Supplementary Materials:
SUPPLEMENTARY TABLE 1: PICOTS FRAMEWORK

	Components	Characteristics
P	**Population**	Children aged 0-5 years. - Subgroup analysis: o Age: < 2 years, ≥ 2 years o History of past wheeze/asthma
I	**Intervention**	Vaccine or Drug intervention (type)
C	**Control**	Vaccine or Drug control (type)
O	**Outcomes**	Wheeze or 'Wheeze equivalents' as adverse events 1. Definition of wheeze: absent/present (statement) a. History: past wheeze/asthma b. Clinical exam • Audible wheeze without a stethoscope • Wheeze on auscultation c. Response to bronchodilator/Bronchodilator use d. Assessors: Number and Qualifications e. Description of timing (post hoc analysis) 2. Assessment of severity of wheeze: no/yes (categories and definitions) 3. Diagnostic certainty of wheeze
T	**Timing**	Trials will be restricted to those ≥ 1970.
S	**Setting**	Any vaccine or Drug clinical trial setting (inpatient, out-patient or community settings)

SUPPLEMENTARY TABLE 2: PUBMED SEARCH STRATEGY: 28TH OCTOBER 2014

	Framework	Search terms	Number of articles
P	**Population** 1.children 2.infants	(Child[mh] OR Child[tw]) OR (Infant[mh] OR infant[tw])	P: **2133191**
I	**Intervention** 1.clinical trials 2.drug 3.vaccine	AND((Clinical Trial[PT] OR Clinical Trials as Topic[mh]) AND (Therapeutic use [sh] OR Therapy[sh] OR Treatment outcome [mh]) AND (Vaccin*[tw] OR Immunization[mh]))	I: **19701** P + I: **5348**
C	**Control**	-	-
O	**Outcome** 1.wheeze 2.rhonchi 3.bronchiolitis 4.bronchitis 5.asthma 6.reactive airway disease 7.respiratory hypersensitivity 8.upper respiratory infection 9.lower respiratory infection	AND (Respiratory Sounds[mh] OR (wheeze[mh] OR wheez*[tw]) OR (rhonchi[mh] OR rhonchi[tw]) OR (bronchiolitis[mh] OR bronchiolitis[tw]) OR (bronchitis[tw] OR asthma[tw] OR reactive airway disease[tw]) OR (respiratory hypersensitivity[mh]) OR (upper respiratory infection) OR (lower respiratory infection))	O: **466415** P + I + O: **1121**
T	**Timing** 1.restricting to articles between 1970 and 2014	AND (1970:2014[dp])	P+I+O+T: **1110**
S	**Setting** 1.restricting to English language articles	AND ("English"[la])	P+I+O+T+S: **1005**

SUPPLEMENTARY TABLE 3: ADDITIONAL DATABASES SEARCHED 28 OCTOBER 2014

Database	Search terms	Articles
EMBASE	'infant'/exp OR infant OR 'child'/exp OR child AND ('vaccine'/exp OR vaccine) AND trial AND ('wheeze'/exp OR wheeze) AND [embase]/lim NOT [medline]/lin	22
Web of Science	TOPIC: ((infant OR child) AND vaccine AND trial AND wheeze)	30
SCOPUS	((infant OR child) AND vaccine AND trial AND wheeze)	13
CINAHL PLUS	((infant OR child) AND vaccine AND trial AND wheeze) *Expanded search by including related words and searching within full text of the articles	66
Cochrane Library	(infant OR child) AND vaccine AND trial AND wheeze)	1
WHO Library Databases (WHOLIS)	(vaccine AND trial AND wheeze) Option: VACCINES+ADVERSE+EFFECTS	60
ClinicalTrials.gov	child AND vaccine AND trial AND wheeze	8

SUPPLEMENTARY TABLE 4: REPORTING DEFINITIONS OF WHEEZE AS AN ADVERSE EVENT

Supplementary Table 4a: Clinical trials of children <5 years reporting definitions of wheeze as an adverse event						
Author	**Country(s)**	**Participants**	**Included children w/ history of wheeze**	**Intervention & Control**	**Wheeze Description**	**Wheeze Severity Definition**
Studies including children age <2 years						
Belshe, 2007[38]	United States 12 countries in Europe and the Middle East, 3 countries in Asia	Children: 6-59 months without a recent episode of wheezing (>42 days) illness or severe asthma (N=8,352).	Yes	*Intervention:* Cold-adapted trivalent live attenuated influenza vaccine *Control:* Trivalent inactivated influenza vaccine	Medically significant wheeze -defined as presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator, respiratory distress, or hypoxemia. Wheezing within 42 days after the administration of dose 1.	No definition provided
Custovic, 2002[33]	UK	High-risk infants (both parents atopic, i.e. skin-prick test positive; no pets) **(**N=291 couples randomized) 'Medium risk' infants (one parent skin-prick test positive; family history of atopy) ages of 6 months and 5 years	No	*High Risk Intervention:* House dust mite-allergen avoidance [high-risk active group (HRA)] *High Risk Control:* No intervention *Medium Risk* Intervention: Fluticasone propionate delivered by a metered-dose inhaler(MDI) spacer (Babyhaler including facemask; 100 mg twice daily)	Physician-verified wheeze. Also used whole-body plethysmography in children for measurement of specific airway resistance.	No definition provided

		(N=547)		*Medium Risk Control:* Placebo		
Rose, 2010 [37]	Germany	Children age 6-24 months recruited from a walk-in clinic with a history of wheezing needing bronchodilators or steroids (N=131)	Yes	*Intervention:* dietary supplementation with *Lactobacillus rhamnosus* *Control:* Placebo supplementation	All patients had wheeze; definition: " at least 2 physician-diagnosed episodes of wheezing (>/= 3 days necessitating B2-bronchodilators or steroids) during past 12 months with one episode within past 3 months." Self report through diary by parents of episodes of asthmatic exacerbations including wheeze and cough, numbers and days of associated hospitalizations, symptom-free days, days without use of rescue medication, and associated inhaled steroid and B-agonist use). Asthma symptom score	Severe asthma was defined as at least five episodes of wheezing annually
Belshe, 1992 [1]	United States	Children: 3-36 months; and 3-10 years (N=95)	No	*Intervention:* Cold passage 18 para-influenza type 3 vaccine (CP18 PIV-3) vaccine diluted in Leibovitz medium (L-15) *Control:* Placebo	Clinical definition of illness: lower respiratory illness, wheezing or pneumonia	"Intermittent" "Mild", and "wheeze did not require bronchodilator treatment"
Corver, 2006 [39]	The Netherlands	Pregnant women enrolled and their children were followed (N=810)	No	*Intervention:* Polyester-cotton mite allergen impermeable mattress & pillow covers (Acb; Allergy Control Products, Saratoga Springs, NY) for the	Wheeze assessed using questionnaire during first four years of life	No definition provided

				parental and child beds *Control:* Cotton placebo covers		
Douglas, 1984 [40]	Australia	Children age 6-54 months of age identified at general practitioners offices (N=1273)	Yes	*Intervention:* 14-valent *Streptococcus pneumoniae* polysaccharide vaccine *Control:* Placebo vaccine	Mothers recorded symptoms in dairies including "cough, deep chest cough, wheezing and breathlessness" and how symptoms restricted activity, medications required and medical or hospital care.	Recorded whether wheeze required hospitalization, medication or restricted activity
Esposito, 2003 [36]	Italy	Children age six months-14 years attending the infectious disease ambulatory clinic (N=127)	No	*Intervention:* Influenza vaccine *Control:* Placebo vaccine	Children excluded for wheeze defined as "at least four acute episodes of wheezing in past 12 months" Parents reported symptoms on dairy cards, and active surveillance requested information about respiratory illness. Wheeze included as a symptom of LRI	No definition provided
Jahani, 2012 [41]	Iran	Asthmatic children in daycare age 6-60 months (N=140)	Yes	*Intervention:* Inactivated trivalent influenza vaccine *Control:* Placebo vaccine	Used symptom score cards to record wheeze, cough and other respiratory symptoms (full text unavailable)	No definition provided
Gaglani, 2008 [4]	United States	Healthy children aged 1.5–18 years with history of intermittent wheezing	No	*Intervention:* Single 0.5 mL dose of LAIV in frozen, single-dose, intranasal applicators each year (for 4 years),	ICD-9 code for Asthma or Reactive Airway Disease and parental report of wheeze	Defined intermittent wheezing as those with a history asthma or reactive airway disease or wheezing who did

		(N=18,780 doses of vaccine over 4 years)		*Control:* Compared rates during pre-vaccine time period (cross-over design)		not use steroids or bronchodilator therapy daily or every other day for asthma control. Not hospitalized or seen in the emergency room for asthma in the past 12 months (past 6 months if less than 2 years old)
Greenhawt, 2012 [34]	United States	Healthy children with an egg allergy (mean age 12 months) (N=31)	No	*Intervention:* TIV vaccine split does *Control:* Full dose	Clinicians observed patients for 30 minutes for symptoms of allergy including wheeze	No definition provided
Piedra, 1990 [42]	USA	Premature newborns (N=92)	No	*Intervention* 1: 10ml/kg Immunoglobulin (Baxter) *Intervention* 2: 10ml/kg Albumin Saline	Wheeze: "musical sound on expiration" Rhonchi on auscultation Both assessed by a doctor.	None provided, however comment on the level of respiratory support e.g. FiO2, PEEP, PIP, MAP, CPAP, and demand ventilation.
Piedra, 1993 [43]	USA	Healthy infants 6-32 months (N=52)	No	1985-1986 cross-over study: (n=10 infants, 5-32 months) *Intervention*: Cold recombinant influenza type A (CRA) vaccine *Control:* Placebo	Parental history of wheeze or rhonchi solicited. Clinical exam included assessing for breathing with musical sound, wheeze, or rhonchi heard on auscultation of the chest for acute respiratory disease (ARD).	None provided.

				1987-1988 study: (n=16 infants, 9-13 months) 1988-1989 study: (n=29 infants, 6-13 months) *Intervention 1*: intranasal CRA *Intervention 2*: intramuscular Trivalent inactivated influenza (TI) vaccine *Control:* Placebo (sterile saline – half intranasal, half intramuscular)	Bronchiolitis was defined as labored breathing with wheeze.	
Studies of children ≥ 2 years						
Ortiz, 2015 [11]	Bangladesh	Children 24-59 months	Yes	*Intervention:* SII LAIV is a live, trivalent seasonal influenza vaccine. *Control:* Inactive placebo identical to SII LAIV in appearance, ingredients, and concentrations	Long high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields. Wheeze can occur in the presence or absence of pneumonia or other medical diagnoses. AMONG CHILDREN MEETING CERTAIN EVALUATION CRITERIA.	Protocol-defined wheezing illness (PDWI) will be graded as follows: 1. Mild: wheezing illness as above without other findings associated with moderate, severe, or life threatening severity. 2. Moderate: Nasal

						flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening.
Brooks, Zaman, PATH [9]	Bangladesh	Children 24-59 months	Yes	*Intervention:* SIIL LAIV is a live, trivalent seasonal influenza vaccine. *Control:* Inactive placebo identical to SII LAIV in appearance, ingredients, and concentrations, except it is missing attenuated influenza virus.	Long high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields. Wheeze can occur in the presence or absence of pneumonia or other medical diagnoses. AMONG CHILDREN MEETING CERTAIN EVALUATION CRITERIA.	Protocol-defined wheezing illness (PDWI) will be graded as follows: 1. Mild: wheezing illness as above without other findings associated with moderate, severe, or life threatening severity. 2. Moderate: Nasal flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening

Diallo, Niang, PATH [10]	Senegal	Children 24-71 months	Yes	*Intervention:* SIIL LAIV is a live, trivalent seasonal influenza vaccine. *Control:* Inactive placebo identical to SII LAIV in appearance, ingredients, and concentrations	Upon physical examination is found to have a wheeze, defined as ―long high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields. Wheeze can occur in the presence or absence of pneumonia or other medical diagnoses. AMONG CHILDREN MEETING CERTAIN EVALUATION CRITERIA.	Protocol-defined wheezing illness (PDWI) will be graded as follows: 1. Mild: wheezing illness as above without other findings associated with moderate, severe, or life threatening severity. 2. Moderate: Nasal flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening

Supplementary Table 4b: Clinical trials of children <5 years reporting wheeze as a part of a definition for respiratory illness or non-specific wheeze definition						
Author	**Country(s)**	**Participants**	**Included children w/ history of wheeze**	**Intervention & Control**	**Wheeze Description**	**Wheeze Severity Definition**
Studies including children age <2 years						
Anderson, 1992 [14]	United States	Children eight months to 14 years whose parents volunteered them (N=89)	No	*Intervention:* Cold adapted influenza B vaccine *Control:* No vaccine	Daily home surveillance of respiratory virus. Wheeze included as symptom detected by surveillance	No definition provided
Ashkenazi, 2006 [21]	Belgium, Czech Republic, Finland, Germany, Italy, Poland, Spain, Switzerland, the United Kingdom and Israel	Children: 0.5-5.9 years (N=2187)	No	*Intervention:* 2 doses of cold-adapted influenza vaccine, trivalent (CAIV-T) *Control:* 2 doses of trivalent inactivated influenza vaccine (TIV)	a. Diary card by parents/guardians. b. Episodes of wheeze associated with influenza-like illness during the surveillance phase were reported on the case report form. c. Practitioner-reported wheeze during the surveillance phase	No definition provided
Belshe, 1998 [44]	United Sates	Healthy children age 15-71 months (N=203)	No	*Intervention:* Cold-adapted, trivalent influenza (CAIV-T) virus vaccine *Control:* Placebo vaccine	Wheezing and shortness of breath were included as a symptom of influenza and identified by parents.	No definition provided
Bergen, 2004 [2]	United States	Health children age 1-17 years in Kaiser Permanente (N=9686)	No	*Intervention:* CAIV vaccine	Wheeze, asthma and other respiratory SAEs were identified through linking to databases that tracked hospitalizations, emergency, and clinic visits. Physicians	No definition provided

				Control: Placebo vaccine	and parents were contacted for follow-up on SAEs.	
Clements, 1996 [45]	United States	Healthy children age 2-36 months recruited from the community (N=78)	No	*Intervention*: Influenza vaccine *Control:* Placebo vaccine	Wheeze included in the definition of LRI	No definition provided
Englund, 2013 [46]	United States	HPIV3 Negative children in good health age 6-36 months (N=70)	No	*Intervention:* 2 doses of the live-attenuated recombinant cold-passage para-influenza type 3 vaccine (CP PIV-3) *Control:* 2 doses placebo vaccine	LRI were defined as "confirmed wheezing, rales, pneumonia, croup, or rhonchi, or radiologic evidence of pneumonia	All LRIs were defined as serious adverse events including wheeze.
Esposito, 2007 [47]	Italy	Healthy infant children presenting at vaccination centers (mean age 82 days) (N=1555)	No	*Intervention: PVC-7 vaccine* *Control:* No vaccine	Parents recorded symptoms in dairies. Wheeze included in the definition of LRI	No definition given
Esposito, 2010 [48]	Italy	Children age 2 and older who had completed cancer therapy for acute lymphoblastic leukemia, Hodgkin disease or no-Hodgkin lymphoma (N=273)	No	*Intervention:* inactivated trivalent, virosome-formulated subunit influenza vaccine. *Control:* No vaccine	Parents recorded symptoms including wheeze. Wheeze included as a symptom of respiratory illness and LRI.	No definition given

Jansen, 2009 [49]	Netherlands	Children age 18-36 months with a previous physician diagnosed respiratory infection (N=597)	Yes	*Intervention 1:* TIV+ PCV-7 vaccine *Intervention 2:* TIV+ placebo vaccine *Control:* HBV + placebo vaccine	Excluded children with chronic asthma or recurrent wheeze (longer than three months) Parents recorded symptoms of respiratory infection including wheeze. If symptoms require a visit to the physician, then doctors completed a form on diagnosis and medication	No definition provided
Kiraly, 2013 [35]	Guinea-Bissau	Low birth weight neonates (n=808 in the BCG study (n=702 in the Vitamin A study)	No	*Intervention:* Early BCG vaccination; Vitamin A supplementation *Control:* Delayed BCG vaccination (as usual) No Vitamin A supplementation	Asthma symptoms assessed using questions from the ISAAC questionnaire. Reported ever wheeze, wheeze in past 12 months, exercise induced wheeze, dry cough after exercise, nocturnal cough	No definition provided
Lum, 2010 [50]	13 countries (Bangladesh, Belgium, Finland, Germany, Hong Kong, Lithuania, Malaysia, Mexico, the Philippines, Poland, Singapore, South Korea, and Thailand)	Children 11-24 months (N=1233)	No	*Intervention: Trivalent* *live attenuated influenza virus vaccine - LAIV (MedImmune)* + Priorix® (GlaxoSmithKline, Rixensart, Belgium) *Control: Placebo vaccine* + Priorix® (GlaxoSmithKline, Rixensart, Belgium)	Mention of wheeze (as a symptom identified through influenza surveillance); bronchospasm and bronchitis (reported as one of the most common SAEs); no mention of asthma/allergy	No definition provided

Madhi, 2005 [51]	South Africa	Children vaccinated at 6, 10, and 14 weeks of age (N=39,836).	No	*Intervention:* 9-valent PCV (Wyeth Vaccines and Pediatrics) *Control:* Placebo	Wheeze part of acute bronchiolitis definition. "Presence of wheezing on chest auscultation performed by one of the study doctors in the absence of documented alveolar consolidation on chest radiography or bronchial breathing on chest wall auscultation" Classification of mild/severe pneumonia without wheezing.	WHO-definitions of pneumonia severity: Mild pneumonia was defined as cough of <14 days duration in a child with tachypnea (defined as >50 breaths/min in children <12 months of age and >140 breaths/min in children >12 months of age) in the absence of lower chest wall in-drawing or other signs and symptoms of WHO-defined severe pneumonia. WHO-defined severe pneumonia was defined as a cough of <14 days duration in a child with lower chest wall in-drawing and/or any of the following signs and symptoms of severe pneumonia: feeding difficulties, convulsions, central cyanosis, or encephalopathy.

Malkin, 2013 [52]	America	Healthy, RSV sero-negative children 5-24 months of age (N=113)	No	*Intervention:* MEDI-559 (developed under a Cooperative Research and Development Agreement by MedImmune, and the National Institute of Allergy and Infectious Diseases (National Institutes of Health). *Control:* Placebo	A medically attended lower respiratory illnesses (MA-LRIs) was defined as a clinical diagnosis made by a healthcare provider which included ≥1 of the following: wheezing, bronchiolitis, bronchitis, croup, pneumonia, rales, rhonchi, and apnea. Assessed by the site investigator for severity and relationship to study vaccination.	Adverse events were classified as: Mild, Moderate and Severe. No further definitions although hospitalization/ resulting to death was considered severe.
Mallol, 2010 [53]	America	Healthy, RSV sero-negative children 5-24 months of age (N=113)	No	Intervention: MEDI-559 developed under a Cooperative Research and Development Agreement by MedImmune, and the National Institute of Allergy and Infectious Diseases (National Institutes of Health). *Control:* Placebo	A medically attended lower respiratory illnesses (MA-LRIs) was defined as a clinical diagnosis made by a healthcare provider which included ≥1 of the following: wheezing, bronchiolitis, bronchitis, croup, pneumonia, rales, rhonchi, and apnea. Assessed by the site investigator for severity and relationship to study vaccination.	Adverse events were classified as: Mild, Moderate and Severe. No further definitions although hospitalization/ resulting to death was considered severe.
Nolan, 2008 [54]	Australia	Healthy infants ≥ 6 months to <9yr born between 36-42 weeks (N=150).	No	*Intervention 1*: 30g H5N1 vaccine with aluminum phosphate (AlPO4) adjuvant *Intervention 2:* 45g H5N1 vaccine with aluminum phosphate (AlPO4)	Wheeze was a solicited systematic AE.	AE graded in intensity from 0 to 4, where 0 was "absent/none" and an intensity of 4 represented an event that was "disabling" or had "life threatening consequences".

				adjuvant		
Nolan, 2008 [54]	Australia	Healthy infants ≥ 6 months to <9yr born between 36-42 weeks (N=150).	No	*Intervention* 1: 0.25ml Thimerosal-free inactivated influenza vaccine (Fluvax; CSL Limited, Parkville, Australia) Given to Group A *Intervention* 2: 0.5ml Fluvax Given to Group B.	Wheeze was a solicited systematic AE.	No classification provided
Nolan, 2009 [55]	Australia	Healthy infants ≥ 6 months to <9yr (N=298)	No	*Intervention* 1: 15 microg hemaglutinin antigen dose of monovalent unadjuvanted 2009 influenza A (H1N1) in a 2 dose regimen administered 21 days apart. *Intervention 2*: 30 microg hemaglutinin antigen dose of monovalent unadjuvanted 2009 influenza A (H1N1) in a 2 dose regimen administered 21 days apart.	Wheeze was a solicited systematic AE.	AE graded in intensity from 0 to 4, where 0 was "absent/none" and an intensity of 4 represented an event that was "disabling" or had "life threatening consequences".

Piedra, 1996 [31]	USA	Children with cystic fibrosis aged 12months to 8 years (N=34)	No	*Intervention:* Respiratory syncytial virus, purified fusion protein (PFP-2) vaccine. *Control:* Saline placebo	The study nurse assessed for wheeze on auscultation of the lungs at home visits following a telephone interview that identified an acute respiratory illness.	None provided.
Piedra, 2002 [56]	USA	Healthy children 15-71 months (1602)	No	*Intervention:* trivalent, cold-adapted influenza vaccine (CAIV-T) *Control:* Placebo	Parental report on wheeze. Physician diagnosed lower respiratory tract illness which includes wheeze. Asthma also mentioned as an SAE.	None provided.
Schonbeck, 2005 [57]	The Netherlands	Healthy children 18-72 months with General Physician (GP)-diagnosed respiratory tract illness (N=230)	No	*Intervention 1*: Trivalent inactivated influenza vaccine (Influvac®, Solvay) twice in the first year and once in the second year combined with the heptavalent pneumococcal conjugate vaccine (Prevnar, Wyeth; containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F); *Intervention 2*: Influenza vaccine and placebo (0.9% NaCl phosphate buffered, Solvay); *Control:* Hepatitis B vaccinations	Acute Bronchiolitis defined as in children and adults: cough and fever with scattered or generalized abnormal chest signs: wheeze, coarse rales, rhonchi or moist sounds; in infants (bronchiolitis): dyspnea and hyperinflation Febrile RTI defined as fever for at least 2 consecutive days accompanied with at least one or more symptoms or signs including wheezing of a score of 2 or 3 on a severity scale ranging from 1 (mild) to 3 (severe). Parental report on wheeze. Physician diagnosed lower respiratory	Severity scale ranging from 1 (mild) to 3 (severe).

				(Engerix-B junior®, GSK)	tract illness which includes wheeze.	
Steinhoff, 1990 [58]	USA	Healthy children 6-48 months (N=107)	No	*Intervention 1*: ah vaccine [A/Mallard/NewY ork/6750/78x influenza/Bethesda/1/85(H3N2) reassortant virus] *Intervention 2*: ca vaccine [influenzaA /Ann Arbor/6/60 x A/Bethesda/ 1/85 (H3N2) reassortant virus] *Control:* placebo	Wheezing mentioned in the definition of lower respiratory tract illness (persistent wheezing or cough observed on 2 or more consecutive days).	No definition provided
Vesikari, 2006 [59]	United Kingdom	Healthy children age 6-36 months enrolled in daycare (N=1784)	No	*Intervention:* CAIV-T *Control:* Placebo vaccine	Children with clinically confirmed respiratory illness with wheeze were excluded. Surveillance through phone contacts, clinic visits and home visits. Nasal swabs for influenza testing were collected if patient had wheezing or shortness of breath, pulmonary congestion, pneumonia, or ear infection.	No definition provided
Studies of children ≥ 2 years						
Belshe, 2000 [60]	United States	Children age 26-85 months who participated in the	No	*Intervention:* Trivalent cold-adapted influenza vaccine	Parents were asked about symptoms of influenza including "wheeze, shortness of breath and pulmonary congestion"	No definition provided

		first year of a previous influenza trial (N=1358)		*Control:* Placebo vaccine	through surveillance by the study. The case definition of a LRI was "any physician-diagnosed croup, bronchitis, pneumonia or wheezing"	
Esposito, 2014 [61]	Italy	Children age 36-59 months with a history of reoccurring respiratory infections (N=70)	Yes	*Intervention:* Intramuscular dose of split-virion trivalent influenza vaccine. *Control:* No injection	Parents recorded symptoms of respiratory infection and LRI. Wheeze included as a symptom of LRI	No definition provided
Jain, 2013 [62]	Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, the Philippines, Thailand, Turkey	Healthy children age 3-8 years. (N=5220)	No	*Intervention:* Quadrivalent influenza vaccine (QIV) *Control:* Hepatitis A vaccine	Wheeze included as a symptom of physician confirmed LRI	No definition provided
Schuller, 1983 [63]	United States	Children with recurrent otitis media age 2-6 years (N=72).	No	*Intervention 1*: no routine medication *Intervention 2:* Antihistamines whenever nasally congested *Intervention 3*: Daily sulfisoxazole (500 mg x 2 day) *Intervention 4:* pneumococcal	Definition for bronchospasm: improvement of wheezing after administration of subcutaneous epinephrine or inhaled isoetharine, and in those who were able to cooperate (81%) by improvement in FEV in 1 second of over 20% after inhalation of isoproterenol.	No definition provided

	vaccine *Intervention 5:* pneumococcal vaccine and sulfisoxazole

Supplementary Table 4c: Clinical trials of children < 5 years reporting definitions of respiratory symptoms other than wheeze						
Author	**Country(s)**	**Participants**	**Included children w/ history of wheeze**	**Intervention & Control**	**Wheeze Description**	**Wheeze Severity Definition**
Studies including children age <2 years						
Belshe, 1982 [32]	United States	Children 6-47 months identified during health maintenance visits to pediatricians (N=510)	No	*Intervention:* Live RSV virus vaccine *Control:* Placebo vaccine	No specific wheeze definition. Parents completed checklist of adverse events each day. Study personnel confirmed symptoms in person. Illness was characterized by laryngotracheobronchitis and wheezing in one patient.	No definition provided
Luaguer, 2002 [64]	Germany	Children followed up at 3, 4.5, 6 and 15 months (N=10,271 vaccinated; 2924 families agreed to participate in the follow-up study)	No	*Intervention: Acellular DTP vaccine (Wyeth-Lederle Vaccines and Pediatrics)* *Control: Whole cell DTP vaccine (Wyeth-Lederle Vaccines and Pediatrics)*	No mention of wheeze/ bronchospasm/ asthma/ allergy; Parents reported on cough illness > 14 weeks with any other symptoms via phone.	No definition provided
Luo, 2013 [65]	China	Children 6-36 months (N=300)	No	Intervention: Seasonal trivalent influenza vaccine [TIV] consisting of influenza A(H1N1), A(H3N2) and B viruses (GlaxoSmithKline) Controls: Two 2010–2011 TIVs	No mention of wheeze/ bronchospasm/ asthma; one mention of allergy - not specified	No definition provided

				manufactured by Sanofi Pasteur and Sinovac Biotech		
Lusingu, 2010 [66]	Kenya and Tanzania	Children 5-17 months (894)	No	Intervention: RTS,S/AS01E (GlaxoSmithKline [GSK] Biologicals, Belgium) Control: Human Diploid Cell Rabies Vaccine (Sanofi-Pasteur)	No mention of wheeze/ bronchospasm/ asthma/allergy; one mention of upper respiratory tract infection - not specified	No definition provided SAEs were classified according to the preferred term in the Medical Dictionary for Regulatory Activities (MedDRA). The intensity of all AEs was graded from 1 to 3, with 3 being the most severe (0=usual; 1= less than usual/no effect on normal activity; 2=interferes with normal activity; 3=prevents normal activity) None specific to respiratory illness
Lucero, 2009 [67]	The Philippines	Children 6 weeks to < 6 months (N=12,191)	No	*Intervention:* 11-valent pneumococcal conjugate vaccine (Sanofi Pasteur) *Control:* Placebo vaccine (saline)	No mention of wheeze/ bronchospasm/ asthma/ allergy; Acute bronchiolitis was included as part of pneumonia definition according to the WHO Adverse Reaction Terminology (WHO-ART)	A severe adverse event (SAE) was defined as any untoward medical occurrence after immunization that resulted in death, was life threatening, required in-patient

						hospitalization or prolonged existing hospitalization, or resulted in persistent or significant disability/ incapacity. (WHO-ART)
Marshall, 2012 [68]	Australia	Healthy children 18-36 months of age (N=99)	No	*Intervention:* Meningococcal Bivalent rLP2086 vaccine *Control:* Hepatitis A vaccine/placebo control	1 episode of asthma reported as an SAE in the vaccine group in a child with a history of wheeze.	No definition provided for severity of adverse events that were not local in nature.
Mendelma, 2001 [69]	Australia	Healthy children 18-36 months of age (N=99)	No	*Intervention*: Bivalent rLP2086 vaccine at 0, 1 and 6 months *Control*: Hepatitis A vaccine/placebo control	1 episode of asthma reported as an SAE in the vaccine group in a child with a history of wheeze.	No definition provided for severity of adverse events that were not local in nature.
Mihrshahi, 2001 [70]	Australia	Pregnant women and unborn children (N=616)	No	*Intervention 1:* Placebo diet, no dust mite reduction *Intervention 2:* Placebo diet, active dust mite reduction *Intervention 3:* Active diet, no dust mite reduction *Intervention 4:* Active diet and	Parental questionnaire of respiratory symptoms and clinical assessment of respiratory status	No definition provided

				dust mite reduction		
Munoz, 2014 [71]	USA	48 pregnant mothers whose infants were followed up from birth to 2 months of age	No	Intervention: Tdap vaccine (Adacel, Sanofi Pasteur) given at 30-32 weeks gestation. Control: Placebo (saline control)	Bronchiolitis requiring hospitalization, respiratory distress/tachypnea reported as a moderate SAE.	Bronchiolitis requiring hospitalization, respiratory distress/tachypnea reported as a moderate SAE.
Nilsson, 1998 [72]	Sweden	Infants age 2 months enrolled in a pertussis vaccine trial and followed to age 36 months for a secondary allergy study (N=711)	No	*Intervention 1:* 2-component acellular pertussis vaccine *Intervention 2:* 5-component acellular pertussis vaccine *Intervention 3:* Whole-cell pertussis vaccine *Control:* Diphtheria and tetanus toxiod vaccine	Asthma was diagnosed using a modified International Study of Asthma and Allergies in Childhood questionnaire, clinical findings, and information in medical records. Bronchial asthma was defined as at least 3 episodes of obstructive bronchitis before 2 years of age or 1 episode of bronchial obstruction after 2 years of age in the absence of other explanations.	No definition provided

Palmu, 2014 [73]	Australia	Healthy children 6-35 months (N=3318).	No	*Intervention* 1: 0.25ml Trivalent inactivated influenza vaccine (TIV) *Fluarix™* *Intervention 2:* 0.5ml *Fluarix™* *Control: Fluzone®*	Asthma, allergy and bronchiolitis were related SAEs.	None provided
Piedra, 2005 [3]	United States	Children age 18 months-18 years (N=11096)	No	*Intervention:* LAIV-T *Control:* Pre-vaccination time period (cross-over design)	Medical encounters with ICD-9 codes for asthma, and "Medically attended acute respiratory illness"	No definition provided
Ramos-Alvarez, 1975 [74]	Mexico	Children from communities near Mexico City age 1-4 years (N=346)	No	*Intervention 1:* Measles vaccine *Intervention 2:* Rubella vaccine *Intervention 3:* Bivalent measles and rubella vaccine *Control:* Placebo vaccine	Clinical observations of "cough" and "bronchitis"	No definition provided

Tam, 2007 [15]	China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, and Thailand	Children age 12-36 months (N=3174)	No	*Intervention:* CAIV-T vaccine (MedImmune) *Control:* Placebo vaccine	Parents and guardians recorded any adverse events occurring within 11 days after vaccination.	No definition provided
Wright, 1976 [13]	United States	Healthy children age 11-19 months enrolled in daycare (N=34)	No	*Intervention:* RSV vaccine *Control:* Placebo vaccine	Daily clinical observations including temperature, respiratory rate, quantification of coughs and rhinorrhea.	No definition provided
Studies of children ≥ 2 years						
American Lung Association Asthma Clinical Research Centers (ALAACRC), 2001 [75]	USA	2032 patients, 3-64 years (712 children: 3-17 years)	No	*Intervention*: Heat-killed trivalent split-virus influenza type A and B vaccine (Fluzone, Aventis-Pasteur) *Control:* Identical-appearing placebo saline solution	Asthma defined as "physician diagnosed asthma". Outcomes were defined as exacerbation of asthma within 14 days after injection: a. decrease of at least 30% in peak expiratory flow rate from second-highest morning peak expiratory flow rate measured during study b. increase in daily use of bronchodilator rescue c. increase in the use of systemic corticosteriods for asthma d. unscheduled use of healthcare for asthma treatment e. number of days without symptoms of asthma f. amount of time lost from work or school due to asthma g. increase in medication for long term control of asthma	No definition provided

Marcucci, 2005 [76]	Italy	Children (4-15 years) with respiratory symptoms due to monosensitization to house dust mites (N=24)	Yes	*Intervention:* Sub-lingual immunotherapy (SLIT) 4 µg of the major allergen for Group 1 and 2 µg of the major mite allergen for Group 2 *Control:* Placebo (same composition and presentation but contained no allergen)	Asthma defined as "cough and breathlessness" as recorded through patients diary cards	Used a 0-3 scale of severity of symptoms: 0=no symptoms, 1=mild, 2=moderate, 3=serious
Ming, 2013 [77]	China	Children age 4-12 years with newly diagnosed, uncontrolled, moderate bronchial asthma (N= 24)	Yes	*Intervention:* Inactivated *M. pheli* *Control:* Salmeterol xinafoate and fluticasone treatment	Asthma was diagnosed using a modified International Study of Asthma and Allergies in Childhood questionnaire, clinical findings, and information in medical records Bronchial asthma was defined as at least 3 episodes of obstructive bronchitis before 2 years of age or 1 episode of bronchial obstruction after 2 years of age in the absence of other explanations.	No definition provided
Sugaya, 1994 [78]	Japan	Children with moderate to severe asthma age 2-14 (N=137)	Yes	*Intervention:* Inactivated trivalent subunit antigen vaccines *Control:* No vaccine	Reported asthma attacks resulting in hospitalization	No definition provided
Tanaka, 1993 [79]	Japan	Hospitalized children and adults with bronchial asthma or severe psychomotor retardation (N=153, including 45 asthmatic children)	Yes	*Intervention:* Trivalent cold recombinant influenza vaccine *Control:* Placebo vaccine	Asthma attacks were recorded by physicians	No definition provided

SUPPLEMENTARY TABLE 5: CHARACTERISTICS OF WHEEZE DEFINITIONS IN TRIAL SETTINGS THAT INCLUDE CHILDREN < 5 YEARS

CHARACTERISTICS OF WHEEZE DEFINITIONS	STUDIES REPORTING THIS CHARACTERISTIC	FREQUENCY (Supplementary 4A* studies)
ASSESSOR QUALIFICATIONS		
Caregiver (Parent/Guardian)	Belshe 2007, Corver 2006, Luabeya 2012, Marucci 2005, Mirshahi 2001, Miller 2011, Ming 2013, Nilsson 1998, Piedra 1993, Piedra 2002, Schonbeck 2005, Belshe 1982, Belshe 1998, Belshe 2000, Douglas 1984, Esposito 2003, Esposito 2007, Esposito 2010, Esposito 2014, Jansen 2009, Vesikari 2006, Rose 2010, Ashkenazi 2006, Jahani 2012, Kiraly 2013, Tam 2007, Belshe 1992, Bergen 2004	21 (7)
Health Worker	Ortiz 2015, Brooks-Zaman-CDC-PATH, Diallo-PATH, Mirshahi 2001, Madhu 2005, Piedra 1990, Piedra 2002, Schonbeck 2005, Greenhawt 2012, Jain 2013, Nilsson 1998, Piedra 1996, Englund 2013, Belshe 2007, Piedra 2005, Schuller 1982, Malkin 2013, Piedra 1993, Steinhoff 1990, Anderson 1992, Vesikari 2006, Wright 1976, Belshe 1992, Bergen 2008, Lum 2010 ("bronchospasm"), Luabeya 2012, Belshe 1982, Belshe 1998, Belshe 2000, Clements 1996, Douglas 1984, Esposito 2003, Esposito 2007, Esposito 2010, Esposito 2014, Jansen 2009, Rose 2010, Ashkenazi 2006, Ming 2013, Gaglani 2008	40 (9)
HEALTH WORKER QUALIFICATIONS		
Physician	Ortiz 2015, Brooks-Zaman-CDC-PATH, Diallo-PATH, Madhu 2005, Piedra 1990, Piedra 2002, Schonbeck 2005, Greenhawt 2012, Jain 2013	10 (5)
Study nurse	Nilsson 1998, Piedra 1996, Englund 2013	3 (0)
Health worker (description not provided)	Belshe 2007, Piedra 2005; Schuller 1982, Malkin 2013, Piedra 1993, Steinhoff 1990, Anderson 1992, Vesikari 2006, Wright 1976, Belshe 1992, Bergen 2008, Lum 2010 ("bronchospasm"), Luabeya 2012, Belshe 1982, Belshe 1998, Belshe 2000, Clements 1996, Douglas 1984, Esposito 2003, Esposito 2007, Esposito 2010, Esposito 2014, Jansen 2009, Rose 2010, Ashkenazi 2006, Ming 2013, Gaglani 2008	27 (7)
NUMBER OF ASSESSORS		
1 assessor – Caregiver only	Corver 2006, Marucci 2005, Kiraly 2013, Miller 2011, Marshall 2012 ,	5 (1)
1 assessor – Health Worker only	Ortiz 2015, Brooks-Zaman-CDC-PATH, Diallo-PATH, Madhu 2005, Malkin 2013, Piedra 1990, Piedra 1996,	20 (7)

	Piedra 2005, Greenhawt 2014, Jain 2013, Englund 2013, Schuller 1982, Steinhoff 1990, Anderson 1992, Wright 1976, Belshe 1992, Lum 2010, Clements 1996, Belshe 1982, Custovic 2002	
> 1 assessor–Both Caregiver and Health Worker	Belshe 2007 Mirshahi 2000, Ming 2013, Nilsson, Piedra 1993, Piedra 2002, Gaglani 2008, Piedra 2002, Schonbeck 2005, Steinhoff 1990, Belshe 1982, Belshe 1998, Belshe 2000, Douglas 1984, Esposito 2007, Esposito 2010, Esposito 2014, Jansen 2009, Vesikari 2006, Rose 2010, Bergen 2004	21 (4)
HEALTH WORKER EXAMINATION DETAILS		
Wheeze audible without a stethoscope	Ortiz 2015, Brooks-Zaman-CDC-PATH, Diallo-PATH, Piedra 1990, Piedra 1993	5 (4)
Wheeze on auscultation	Belshe 1992, Ortiz 2015, Brooks-Zaman-CDC-PATH, Diallo-PATH, Madhu 2005, Piedra 1990, Piedra 1993, Piedra 1996, Englund 2013	9 (6)
Characteristic findings of wheeze on auscultation	Ortiz 2015, Diallo-PATH and Brooks-Zaman-CDC-PATH***: "Long high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields."*** Piedra 1990***:" Wheeze: musical sound on expiration; Rhonchi on auscultation"***	4 (4)
Bronchodilator response	Schuller 1982 ***("Bronchospasms proved by improvement of wheezing after administration of subcutaneous epinephrine or inhaled isoetharine or improvement of lung function tests ")***	1 (0)
Additional tests: pulmonary function test[a]/ plethysmography[b]	Ming 2013[a], Schuller 1982 [a], Custovic 2002[b]	3 (1)
TIMING OF WHEEZE OR WHEEZE EQUIVALENT		
Reference made to timing of wheeze or wheeze equivalent	Greenhawt 2012, Tam 2007, ALLACRC 2001, Belshe 2007, Rose 2010, Kiraly 2013, Corver 2006	7 (4)
Within minutes/hours	Greenhawt 2012 – "Clinician observed patient for 30 minutes for symptoms of allergy including wheeze" – Influenza vaccine	1 (1)
Within days	Tam 2007 – "Any adverse event within 11 days after vaccination" – Influenza vaccine	1 (0)
Within weeks	ALLACRC 2001 – "Exacerbation of asthma within 14 days after injection" – Influenza vaccine	1 (0)
Within months	Belshe 2007 – "Wheezing within 42 days after the administration of dose 1" - Influenza vaccine Rose 2010 – "2 episodes during past 12 months with 1 episode within past 3 months" - *Lactobacillus rhamnosus*	1 (1) 1 (0) 1 (1)

	Kiraly 2013 – "Ever wheeze or wheeze in past 12 months" – BCG vaccination and Vitamin A supplementation	
Within years	Corver 2006 – "Wheezing during first 4 years of life" - Polyester-cotton mite allergen impermeable mattress & pillow covers	1 (1)
OPERATIONALIZATION OF ASSESSMENT		
Questionnaire	Mirshahi 2000, Ming 2013, Nilsson 1998, Corver 2006	4 (1)
Diaries/ checklists/ symptom score cards	Douglas 1984, Esposito 2007, Esposito 2010, Esposito 2014, Jansen 2009, Rose 2010, Ashkenazi 2006, Jahani 2012, Belshe 1982	9 (4)
Telephone interview/contact	Vesikari 2006, Piedra 1996, Bergen 2004	3 (0)
Home visits	Vesikari 2006, Piedra 1996, Ashkenazi 2006, Anderson 1992, Rose 2010	5 (1)
Facility based patient presentation	Most studies in which assessments are made by health workers	40 (11)
ICD-9 codes for asthma/ reactive airway disease/ medically attended acute respiratory illness	Gaglani 2008, Piedra 2005	2 (1)

Supplementary Table 4A studies: An explicit wheeze definition is provided.

SUPPLEMENTARY TABLE 6: CATEGORIES OF SEVERITY ASSESSMENT OF WHEEZE IN TRIAL SETTINGS THAT INCLUDE CHILDREN < 5 YEARS

Author	Tachypnea	Lower chest wall indrawing	Grunting	Inability to talk/drink /breastfeed	Cyanosis	Pulse oximetry	BGA	Required Bronchodilator	Other	DAIDS severity grades ascertained*
Supplementary Table 4A studies which included specific wheeze definitions in children < 2 years										
Belshe 1992	-	-	-	-		-	-	"wheeze did not require bronchodilator treatment"	"intermittent", "mild"	Grade 1
Belshe 2007	Respiratory distress				Hypoxemia			"with a prescription for a daily bronchodilator"		Grade 1 Grade 2 Grade 3
Douglas	-	-	-	+	-	-	-	+	Recorded whether wheeze required medication, restricted activity or hospitalization,	Grade 1 Grade 3
Englund	-	-	-	-	-	-	-	-	All LRIs were defined as serious adverse events including wheeze.	Grade 1
Gaglani	-	-	-	-	-	-	-	-	"medically attended wheeze"	Grade 3
Mihrshahi	-	-	-	-	-	-	-	-	Wheeze Frequency 1–2 episodes, 2–3 episodes, more than 4 episodes, or persistent.	Grade 1 Grade 4

									Duration (that lasted a week or more) Use of asthma medication (persistent asthma) Requiring hospitalization	
Munoz	+	-	-	-	-	-	-	-	Related moderate adverse event included: Respiratory distress/ tachypnea. Bronchiolitis requiring Hospitalization,	Grade 1 Grade 4
Nilsson	-	-	-	+	-	-	-	-	1.Wheezing/whistling in the chest in the last 12 months? 2.Number of episodes (frequency) in the last 12 months? 3.Number of nights/week (frequency) disturbed by wheezing in the last 12 months? 4."So severe could only say 1 to 2 words between the breathing".	Grade 3 Grade 4
Supplementary Table 4A studies which included specific wheeze definitions in children ≥ 2 years										
Ortiz	+	+	-	-	-	+	-	-	1. Mild: wheezing illness without other findings associated with	Grade 1 Grade 3

									moderate, severe, or life threatening severity. 2. Moderate: Nasal flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening.	Grade 3 Grade 4
Brooks-Zaman-PATH	+	+	-	-	-	+	-	-	1. Mild: wheezing illness without other findings associated with moderate, severe, or life threatening severity. 2. Moderate: Nasal flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening.	Grade 1 Grade 2 Grade 3 Grade 4
Diallo-PATH	+	+	-	-	-	+	-	-	1. Mild: wheezing illness as above without other findings associated with moderate, severe, or life threatening severity. 2. Moderate: Nasal flaring OR chest indrawing OR Pulse oximetry 90 – 95%. 3. Severe: Dyspnea at rest causing	Grade 1 Grade 2 Grade 3 Grade 4

									inability to perform usual social & functional activities OR Pulse oximetry < 90%. 4. Life threatening.	
Supplementary Table 4B studies including non-specific wheeze definition or wheeze as a symptom of another disease in children <2										
Madhi	+	+	-	+	+	-	-	-	WHO-definitions of pneumonia severity: Mild pneumonia was defined as cough of <14days duration in a child with tachypnea (defined as >50 breaths/min in children <12 months of age and >140 breaths/min in children >12 months of age) in the absence of lower chest wall in-drawing or other signs and symptoms of WHO-defined severe pneumonia. WHO-defined severe pneumonia was defined as a cough of <14 days duration in a child with lower chest wall indrawing and/or any of the following signs and symptoms of severe pneumonia: feeding difficulties, convulsions, central cyanosis, or encephalopathy.	Grade 1 Grade 2 Grade 3
Malkin	-	-	-	-	-	-	-	-	Adverse events were classified as: Mild, Moderate and Severe. No further definitions although hospitalization/ resulting to death was considered severe.	Grade 3 Grade 4
Ming	-	-	-	-	-	-	-	-	Safety and tolerability were	Grade 3

									assessed in terms of frequency, duration and severity of adverse events and the registered relationship to the test drug; causing death, carcinogenic, teratogenic and permanent damage to the organ; life-threatening resulting in hospitalization; special treatment with adverse reactions; clinically significant changes in laboratory measure and vital signs;	Grade 4
Nolan, 2008	-	-	-	+	-	-	-	-	AE graded in intensity from 0 to 4, where 0 was "absent/none" and an intensity of 4 represented an event that was "disabling" or had "life threatening consequences".	Grade 3 Grade 4
Nolan, 2009	-	-	-	-	-	-	-	-	Parents graded severity of adverse of events. No classification provided.	N/A
Piedra, 1996	-	-	-	-	-	-	-	-	An SAE was defined as an event that was fatal; was immediately life-threatening; or resulted in or prolonged a hospitalization, a permanent or substantial disability, an important medical event, or a congenital anomaly (an offspring of participant regardless of the time to diagnosis).	Grade 3 Grade 4
Piedra, 2002	+	+	--	-	+	-	+	-	None provided, however comment on the include signs such as tachypnea, sternal retraction, cyanosis and arterial oxygen; level of respiratory support e.g. FiO2, PEEP, PIP, MAP, CPAP, and	Grade 1 Grade 2 Grade 3 Grade 4

									demand ventilation;	
Rose	-	-	-	-	-	-	-	-	**Hospitalizations reported (SAE)**	Grade 3
Schonbeck	-	-	-	-	-	-	-	-	Severity scale ranging from 1 (mild) to 3 (severe).	N/A
Schuller	-	-	-	-	-	-	-	-	**Hospitalizations reported (SAE)**	Grade 3
Sugaya	-	-	-	-	-	-	-	-	**Hospitalizations reported (SAE)**	Grade 3
Supplementary Table 4B studies including non-specific wheeze definition or wheeze as a symptom of another disease in children ≥ 2 years										
Tam	-	-	-	-	-	-	-	-	**Hospitalizations reported (SAE)**	Grade 3
Supplementary Table 4C studies including definitions of respiratory symptoms other than wheeze in children ≥ 2 years										
Marcucci	-	-	-	-	-	-	-	+	Symptom Score 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = serious symptoms Medication score Medications taken daily (systemic	N/A

									antihistamines, nasal chromoglycate, ocular cromoglycate, beta-2-agonist) 1 point for each application of nasal &/or ocular chromoglycate, drops in both nostrils or eyes; 2 points for every inhalation of beta-2-agonist; 3 points for every antihistamine taken.	

*DAIDS –Division of AIDS table for grading severity of adverse events in adult and pediatric populations. The grading system produce by DAIDS was applied to each definition to ascertain which grades of SAEs could be detected by the definition.

Supplementary Table 4A studies: An explicit wheeze definition is provided

Supplementary Table 4B studies: Wheeze is described as part of a respiratory illness without an explicit definition

Supplementary Table 4C studies: Wheeze equivalents (e.g. asthma, bronchiolitis) descriptions are provided

SUPPLEMENTARY TABLE 7: PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3 and 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available online
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 and 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Supplementary Tables 2 and 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7—9; Supplementary

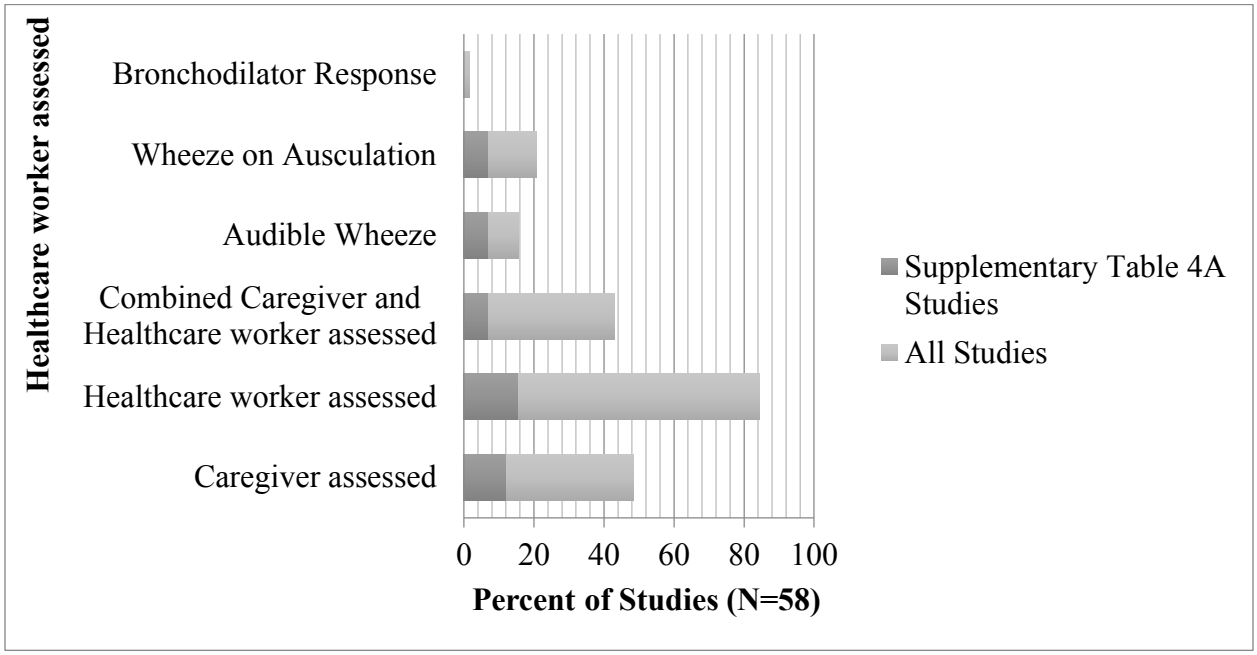
			Table 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-9; Supplementary Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not Applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not Applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not Applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not Applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not Applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not Applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 1 and 2; Figure 2; Supplementary

			Tables 5 and 6; Supplementary Figures 1 and 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not Applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENTARY FIGURE 1: FREQUENCY CHART OF COMPONENTS OF WHEEZE DEFINITIONS



SUPPLEMENTARY FIGURE 2: FREQUENCY CHART DEPICTING OPERATIONALIZATION ASPECTS OF WHEEZE DEFINITIONS IN PAEDIATRIC DRUG AND VACCINE TRIALS