016;149:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

1 <sup>st</sup> author, publication yr; country	Setting ; Study design	Inclusion criteria; Exc or definitions	No. enrolled, No. completed; Age	Main aim(s)	Key findings on pathobiology PBB	Specimen; microbiology results, cell count and differential
<b>Marchant {4395} 2008; Australia</b>	Single center, Resp OPD; cross-sectional	PBB=chronic wet cough (>3 w), BAL bacterial culture ( $\geq 10^5$ CFU/mL) & response to Abs (cough resolved 2 w); Other etiologies =other chronic cough aetiologies in cohort,{3095} Controls=children with stridor, but without chronic cough	<b>PBB=38</b> , other Dx=25, SR=22, controls=15; Respective median age (IQR): 2.4 y (0.9-4.2), 2.6 y (1.1, 9.6), 3.8 y (0.9, 6.8), 2.8 y (0.6, 9.8)	To: (a) describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL of children with PBB compared to children with other etiologies and controls without cough, (b) explore selected innate immunity signaling receptors, specifically TLR-2,-4	BAL in PBB group had significantly elevated total cell counts, airway neutrophilia, IL-8, and active MMP-9 compared to other groups; IL-8 0.67 ng/ml (cf controls 0.06) $p<0.0005$ ; MMP-9 active 7.25 ng/ml (cf controls 0.38) $p<0.0005$ ; IL-8 levels significantly correlated with BAL neutrophil% and MMP-9; TLR-2 and -4 mRNA relative expression ratio in BAL of PBB group was significantly higher than controls (p 0.013, p 0.009 respectively)	BAL: Hi=45%, Spn=32%; Mcat=24%  <u>Cell count:</u> TCC $\uparrow$ 372.5 (IQR 199.5,1050) $p=.002$  Neutro $\uparrow$ = 43% (IQR 11,75.5%) $p<.0005$  Macro $\downarrow$ = 42.5% (IQR, 11,79%) $p<.0005$
<b>Chang{5188} 2012; Australia</b>	Single center, Resp OPD; cross-sectional	PBB=chronic wet cough, response to ABs with resolution of cough within 2 w & absence of signs or symptoms of other dis; PBB well=previous	<b>Current PBB=61</b> , PBB well=20, Controls=21; Respective mean age (SD) =2.5 y (2.3), 4.2 y (3.0), 2.2 y (2.8)	To determine whether BAL levels of hBD2, SP-A, and MBL: (a) differed between children with current PBB, PBB well, and controls; and (b) related with airway	hBD2 and MBL levels in BAL were significantly higher in children with PBB compared with PBB well group and controls.  hBD2 levels were associated with airway infection and are related to airway neutrophilia	BAL; microbiology NR  Current PBB Grp TCC $\uparrow$ 305 (IQR 157,498) $p=.0001$  Neutro $\uparrow$ = 41.5% (IQR

		PBB, but no cough when FB done		neutrophilia and endobronchial infection	and MBL SP-A levels in the BAL and cytokine production of stimulated BAL cells similar between groups.	18.7,69%) p<.0001 Macro ↓= 45.5% (IQR, 26,68.5%) p<.0001 Eos and Lymph % no diff
Wurzel{54 58} 2014; Australia	Single center, Resp OPD; cross-sectional Retrospective	<b>PBB=clinical def;</b> Controls=chronic resp symptoms, but no PBB, CSLD	<b>PBB=104,</b> Controls=49; median age (IQR)=19mo (12-30), and 20mo (8-63)	To provide extensive clinical, laboratory, and BAL characterization of PBB	Risk factor for PBB: attendance at daycare (p=0.001 cf control group); Normal IgG, IgA, IgM, IgG subclasses, and vaccine responses (Hib and tetanus vaccines); Normal propensity to atopy (IgE and RAST normal); Elevated NK-cell levels: median CD56 and CD16 natural killer (NK) cell levels increased for age	<u>BAL micro</u> ( $\geq 10^4$ cfu/ml): In PBB grp; Hi=72%, Spn=39%; Mcat=43%; HAdV=23%; Any virus=38% <u>Cell count:</u> Neutrophils ↑ = 42% (IQR 19-66%) p<0.001 cf controls 4% Neutrophils higher in HAdV+ 43% vs 16% (p=0.044); Macro ↓= 45% (IQR, 24-68%) p<.001 No diff Eos and Lymph Eos: 0% both groups
Wang{606 1} 2015; China	Single centre, Hospitalised, retrosp	<b>Chronic cough (&gt;4 w)</b> without acute lower resp infection and no response to conventional Rx.	66 with wet cough of which <b>50 had PBB;</b> median age=10 mo (5.8–14 <sup>3</sup> )	To describe the clinical characteristics children aged < 3 y with PBB	IgA, IgM, IgG = normal; CD3+ and CD3+CD4+ cells lower in PBB group (p<0.01); CD19+, CD16+CD56+ and CD23+ cells were elevated ; All subtle difference in lymphocyte subsets (vs diseased controls). Lymph subsets did not relate to cough duration/severity	BAL ( $\geq 10^4$ cfu/ml); Hi=47%, Spn=37%, E. Coli=6% Enterobacter=5% <u>Cell count</u> Neutro ↑ = 29.2% (+/- 30.2, p<0.01 cf no-PBB) Macro ↓= 61% (+/- 32.7%, p<0.01) No diff Eos and Lymph
Hodge{59 52} 2016; Australia	Single center, Resp OPD;	PBB-micro; Controls=no cough and FB undertaken for	<b>PBB=13,</b> BE=55, controls=13. Median ages	(a) Quantify phagocytosis of airway apoptotic cells and NTHi by	Macrophage phagocytic capacity significantly lower in PBB and BE c.f. controls (p=0.003 and <0.001 for	BAL data: Micro – NTHi in BAL n=5 PBB (38.4%), n=20 (36.4%) BE cf n=0 controls

	cross-sectional	other reasons (e.g. stridor); BE=CT defined with clinical symptoms	and IQR: PBB=6.5 mo (1.6, 14) BE=22 mo (14, 33) Controls=5.5 (4, 9.9)	alveolar macrophages in children with PBB and BE; (b) Determine if phagocytic capacity was associated with clinical or demographic variables, and differing patterns of airway inflammation	efferocytosis and 0.041 and 0.004 for phagocytosis of NTHi; PBB and BE respectively); Median phagocytosis of NTHi: BE=13.7% (IQR 11-16%) PBB=16% (11-16%), controls=19.0% (13-21%); Median efferocytosis: BE=14.1% (10-16%), PBB=16.2% (14-17%), controls=18.1% (16-21%); IL-1 $\beta$ levels $\uparrow$ in BE and PBB groups (cf controls). IL-1 $\beta$ levels significantly correlated BAL %neutrophil (r=0.93 p=0.0001). Negative, but non-significant correlations between IL-1 $\beta$ and phagocytosis of apoptotic cells or NTHi (r= -0.37 p=0.080, -0.43 p=0.099 respectively)	<u>BAL Cell count PBB:</u> TCC 188 (IQR 94,411)  Neutrophils $\uparrow$ = 25.5% (IQR 5,58%) p=.039  Macro $\downarrow$ = 50% (IQR 21,81%) p=0.002  No diff Eos and Lymph E 0% all groups
Baines{56 93} 2014; Australia	Single center, Resp OPD; exp & validation cohorts	Children with PBB= history of chronic (>4 w) wet cough and a response to AB with cough resolution within 2 w in the absence of signs and	Exp: <b>PBB=21</b> ; Controls=33; Respective mean age=2.3 and 9.7 y; Validation: <b>PBB=36</b> ; Controls=11; Respective	To evaluate the IL-1 and TNF- $\alpha$ /NF- $\kappa$ B pathways and mediators in 2 cohorts of PBB and control children	PBB = $\uparrow$ IL-1 $\beta$ , $\alpha$ -defensin gene and protein expression; $\uparrow$ expression N chemokine receptor CXCR, $\uparrow$ IL-1RA protein in PBB; Activation of IL-1 signaling predicts PBB recurrence, IL-1 $\beta$ levels are correlated to duration of cough and BAL	BAL data: Micro – NR  <u>BAL Cell count PBB:</u> TCC 365 (IQR 196,632)  Neutro $\uparrow$ = 34% (IQR 10,44%) p=.001

		symptoms of other diseases. Controls: age matched children undergoing gastroscopy or bronchoscopy without chronic cough or resp illness	mean ages=2.0 and 0.7 y		neutrophilia (r=0.29, p=0.049); IL-1 pathway signalling molecule significantly higher at baseline in those with recurrent vs non-recurrent PBB; Increased IL-1 $\beta$ pathway activation in PBB	Macro $\downarrow$ = 52% (IQR 43,79%) p=.001  Lymph $\uparrow$ =12% (IQR 7,22) p=.001  Eos= 0% all groups
Other potentially relevant studies						
Grissell{3159} 2007; Australia	Single centre, Gastro OPD non-bronch BAL	Children undergoing upper GI endoscopy, cough questionnaire. Exclusion: neurodevelopmental abn, underlying cardioresp dis, primary aspiration  <b>*Group defined on +ve bacterial culture not PBB</b>	69 children; 10 positive bacterial growth non-bronch BAL, control group n=59	To examine the expression of neurokinins, neurotrophins and TLRs in the lungs of children.	Cough 90% with positive bacterial culture (p=0.001); Evidence of neutrophilic airway inflammatory response including CXCR1 expression: $\uparrow$ expression neutrophil chemokine receptor CXCR1 0.93 (cf controls 0.02 p=0.006) , $\uparrow$ IL-8 195.1 pg/ml (cf controls 52.94) p<0.018 $\uparrow$ MMP-9 active 2.8 ng/ml (cf controls 0.97) p<.0045 $\downarrow$ TAC1 143.1 (cf control 357.4 p=.0001) and $\downarrow$ TLR4 2.7 (cf controls 4.7 p=0.021) $\uparrow$ TLR3 209.8 (cf 115.7, p=0.013)	<u>BAL micro:</u> In Postitive grp: Hi=10%, Spn=80%; Mcat=20%;  <u>Non-bronch BAL cell count</u> +ve bacteria culture:  TCC 108 Neutrophils $\uparrow$ = 26% p=.0001 Macro $\downarrow$ = 66% p=.0001 Lymph $\uparrow$ =5% p=.005 Eos 0% all groups  Limitations: *n=10
Pizzutto{5728}	Single centre,	Children for investigation of	n=80 children with CSLD	Identify features of innate, cell-mediated	CSLD grp >18 months: $\downarrow$ IFN $\gamma$ in response to NTHi (cf	Hi=24%, Spn=5%; Mcat=5%;Ps.a=2.5%,

2014; Australia	Resp OPD, prosp Cross sec	chronic wet cough. Healthy controls: no acute infection or history chronic illness <b>(NOT PBB)</b>	n=51 aged- matched healthy controls 75% total cohort (n=80) ages <3.5 y	and humoral immunity that may increase susceptibility to resp infections in children with CSLD	controls) Altered cell-mediated immune responses, <i>in vitro</i> , may contribute to pathogenesis CSLD	K. pneumoniae=1% *NB: 45% on ABs at time sampling  Cell differential: NR
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**Supplement Table S5.2****Studies involving children with protracted bacterial bronchitis or chronic wet cough, and association with tracheomalacia (part KQ5)**

[modified with permission from Chest 20016;149:120-42,{6008} Chest 2016;149:106-19{5954} and Pediatric Pulmonology 2016{5970}]

1 <sup>st</sup> author, publication yr; country	Setting ; Study design	Inclusion criteria; Exc or definitions	No. enrolled, No. completed; Age	Main aim(s)	BAL microbiology	Tracheomalacia findings
<b>Wang{606 1} 2015; China</b>	Single centre, Hospitalised, children's hosp, retro	Chronic cough (>4 w) without acute lower resp infection and no response to conventional Rx.	66 with wet cough of which 50 had PBB; median age=10 mo (5.8–14 <sup>3</sup> )	To describe the clinical characteristics children aged < 3 y with PBB	BAL ( $\geq 10^4$ cfu/ml); Hi=47%, Spn=37%, E. Coli=6% Enterobacter=5%	Total airway malacia n=22 (44% cases); Laryngomalacia=32%, tracheomalacia=14%, bronchomalacia=41% Laryngo-bronchomalacia=9%, tracheobronchomalacia=4% “The clinical manifestation, immune function, cellularity and bacterial culture of BALF from patients with airway malacia did not differ from those without malacia”
<b>Gedik{606 2} 2015, Turkey</b>	Single center, pediatric or Allergy dept; Cohort prosp	Aged < 17 y, persistent cough >4 w. Exc: known chronic resp, neuromuscular, growth, or cardiac problems, syndromes, or prematurity	n=563 (total cohort)  <b>Wet cough n=85 had FB PBB diagnosed =67</b>  Mean age=5.4 SD 3.8	The evaluation of children with chronic cough and aged-based etiological factors	BAL micro: (n=67 +ve 79% wet cough)  Hi=43.2% Spn=23.9% Mcat=23.9% Sa=3% S.py=6%	Vascular ring (n=1) and TBM (n=3)
<b>Wurzel{54 58} 2014; Australia</b>	Single center, Resp OPD;	<b>PBB=clinical def;</b> Controls=chronic resp symptoms, but no PBB,	PBB=104, Controls=49; Respective median age	To provide extensive clinical, laboratory, and BAL characterization of PBB	BAL; In PBB grp; Hi=72%, Spn=39%; Mcat=43%;	TBM in n= 71 (68%) compared to n=26 in control group (53%) p=0.068

	cross- sect Prosp	CSLD	(IQR)=19mo (12-30), and 20mo (8-63)		AdV=23%; Any virus=38%	
<b>Marchant {5280} 2012; Australia</b>	Single center, Pediatr ic and resp OPD; RCT prosp	Aged 0.5-18 y, doctor observed <b>wet cough &gt;3 w</b> ; Exc: chronic lung, cardiac or neuro- developmental disorders, ABs in last 2 w or if acutely unwell	50, 3 lost to FU that were analyzed as failures. Mean=1.8 y for Rx gp and 2.8 y for placebo group	Efficacy of 2 w of oral amox-clav (compared with placebo) in achieving cough resolution in children with chronic wet cough	BAL; Hi=38%, Spn=24%; Mcat=19%	BAL in subgroup (n=37)  Of those without total clinical resolution in 2 w trial >50% had TM or BM or TBM
<b>Zgherea{5 093} 2012; USA</b>	Resp OPD; Retro	<b>Chronic wet cough &gt;4 weeks</b> , *children ages 0-3 years (majority results)	n=197; n=108 0-3 y, n=71 3-7 y, n=18 >7 y	Review of bronchoscopy and BAL results	BAL growth 91% with purulent bronchitis  Hi=49%; Spn=20% Mcat=12%; Sa=12%	Laryno/tracheomalacia n=33 (30.3%) 0-3 y.  TM n=15 (14%), 0-3 y age;  Rates in older age grps NR
<b>Kompare{ 5095} 2011; USA</b>	Resp & allergy OPD ; retro	<b>Protracted Cough (n=51), wheeze (n=27) or noisy breathing (n=17) (n=27 two symp, n=3 three symp) for &gt;1mo</b> , BAL ( $\geq 10^4$ CFU/mL) and response to $\geq 2$ w AB Rx (PBB)	n=70; Summary age NR	Review all BAL ( $\geq 10^4$ CFU/mL) cultures of children aged <5 y with cough, wheeze or noisy breathing for >1mo without other diagnoses so as to determine if PBB was present	BAL micro: Hi=56% Spn=37% Mcat=59%	BM n=30 (43%) TM n=14 (20%) TBM n=8 (11%)  <b>Total n=52 (74%)</b>
<b>Douros{50 27} 2011, Greece</b>	Allergy- Resp OPD;	Chronic (>6 w) wet cough with FB undertaken for	n=93; Mean=5.8 y SD 3.6	In children with chronic wet cough: (a) Comparison of chest	Quantitative BAL ( $\geq 10^4$ cfu/ml) Hi=37%, Spn=27%;	BM n=39 (42%)



	Retro	criteria++ Exc: CF, immune-deficiency, neuromuscular, aspiration		CT and FB in detecting airway abnormalities, (b) explore radiologic and FB/BAL associations	Mcat=18% Gram negative bacteria=12%; Sa=5% Pa=5%	
Donnelly{ 3644} 2007; England	Resp OPD; review of clinic letters; retro	Persistent, wet cough present for 1mo that resolved with “appropriate” AB Rx	n=81; Median=3.8 y (range 0.4, 14.8)	Review the outcomes in 81 randomly selected patients diagnosed with PBB	Cough swab (n=51). Of infected specimens (>50%): Hi=81%; Spn=37% (both in 30%); BAL n=19	Malacia 2/19 who had FB (10.5%)  Note: Details on culture not detailed but reported to be similar to cough swabs and neutron dominated
Marchant {3095} 2006; Australia	Single center, Resp OPD; prosp	>3 w cough, age <18 y and newly referred Exc: NR	No. with PBB=43; Median age of whole cohort=2.6 y (IQR 1.2-6.9)	In children with chronic cough, to; (a) evaluate the use of an adult- based algorithmic approach in the management, (b) describe the etiology	BAL median total cell count and neutrophil% in PBB (350 x10 <sup>6</sup> /L, 40%) Micro: Hi =47%, Spn=35%, cat=26%	Tracheomalacia found as secondary diagnosis in 33% of cohort with chronic cough (n=96, 89% of cohort had wet cough)
Chang{19 20} 2002, Australia	Resp OPD, retro	CSLD (>4 mo wet cough), indigenous children	n=65; (n=33 FB) Med age=3.8 y (*n=28 of 33 radiological BE)	Children prospectively identified and charts reviewed retrospectively to describe airway abnormalities and relate to HRCT chest	NR	Structural airway lesions in 39.7% of n=33 who had bronchoscopy
Thomson{ 1698} 2002, Australia	Resp OPD	Chronic cough > 4 weeks	n=49 Med age=39 mo (range 4 mo-14 y)	Children prospectively identified and chart information collected	NR	Structural airway lesion 47%

### Supplement Table S6: Studies involving KQ6

In children with chronic wet or productive cough unrelated to an underlying dis and without any specific cough pointers (e.g. coughing with feeding, digital clubbing, etc.); (a) How effective are ABs in improving clinical outcomes (eg. cough resolution)? (b) What is the most suitable AB?

(c) For how long should ABs be prescribed? (d) Does Rx dose and duration influence risk of recurrence in the following 12-months?

Randomised, controlled trials							
1 <sup>st</sup> author, publication year, country	Setting; Study design	Inclusion criteria; Exclusion (Excl) or definitions	Intervention	No. enrolled, No. completed, Follow-up duration, Age	Main aim(s) of study	Primary findings relating to KQ	Duration of cough and other comments
<b>Darelid{2263}, 1993, Sweden</b>	3 Paediatric OPD  Open label RCT	Age 0.5-6 y  Cough >10days  Exc: Asthma/allergy, cardiac, AOM, tonsillitis, pneumonia or suspected pertussis	Erythromycin 50mg/kg bid for 7days	88, 1 with- drawn from vomiting AB; 3mo follow- up  Modal age group; 13-24 mo	If erythromycin resolved cough on day7 based on questionnaire and doctor's judgement	35/41 (87%) cured in erythromycin group vs 17/47 (36%) controls (p<.01)	50% had cough >21days; 4 had pertussis; No recurrences in 3 mo follow-up; Worse by day14 in 2 Rx and 14 controls (p<0.01); 7 cases of AOM in controls only (p<0.05).
<b>Gottfarb{1877} 1994, Sweden</b>	3 Paediatric outpatient clinics  Double- blind, placebo containing RCT	LRTI with cough >10days  Excl: AOM, pneumonia or suspected pertussis	Amoxycillin- clavulanate 20mg/kg/d for 7days	52 children, but just 37 children in analysis (12 pertussis, 2 lost to follow-up, 1 refused Rx)  14d FU Median age:	To evaluate nasopharyngeal organisms in children with persistent cough and effects of amoxycillin- clavulanate	AB treated group had better clinical recovery by doctor's assessment (p=.02) and parental opinion (71% vs 22%; p=.002)	Mean cough for 3-4 w.  12 cases of pertussis  Low AB dose used.

				Rx arm: 2.6 y; controls: 2.7 y (range 7 mo-7 y)			
<b>Marchant{5280} 2012, Australia</b>	Single centre, Paediatric outpatient clinic  Double-blind, placebo containing RCT	Age 0.5-17 y  Wet cough >3 w  Excl; Neuromuscular, heart or lung disorders, ex-preterm infants, ABs in prior 2 w, penicillin allergy, or acutely unwell	Amoxycillin-clavulanate 22.5mg/kg bid for 14days	50 subjects, 3 lost to FU  14 d FU post-intervention  Median (IQR) age 1.75 (0.9,4.6) (Rx) and 2.8 (0.95, 5.25) (placebo) y	Assess the efficacy of 2 w of amoxycillin-clavulanate at achieving cough resolution	Cough resolution in 12 (48%) in AB group vs 4 (16%) in placebo group; p=.015	Median (IQR) cough duration was 15 (8.5-59) (Rx group) and 11 (4.0-28) (placebo group) w respectively  BAL in 37 ( $\geq 10^5$ cfu/mL): Hi (14; 38%), Sp (9; 24%) and Mc (7; 19%)  Follow-up limited to just 14 d post-intervention.

### Prospective, cohort studies

1 <sup>st</sup> author, publication year, country	Setting; Study design	Inclusion criteria; Exclusion or definitions	Intervention	No. enrolled, Follow-up duration, Age	Main aim(s) of study	Primary findings relating to KQ	Duration of cough and other comments
<b>Marchant{3095} 2006, Australia</b>	Single centre, Paediatric OPD clinic; Prospective cohort study	Age <18 y and >3 w cough  Excl: Neuromuscular, heart or lung disorders, ex-	Amoxycillin-clavulanate 22.5mg/kg bid for 2 w	108 children  Follow-up: at least 2 w  Median (IQR) age 2.6	To describe the aetiology of chronic cough using a diagnostic algorithm	43 (40%) had PBB, based on a chronic moist cough >3 w and cough resolution with 2 w of ABs	Median (IQR) cough duration was 6 (3-12) mo; 19/43 – probable PBB based on chronic wet cough, BAL cultures $10^{3-4}$ cfu/mL and

	June 2002-June 2004	preterm infants		(1.2- 6.9) y			needing >2 w ABs for cough resolution
<b>Asilsoy{4030} 2008, Turkey</b>	Single centre, Children's Hospital  Prospective cohort study  November 2006-May 2007	Presenting to Hospital with cough >4 w  Excl: Neuromuscular, heart or lung disorders, ex-preterm infants or acute respiratory tract infection in last 4 w	2006 ACCP guideline  Clarithromycin 15mg/kg/d for 10days	108 children  Follow-up: at least 4 w  Mean (SD) age 8.44 (2.13); range 6-14 y	Evaluate guideline	39 children had wet cough. After 14d Abs, 25 (64%) had 'improved' cough, while 14 now had a dry cough, which in 10 recovered completely within 2-4 w following ICSs	Mean (SD) cough duration 4.16 (4.94) mo  Variable response of wet cough to ABs, but no controls and a highly heterogeneous population.
<b>Karabel{5644} 2014, Turkey</b>	Single centre, Paediatric clinic  Prospective cohort study	Chronic cough >4 w  Excl: Neuromuscular, heart or lung disorders, ex-preterm infants or acute respiratory tract infection in last 4 w	2006 ACCP guideline  Clarithromycin 15mg/kg/d for 10 d	270 children  Follow-up: 12 mo  Mean (SD) age 6.5 (2.3) y Range 7 mo-17 y	Evaluate guideline	97 (36%) had a wet cough.  37 had a hx of recurrent bronchitis (22/37 (59%) had BE); 55 received ABs, but just 12/55 (22%) responded and were diagnosed as PBB	Cough duration – not reported  No controls, highly heterogeneous study population  Incomplete data presented.
<b>Usta{5929} 2014, Turkey</b>	Single centre, Paediatric clinic; Prospective cohort; September 2009-September	Chronic cough >8 w in children aged 5-16 y old Excl: Neuromuscular, heart or lung disorders, failure to thrive, ex-preterm infants,	2008 BTS guideline  Clarithromycin 15mg/kg/d for 10days	156 children  Follow-up: 18 mo  Mean (SD) age 8.4 (2.6) y	Evaluate guideline	42 (27%) had a wet cough  25 had both a dry and wet cough  23 with a wet cough and normal physical examination	Mean (SD) cough duration 3.99 (3.21) mo  No controls, highly heterogeneous study population

	2010	active cigarette smoking or unable to perform spirometry				received ABs, cough in 19/23 (83%) resolved = PBB, while 2 had asthma and 2 had BE	
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### Retrospective studies

1 <sup>st</sup> author, publication year, country	Setting; Study design	Inclusion criteria; Exclusion or definitions	Intervention	No. enrolled, Follow-up duration, Age	Main aim(s) of study	Primary findings relating to KQ	Duration of cough and other comments
<b>Smith{5958} 1985, USA</b>	Children's Hospital  Retrospective chart review  Jan 1980-August 1983	Undergoing flexible bronchoscopy for respiratory symptoms  Excl; Cystic fibrosis or other chronic lung disorder leading to chronic bronchitis	cefaclor, ampicillin, or trimethoprim-sulphamethoxazole	148 charts reviewed, 20 had chronic bronchitis on visual inspection (n=7) and/or biopsy (n=13), another 2 included on clinical grounds; Mean age 5.7 (range 0.4-14) y	Describe the features of chronic bronchitis in children	All had been diagnosed with poorly controlled asthma  11 received ABs on basis of bronchoscopy findings and 9 improved vs only 6/11 who did not receive ABs	Cough duration of 3 mo to 3 y  Non-systematic approach to Rx  Outcomes were not defined.
<b>Donnelly {3644} 2007, UK</b>	Single Children's Hospital  Retrospective	PBB as defined by persistent wet cough >4 w that resolves with "appropriate"	Amoxycillin-clavulanate 20mg/kg bid for 2 w  If cough resolved,	81 children  Previous 5 y  Median age	Outcomes following Rx	41 (51%) completely free of cough symptoms after 2 AB courses	48 (59%) had cough duration >1 y;  Uncontrolled observations;

	chart review from prior 5 y	ABs''  Exc: Significant neurological disorders	then AB continued for another 4-6 w	3 y 9 mo (range 5 mo to 14 y)		11 (13%) required $\geq 6$ AB courses or had continuous Rx for at least one winter	Originally all diagnosed as PBB, 4 later had HRCT scan evidence of BE, which resolved in 2 children who had become asymptomatic.
<b>Kompare{5095} 2012, USA</b>	Single Children's Hospital  Retrospective bronchoscopy database review  1999-2009	Children <5 y with resp symptoms for >4 w without other diagnoses and BAL cultures $>10^4$ cfu/mL of respiratory bacterial pathogens; Excl: Asthma, cystic fibrosis and other chronic diseases	Amoxycillin-clavulanate (n=33) Trimethoprim-sulphamethoxazole (n=16) Unspecified other agents (n=12).  AB duration $\geq 2$ w	70 children  AB and outcome data for 61 (87%) children	Describe BAL findings in children with unexplained chronic respiratory symptoms that included cough	Symptoms resolved in 60/61 children  Recurrence of symptoms requiring repeated Rx courses occurred in 43 (70%) cases with good effect (nature of symptoms and Rx unknown)	Median symptom duration 5 (range 1-60) mo  Uncontrolled observations and incomplete data  Sp, Hi, Mc were the most common bacteria in BAL  Airway malacia in 74%
<b>Goyal{5600} 2014, Australia</b>	Single Children's Hospital  Retrospective radiology database and chart review  April 2010-August 2012	Referred children with chronic wet cough >4 w and undergoing multi-detector CT scans  Excl; Asthma, cystic fibrosis, known	Amoxycillin-clavulanate for $\geq 4$ w	144  Median age 56.9 (range 3-204) mo	To determine if a poor response to $\geq 4$ w of ABs predicts risk of BE	106 had CT scan evidence of BE.  Of 105 with persistent cough despite $\geq 4$ w of ABs, 88 (84%) had BE, while of 24 children whose cough resolved, only 6 (25%) had	Median cough duration 12 (range 1.5-144) mo  <b>OR</b> for BE: Indigenous 5.9 (95%CI 1.2, 29), poor response to ABs 21 (95%CI 5.4, 82), cough $\geq 12$ mo 3.0 (95%CI 0.97,

		BE, scans requested by oncology, surgical, intensive care and trauma teams				scan evidence of BE	9.3); Poor response to ABs as a predictor of BE: PPV 84% (95%CI 75, 90); NPV 75% (95%CI 53, 90)
<b>Pritchard{5767} 2015, UK</b>	Children's Hospital  Retrospective chart review  2011-2013	Children diagnosed with PBB between  Median (IQR) age 2.7 (1.5- 4.0) y	Amoxycillin-clavulanate (n=27),  Others: flucloxacillin, amoxycillin or clarithromycin (n=17)  Course duration of 6-8 w	44, 1 lost to follow-up; Median (IQR) follow-up duration 11.3 (8.3-14.7) mo; Median (IQR) age 2.7 (1.5-4.0) y	Cough resolution with ABs	33/43 (77%) had complete response to initial AB, 25/33 (76%) had recurrent episodes, and of these, 9 (27%) were given prophylactic amox-clav, including 3 (9%) with $\geq 3$ PBB episodes	Median (IQR) cough duration 11.0 (9.0-14.7) mo  10/43 (23%) did not respond to initial ABs, thus by definition did not have PBB.

**Supplement Table S7: Studies involving KQ7**

In children aged ≤18-years with chronic wet or productive cough unrelated to an underlying dis and without any specific cough pointers (e.g. coughing with feeding, digital clubbing, etc.), (a) What is the role of prophylactic ABs? (b) What is the risk of AB resistance? and (c) How should recurrences be managed?

Retrospective studies							
1 <sup>st</sup> author, publication year, country	Setting; Study design	Inclusion criteria; Exclusion or definitions	Assessed treatment(s)	No. enrolled, Follow-up duration, Age	Main aim(s) of study	Primary findings relating to KQ	Duration of cough, Rx response and other comments
<b>Donnelly{3644}</b> 2007, UK	Single Children's Hospital  Retrospective chart review from prior 5 y	PBB as defined by persistent wet cough >4 w that resolves with "appropriate" ABs"  Excl: Significant neurological disorders	Amoxycillin-clavulanate 20mg/kg bid for 2 w  If cough resolved, then AB continued for another 4-6 w	81 children  Previous 5 y  Median age 3 y 9 mo (range 5 mo to 14 y)	Outcomes following Rx	11 (13%) required ≥6 AB courses or had continuous Rx for at least one winter  No AB or AB resistance details provided	48 (59%) had cough duration >1 y; No controls, few details on when cultures taken ; 4/81 children later had HRCT scan evidence of BE, which resolved in 2 children who had become asymptomatic
<b>Pritchard{5767}</b> 2015, UK	Children's Hospital  Retrospective chart review  2011-2013	Children diagnosed with PBB between  Median (IQR) age 2.7 (1.5- 4.0) y	Amoxycillin-clavulanate (n=27),  Others: flucloxacillin, amoxycillin or clarithromycin (n=17)  Course duration of 6-8 w	44, 1 lost to follow-up  Median (IQR) follow-up duration 11.3 (8.3-14.7) mo  Median (IQR) age 2.7 (1.5-4.0) y	Cough resolution with ABs	33/43 (77%) had good response to initial ABs, but 25/33 (76%) had recurrent episodes, and of these, 9 (27%) were given prophylactic amoxycillin-clavulanate, including 3 (9%) with ≥3 PBB episodes	Median (IQR) cough duration 11.0 (9.0-14.7) mo  10/43 (23%) did not respond to initial ABs, thus by definition did not have PBB  No controls and no AB resistance details provided.



**Abbreviations:** AB=ABs; Abn=abnormality; ACCP=American College of Chest Physicians; AdV=adenovirus; Amox-clav=amoxicillin-clavulanate; BAL=bronchoalveolar lavage; BE=BE; CF=cystic fibrosis; CFU=colony-forming unit; Clarithro=clarithromycin; CSLD=chronic suppurative lung dis; CT=chest computed tomography; CXR=chest radiograph; d=d; DB=double blinded; Def=definition; Dis=dis; Dx=diagnosis; Exc=exclusion criteria; Exp=exploratory; FB=flexible bronchoscopy; FU=follow-up; mo=months; Gastro=gastroenterology; GI=gastrointestinal; GOR=gastro-oesophageal reflux; Hi=*Haemophilus influenzae*; HRCT=high-resolution computed tomography; ICS=inhaled corticosteroids; ICU=intensive care unit; IL=interleukin; IQR=interquartile range; KQs=key questions; MBL=mannose binding ligand; Mcat= *Moraxella catarrhalis*; Micro=microbiology; mo=months; Mx=management; N=number; ND=not defined; NF=nuclear factor; NR=not reported; NTHi=non-typeable *Haemophilus influenzae*; OPD=outpatients department; OR=Odds ratio; PBB=protracted bacterial bronchitis; PCD=primary ciliary dyskinesia; RCT=randomized control trial; Resp=Respiratory; Rx=Rx; Sa=*Staphylococcus aureus*; SD=standard deviation; SPA=surfactant protein A; Spn=*Streptococcus pneumoniae*; SR=spontaneous resolution; TLRs=toll-like receptors; TNF=tumour necrosis factor; w=week(s); y=year(s)

\*Not all children in cohort had PBB i.e. some had BE

^Unclear what these figures refer to as figure in the table differed from the text

Δ Included only if study termed the condition PBB or persistent bacterial bronchitis

#children who failed therapy included in numbers but those lost to FU were excluded

@Two studies{5444, 3521} that included the same children but reported on different outcomes were excluded from this systematic review

++ criteria used = “(1) recurrent pneumonia, (2) persistent (>1 month) atelectasis, (3) assessment of airway anatomy and dynamics when the wet-sounding cough also had a “brassy” quality, (4) clinical picture that was not compatible with HRCT scan findings, and (5) failure to respond to empiric antibiotic therapy and chest physiotherapy for 2 to 3 weeks”{5027}

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