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Journal of Clinical Virology 61 (2014) 181–188

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—A systematic review

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ARTICLE INFO

Article history:
Received 30 March 2014
Received in revised form 16 June 2014
Accepted 25 June 2014

Keywords:
Pulmonary disease, chronic obstructive
Exacerbation
Viruses
Polymerase chain reaction
Systematic review

ABSTRACT

Background: Despite the increasing knowledge on the role of viruses in exacerbations of COPD (AECOPD), it is less clear which viruses are involved and to what extent they contribute to exacerbations. This review aims to systematically combine and evaluate the available literature of the prevalence of respiratory viruses in patients with AECOPD, detected by PCR.
Methods: An electronic search strategy was performed on PubMed and Embase and reference lists were screened for eligible studies. Cross-sectional, prospective studies and case-control studies were included. The primary outcome measure was the prevalence of respiratory viruses (adenovirus, bocavirus, coronavirus, EBV, hMPV, influenza, parainfluenza, rhino-/enterovirus, RSV) in respiratory secretions of patients during an AECOPD. Secondary outcomes were the odds of the presence of the viruses in different respiratory secretions and the odds of the presence of viruses in upper and lower respiratory tract (URT/LRT) samples.
Results: Nineteen studies with 1728 patients were included. Rhino-/enteroviruses (16.39%), RSV (9.90%) and influenza (7.83%) were the most prevalent viruses detected with lower detection rates of coronaviruses (4.08%) and parainfluenza (3.35%). Adenovirus (2.07%), hMPV (2.78%) and bocaviruses (0.56%) appear to be rare causative agents of AECOPD. Definitive conclusions regarding the role of EBV cannot be made. Seven of the eight analyzed viruses had a higher prevalence in LRT samples. Coronaviruses were detected more frequently in the URT.
Conclusions: Respiratory viruses are frequently detected in both URT and LRT samples in AECOPD with rhino-/enteroviruses, RSV and influenza viruses the most prevalent viruses. Detection rates vary between the two sites for different viruses.

Contents

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; EBV, Epstein–Barr virus; ECHO, enteric cytopathogenic human orphan; FEV1, forced expiratory volume in one second; hMPV, human metapneumovirus; ICTV, International Committee on Taxonomy of Viruses; LRT, lower respiratory tract; PCR, polymerase chain reaction; qRT-PCR, quantitative quantitative real time-polymerase chain reaction; QUADAS, quality assessment of diagnostic accuracy studies; RSV, respiratory syncytial virus; RT-PCR, reverse transcriptase-polymerase chain reaction; URT, upper respiratory tract.

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http://dx.doi.org/10.1016/j.jcv.2014.06.025
1386-6532/

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow obstruction with the most important risk factor for the development of COPD being exposure to cigarette smoke. The course of the disease is progressive and punctuated by the occurrence of exacerbations that can accelerate lung function decline and increase mortality [1,2]. The global initiative for chronic obstructive lung disease (GOLD) classification defines an exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" [3]. Mortality in COPD increases with the number of exacerbations [2] and exacerbations often lead to hospitalization with high treatment costs [1]. Therefore, prevention and optimal management is of high importance. Acute exacerbations are frequently triggered by respiratory tract infections [3]. Respiratory viruses are frequently detected in COPD exacerbations [4], but their role in the pathogenesis remains unclear [5]. The first studies investigating a possible causal role of viruses in COPD exacerbations identified respiratory viruses by serology and viral culture; however, detection rates were generally low. More recently, more sensitive and specific diagnostic methods have become available for detection of respiratory viruses utilizing PCR and its derived forms [6]. Despite the increasing knowledge on the role of viruses in exacerbations of COPD, it is less clear which viruses are involved and to what extent they contribute to exacerbations. The prevalence of viral infection detected by PCR in COPD exacerbations has been reviewed systematically by Mohan [7]. The review demonstrated the relatively high prevalence of picornaviruses and influenza viruses in COPD exacerbations [7]; however, only eight studies were included. In order to further investigate the role of respiratory viral infections in COPD exacerbations on the basis of more recent studies, the present review systematically evaluates additional publications based on an extended selection of articles, selected by a more systematic search strategy. Beside the pooled prevalences of the respiratory viruses, detection in the upper respiratory tract (URT) or the lower respiratory tract (LRT) are also evaluated.

2. Methods

2.1. Protocol and registration

This systematic review was written according to the guidelines of the PRISMA statement for reporting systematic reviews [8].

2.2. Eligibility criteria

2.2.1. Studies and patients

Cross-sectional, prospective studies and case-control studies were included provided the main aim was to determine the prevalence of respiratory virus(es) in COPD exacerbations. The full, original paper of the study or a letter had to be available. Other studies with retrospective inclusion of patients (i.e. sample-related or laboratory-based studies) and studies in an intensive care setting were not included. Intensive care patients represent a distinct group because of significant changes in oropharyngeal flora, hence studies involving these patients were not evaluated in this review. All patients included were diagnosed with COPD by lung function measurements and were evaluated at the time of exacerbation. Patients with asthma or immunosuppressed patients were excluded.

2.2.2. Types of outcome measures

The primary outcome measure was the prevalence of (one or more) respiratory viruses (adenovirus, bocavirus, coronavirus, Epstein–Barr virus (EBV), human metapneumovirus (hMPV), influenza, parainfluenza, rhino-/enterovirus, and respiratory syncytial virus (RSV)) in respiratory secretions of patients during an exacerbation of COPD. Nosocomial infections (hospitalization within the last four weeks or collection of samples later than 48 h after hospitalization) were excluded. Secondary outcomes were the odds of the presence of the viruses in several respiratory secretions and the odds of the presence of viruses in URT and LRT samples.

2.3. Information sources

The publications used for this systematic review were obtained by a full electronic search strategy using the search engine on the databases PubMed and Embase, last performed on May 10th 2014. The resulting manuscripts were carefully analyzed and included when meeting the eligibility criteria by two authors (WZ, PM). Subsequently, the reference lists of the selected articles were screened to ensure no relevant papers were missed.

2.4. Search

The described search strategy was performed by using the following syntax in PubMed:

(((((((“Pulmonary Disease, Chronic Obstructive”[Mesh])) AND (“Disease Progression”[Mesh]))) OR (((copd)) AND (exacerbation)))) AND ((((“Viruses”[Mesh])) OR (respiratory viral

infections)) OR (respiratory virus))) AND (((“Polymerase Chain Reaction”[Mesh])) OR (virus pcr)).

In addition, Embase was searched for relevant studies by using the following terms free text words: ‘chronic obstructive pulmonary disease’ AND ‘exacerbation’ AND ‘respiratory viruses’ AND ‘polymerase chain reaction’.

Subsequently, two independent reviewers (WZ, PM) screened reference lists of the included articles. Any disagreements between the reviewers were resolved by consensus.

2.5. Data collection process

Case-control studies which met the inclusion criteria were included in this systematic review, from these studies only the outcomes of the patients with exacerbations were extracted; no results from control subjects were used in this review. The quantitative results of studies which used quantitative real-time PCR (qRT-PCR) were not evaluated; only the qualitative results of the detection of respiratory viruses in patients were included.

Important missing data were retrieved by electronic approach of the corresponding authors of the article. If information in the paper was unclear, authors were approached to avoid uncertainties. Some articles referred to other papers for methodological information and in these cases the index reference was studied. A few articles used the same population for detection of different viruses and it was assumed that data from the first published articles could be extrapolated to the latest published article [9–11].

2.6. Data items

Double data extraction was performed by two independent reviewers (WZ, MW). From each individual study data were extracted based on (i) number of patients, (ii) definition of exacerbation, (iii) percentage of the predicted forced expiratory volume in one second (FEV1% predicted), (iv) mean age of the patients, (v) detection period, (vi) type of PCR method, (vii) primary outcome measure (prevalence of viral infection in COPD patients undergoing an exacerbation), (viii) secondary outcome measures (presence of the viruses in several respiratory secretions and detection rates of viruses in URT and LRT), (ix) study design, and (x) percentage vaccinated patients against influenza.

For the purpose of this review it was assumed that sputum was not contaminated with material from the URT, and therefore represents the prevalence of respiratory viruses in the LRT. Furthermore, the different subtypes of the influenza, parainfluenza, RSV, hMPV and coronaviruses were not evaluated individually, since not all included articles evaluated the same subtypes. Prevalences of the genera of these viruses were calculated by the cumulative prevalence of the subtypes of the viruses extracted from the included studies that differentiated the subtypes.

Since 2007, the International Committee on Taxonomy of Viruses (ICTV) has decided to subdivide the species of human rhinoviruses into the genus *Enterovirus*. In this systematic review, the cumulative prevalence of the rhino- and enterovirus is reported and referred as rhino-/enterovirus, since several important articles are published before the new the subdivision was announced. In addition, Dimopoulos measured the Enteric Cytopathogenic Human Orphan (ECHO-)virus and the enterovirus separately by PCR [12]. The ECHO-virus is a subtype of the genus of human enterovirus B. This systematic review added the prevalence of the ECHO-virus to the prevalences of the enterovirus and the rhinovirus to calculate the prevalence of the rhino-/enterovirus.

It was assumed that the nasopharyngeal samples in the study of Seemungal were all aspirates, since it was not mentioned which samples were swabs [13]. In the studies from McManus et al. sputum samples were obtained by either spontaneous production or following nebulization of hypertonic saline [9–11]. For the analysis it was assumed that the virus-positive samples were obtained by spontaneous production, since sputum induction was not used in the patients with exacerbations of COPD [10]. Viruses detected in either oro- or nasopharyngeal lavage were considered to originate from the same anatomical region, hence the accumulation of these specimens is used in this review.

Hutchinson provided prevalences of respiratory viruses on the day of identification, the first day after the onset of symptoms, and five to seven days later [14]. To avoid the possibility of nosocomial infection, data on virus detection at onset and on the first day of the exacerbation were used only. Beckham included two populations, one with hospitalized patients with an admission diagnosis of congestive heart failure or acute respiratory illness and one with patients suffering from COPD [15]. Only the second population has been included.

2.7. Risk of bias in individual studies

Two independent reviewers assessed the methodological quality of the papers by using the criteria for the assessment of quality (WZ, MW). These criteria, based on the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS2-)tool [16], were used to assess the risk of bias at the study level by judgment of an adequate or inadequate method. Among others, these criteria focused on the seasonal selection bias, information bias and reporting bias.

Studies scored one point when meeting one of the described criteria for the assessment of quality. Disagreements were resolved by consensus. The maximum achievable score was 14. High values indicate a low risk of bias.

2.8. Summary measures

The principal summary measures were the prevalence of nine respiratory viruses retrieved from the included studies. The prevalence was calculated as the number of virus positive samples divided by the total of samples collected during an exacerbation. In addition, the prevalence of the same viruses in URT and LRT samples was reviewed. Another secondary outcome measure was the prevalence of viruses in respiratory secretions (nasal aspirate, oro-/nasopharyngeal lavage, nasal swab, spontaneously secreted sputum and induced sputum). Secondary outcome data were converted by either using the data in the original paper or by electronic approach of the author for original data of the study.

2.9. Synthesis of results

The pooled prevalence was calculated using the following formula:

$$\text{pooled prevalence} = \frac{\Sigma n_x p_x}{\Sigma n_x} \quad \begin{array}{l} n = \text{number of study samples of study } x \\ p = \text{prevalence of respiratory virus } x \end{array}$$

The 95%-confidence intervals were calculated, assuming a 100% test sensitivity and specificity.

3. Results

3.1. Study selection

The search strategy resulted in 42 articles. The assessment of eligibility was performed by screening the titles and abstracts by two authors (WZ, PM). Twenty-five articles were reviewed for meeting the inclusion criteria, of which twelve met the criteria for eligibility. Seven relevant papers [11,12,15,17–20] were added after

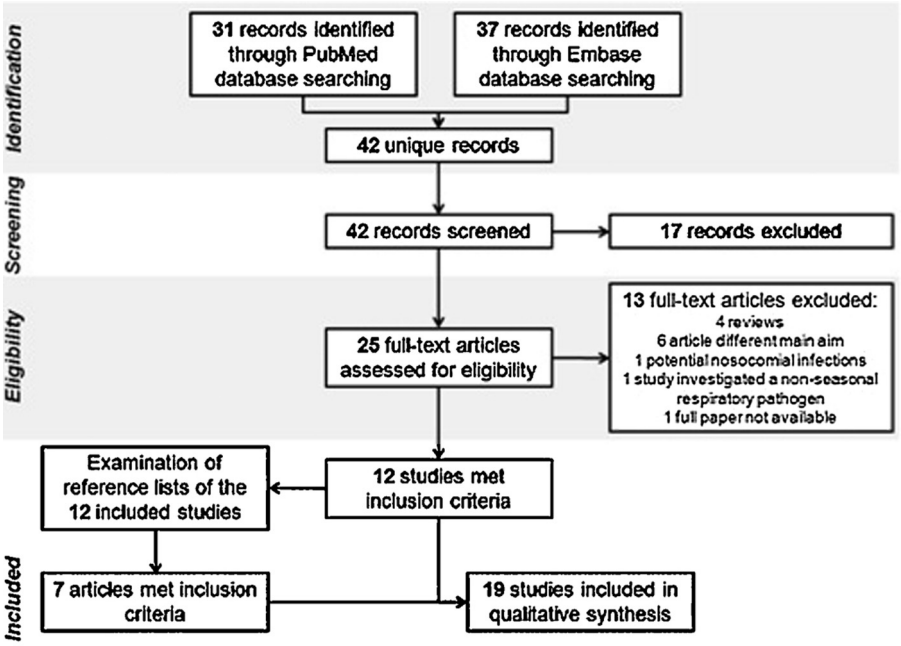

Fig. 1. Flowchart of the selection process, adapted from the PRISMA statement [8].

screening the reference lists and therefore nineteen studies with 1728 patients were included. Fig. 1 represents a flowchart of the selection process. Seven of the included studies were case-control studies, five studies were cross-sectional, and seven longitudinal studies were included. The study characteristics are summarized in Table 1.

3.2. Risk of bias within studies

The criteria of quality of assessment and the risk of bias within studies are summarized in Table 2. The mean score of the quality assessment was 9.53, scores ranged from 7 to 12. None of the studies were completely free of bias.

3.3. Primary outcomes

Table 3 summarizes the pooled prevalences of the respiratory viruses. EBV had the highest pooled prevalence rate (47.79%), but only a single study performed PCR on this virus. Rhino-/enteroviruses (16.39%), RSV (9.90%) and influenza (7.83%) were the most prevalent viruses detected with lower detection rates of parainfluenza (3.35%) and coronaviruses (4.08%). Adenovirus (2.07%), hMPV (2.78%) and bocaviruses (0.56%) showed the lowest prevalence.

3.4. Secondary outcomes

3.4.1. Upper versus lower respiratory tract

Table 3 also presents the pooled prevalences of the respiratory viruses in the URT and LRT. Based on the results of the studies included, seven of the eight analyzed viruses (adenovirus, bocavirus, hMPV, influenza, parainfluenza, rhino-/enterovirus, RSV) had a higher prevalence in LRT samples. Coronaviruses were detected more frequently in the URT. EBV is not included in the table since these were detected in only one of the tracts. Table 4 demonstrates the pooled prevalence of the viruses in the various respiratory samples. The virus that was detected in a single specimen by solely one study (EBV) is not included in the table. Adenovirus and rhino-/enterovirus were most often detected in spontaneous sputum, whereas the highest prevalence of bocavirus, influenza and parainfluenza virus was found in induced sputum. RSV was the only virus which was more frequently detected in oro- or nasopharyngeal lavage specimens. Coronaviruses and hMPV had the highest pooled prevalence in nasal swabs. The result per specimen varied considerably. Table 5 shows the results of the studies investigating influenza virus, the percentage of vaccinated persons against influenza and the detection period. Most studies included patients in all seasons of the year. The number of vaccinated patients and the prevalence of influenza were not correlated.

4. Discussion

This review systematically combined and evaluated the available literature on the prevalence of respiratory viruses in COPD exacerbations as detected by PCR. Nineteen studies were included with a total of 1728 patients. Rhino-/enteroviruses, RSV and influenza viruses were the most prevalent viruses detected with lower detection rates of parainfluenza and coronaviruses. Adenovirus, hMPV and bocaviruses appear not to be associated with COPD exacerbations. Viruses can be detected in both the upper and lower airways but detection rates vary between the two sites for different viruses. The clinical relevance of respiratory viruses in COPD exacerbations detected by PCR are demonstrated in this systematic review.

The most commonly detected viruses were the rhino-/enteroviruses with a pooled prevalence of 16.39%. The range of prevalence for the rhino-/enteroviruses was large ranging from 0% to 26.56%. The lowest value was observed by Aaron [21], but the low number of subjects (14 patients) and the very low prevalence of any virus (only two positive out of 14: one RSV, one Influenza A) makes the study less reliable and it may be considered as an outlier. Also, the study of Camargo reported a relatively low prevalence of 5.26% [22] but this may be accounted for by the fact that the study was performed during the winter only. Since 2007, ICTV has subdivided the species of human rhinoviruses into the genus *Enterovirus*. Before this reclassification was announced, several studies studied the family of *Picornaviridae* and distinct rhinoviruses and enteroviruses. The authors of these studies were

Table 1
Characteristics of the studies included.

Study	Sample size	Age (years)*	FEV1% pred	Definition exacerbation	Quality	Detection method	Study design	Season detected
Ringshausen [29]	134	67.8 ± 8.7	36.8	GOLD criteria	10	qRT-PCR	Case-control	All
McManus [10]	136	70.2 ± 9.4	39.0	NA	7	Nested PCR	Case-control°	All
McManus [9]	136	70.2 ± 9.4	39.0	GOLD criteria	7	Nested PCR	Case-control	All
Zakharkina [26]	29	70.7 ± 8.1	39.4	Anthonisen criteria**	8	RT-PCR	Cross-sectional	Winter–spring
Rohde [25]	85	67.1 ± 8.6	37.9	Anthonisen criteria**	12	Nested PCR	Case-control	All
Aaron [21]	14	71.6 ± 7.7	35.0	Anthonisen criteria**	11	Multiplex PCR	Longitudinal	NA
Seemungal [13]	43	65.4 ± 8.2	40.0	Anthonisen criteria**	8	RT-PCR	Longitudinal	NA
Kherad [23]	86	71.0 ± 9.0	NA	GOLD criteria	9	RT-PCR	Cross-sectional	All
Camargo [22]	76	71.8 ± 9.3	NA	Physician diagnosis of AECOPD with any combination of increased cough, purulent sputum, dyspnoea, fever, and chest congestion present for <10 days	9	Nested PCR	Cross sectional	Winter
Hutchinson [14]	148	72.0 ± NA	40.0	Anthonisen criteria**	7	Multiplex PCR	Case-control	All
Seemungal [24]	168	66.6 ± 7.1	42.4	Anthonisen criteria**	12	RT-PCR	Longitudinal	All
Papi [18]	64	70.6 ± 2.5	39.4	GOLD criteria	10	RT-PCR	Longitudinal	All
Rohde [19]	130	66.0 ± NA	35.2	GOLD criteria	9	qRT-PCR	Case-control	All
Ko [17]	262	75.7 ± 7.7	39.6***	Anthonisen criteria**	11	Multiplex PCR	Cross-sectional	All
McManus [11]	136	70.2 ± 9.4	39.0	GOLD criteria	10	Nested PCR	Case-control°	All
Dimopoulos [12]	200	69.7 ± 9.1	NA	Burge and Wedzicha criteria****	12	Multiplex PCR	Cross sectional	All
Beckham [15]	117	66.7 ± 7.1	NA	Anthonisen criteria**	10	RT-PCR	Longitudinal	All
Tan [20]	14	71.0 ± 11	40.0	NA	7	Nested-PCR/RT-PCR	Longitudinal	All
Perotin [27]	45	63.0 ± 9	44.0	Anthonisen criteria**	12	Multiplex PCR	Longitudinal	All

* Data presented as mean ± SD.
** Criteria of Anthonisen et al.: Type I as an increase in dyspnoea, sputum volume and sputum purulence for more than 24 h, Type II as any two of the above symptoms and Type III as one of the above symptoms accompanied by sore throat and nasal discharge within 5 days, fever without other cause, increased cough and an increase in respiratory rate or heart rate 20% above baseline values [32].
*** Spirometry before and after bronchodilation was performed at two to three months after discharge from the hospital (i.e. stable COPD) according to the American Thoracic Society standard [33].
**** An exacerbation of COPD is a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD [34]; NA = data not available; FEV1% pred = percentage of predicted Forced Expiratory Volume in one second; qRT-PCR = quantitative real time-polymerase chain reaction; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase-polymerase chain reaction.
° A selected group of patients was followed longitudinal in time. Since only the initial data are used, the design is considered case-control.

contacted and all demonstrated that the contribution of the rhinovirus was much higher, compared to the enterovirus [15,23–25]. The rhino-/enteroviruses were more frequently detected in LRT, compared to URT samples (16.50% and 13.50%, respectively) with the highest detection rates in spontaneous sputum (23.53%).

RSV and influenza viruses were also major contributors to COPD exacerbations with pooled prevalence rates of 9.90% and 7.83%, respectively. However, the rhino-/enteroviruses detection rates differed markedly between studies. Influenza was present in almost half of the patients in the study of Zakharkina [26], whereas Seemungal observed a prevalence of only 1.19% [24]. In addition, Tan found a relatively high prevalence of 35.71% and the authors of the article claimed that this prevalence was due to the low number of influenza vaccinated patients [20]. However, the percentage of vaccinated patients was not reported. No relationship between the percentage of vaccinated patients and the prevalence of influenza infections was found in this review (Table 5). The influenza A virus was the most common influenza type detected [11,12,14,15,17,20–22,25,27] apart from the study of Seemungal where influenza B virus was more prevalent [24]. Influenza viruses were detected in 5.43% of URT samples and in 9.88% of LRT samples, with the highest detection rates in induced sputum (11.14%). The prevalence of RSV varied from <3% [11,14,17,20,27] to 40.50% in the study by Dimopoulos [12]. The authors suggested that the relatively high prevalence was due to limitations of multiplex PCR, since distinction between carriage and active infection was not possible [12]. On the other hand, other studies demonstrated lower prevalences of RSV using the same PCR technique [14,17,21,27]. Based on these results, there was no association between the PCR method used (i.e. nested PCR, multiplex PCR and RT-PCR) and the

Table 2
Criteria of quality of assessment and risk of bias summary.

	Was the spectrum of patients representative of the disease studied?	Were the selection criteria (i.e. in-/exclusion criteria) clearly described?	Was the definition of study group adequate (i.e. exacerbation well-defined)?	Did all patients undergo the same tests?	Were multiple inclusions per patients prohibited?	Were positive and/or negative controls used for PCR?	Was the collection of sample documented in sufficient detail?	Was the use of inhaled corticosteroids described?	Was the selection process of the participants clearly described?	Were samples of more than one season included?	Were the patient's characteristics clearly described?	Was the method of patient recruitment consecutive?	Were withdrawals from the study explained?	Were uninterpretable/intermediate test results reported?	Total score
Ringshausen [29]	1	1	1	1	0	1	0	1	0	1	1	0	1	1	**10**
McManus [10]	1	1	0	1	0	0	1	1	0	1	1	0	0	0	**7**
McManus [9]	1	1	1	1	0	0	1	0	0	1	0	0	0	1	**7**
Zakharkina [26]	1	1	1	1	0	1	1	0	0	0	1	1	0	0	**8**
Rohde [25]	1	1	1	1	0	1	1	1	1	1	1	1	1	0	**12**
Aaron [21]	0	1	1	1	1	1	1	1	1	1	1	0	1	0	**11**
Seemungal [13]	1	1	1	0	0	0	1	1	1	0	1	0	1	0	**8**
Kherad [23]	1	1	1	0	0	0	0	1	1	1	1	1	1	0	**9**
Camargo [22]	1	1	0	1	1	0	1	1	1	0	1	0	1	0	**9**
Hutchinson [14]	1	1	1	1	0	0	0	0	0	1	1	0	1	0	**7**
Seemungal [24]	1	1	1	1	0	1	1	1	1	1	1	0	1	1	**12**
Papi [18]	1	1	1	1	0	0	1	1	1	1	1	0	1	0	**10**
Rohde [19]	1	1	1	1	0	1	1	0	1	1	1	0	0	0	**9**
Ko [17]	1	1	1	0	0	1	1	1	1	1	1	1	1	0	**11**
McManus [11]	1	1	1	1	0	1	1	1	0	1	1	0	0	1	**10**
Dimopoulos [12]	1	1	1	0	0	1	0	1	1	1	1	1	1	1	**12**
Beckham [15]	1	0	1	1	0	1	1	0	1	1	1	0	0	1	**10**
Tan [20]	1	0	0	0	0	1	1	1	0	1	1	0	0	1	**7**
Perotin [27]	1	1	1	1	0	1	1	1	1	1	1	1	0	1	**12**

Table 3
Pooled prevalences by virus and upper versus lower respiratory airways.

Virus	Number of studies	Pooled prevalence [95%-CI*]	Upper respiratory airways [95%-CI*]	Lower respiratory airways [95%-CI*]
Adenovirus	11	2.07 [1.41–3.01]	0.34 [0.07–1.03]	3.94 [2.64–5.82]
Bocavirus	2	0.56 [0.00–3.41]	0.00 [0.00–3.35]	0.56 [0.00–3.41]
Coronavirus	8	4.08 [3.04–5.45]	4.80 [3.53–6.49]	1.12 [0.40–2.68]
Epstein–Barr virus	1	47.79 [39.58–56.13]		
hMPV**	9	2.78 [1.95–3.93]	1.84 [1.11–2.99]	2.96 [1.82–4.72]
Influenza	14	7.83 [6.55–9.33]	5.43 [4.25–6.91]	9.88 [7.71–12.58]
Parainfluenza	12	3.35 [2.52–4.44]	2.19 [1.47–3.23]	4.60 [3.10–6.72]
Rhino-/enterovirus	14	16.39 [14.58–18.38]	13.50 [11.67–15.57]	16.50 [13.74–19.69]
RSV***	14	9.90 [8.46–11.56]	9.02 [7.49–10.83]	11.93 [9.54–14.81]

* 95%-CI = 95%-confidence interval.
** hMPV = human metapneumovirus.
*** RSV = respiratory syncytial virus.

Table 4
Prevalence (%) of viruses sets sorted by respiratory secretion.

	Adenovirus	Bocavirus	Coronavirus	hMPV*	Influenza	Para influenza	Rhino-Enterovirus	RSV**
Nasal aspirate	0.23 [0.00–1.44]		4.42 [2.81–6.84]	0.38° [0.00–2.35]	6.28 [4.32–9.01]	1.16 [0.42–2.77]	12.05 [9.40–15.31]	5.35 [3.56–7.93]
Oro-/Naso-pharyngeal lavage	0.32 [0.00–1.95]	0.00° [0.00–3.35]	4.10 [2.35–6.95]	1.12 [0.40–2.67]	6.72 [4.62–9.63]	3.23 [1.85–5.51]	12.69 [9.76–16.32]	17.41 [14.01–21.44]
Nasal swab	0.68° [0.00–4.11]		9.30° [4.56–17.52]	6.17 [3.26–11.12]	2.58 [1.23–5.10]	2.26 [1.00–4.68]	16.77 [13.01–21.35]	3.23 [1.68–5.91]
Sputum induced	1.19 [0.35–3.12]	0.56 [0.00–3.41]	1.29 [0.38–3.40]	3.42 [2.04–5.61]	11.14 [8.46–14.52]	4.90 [3.16–7.49]	14.44 [11.52–17.94]	15.40 [12.26–19.17]
Sputum spontaneous	7.35 [4.76–11.14]		0.74° [0.00–4.46]	1.47° [0.07–5.54]	6.67 [3.64–11.66]	3.68° [1.35–8.54]	23.53° [17.15–31.36]	3.03 [1.11–7.09]

* hMPV = human metapneumovirus.
** RSV = respiratory syncytial virus.
° Based on a single study.

prevalence observed. qRT-PCR could offer a solution and studies using this technique demonstrated a significant higher sensitivity, compared to nested PCR [28].

Other respiratory viruses detected at lower rates included parainfluenza (3.35%), coronaviruses (4.08%), adenoviruses (2.07%), hMPV (2.78%), bocavirus (0.56%), but again there were considerable differences between individual studies in virus detection rates. The pooled prevalence of adenovirus in COPD exacerbations was 2.07% but was much higher in two studies of McManus and the study of Tan [9,11,20]. McManus and co-authors explained their high detection rates with a higher sensitivity of the nested PCR compared to other PCR-techniques [9]. Only two studies investigated the role of human bocavirus [27,29] and we found a pooled prevalence of 0.56%, consequently it may not be a significant cause of COPD exacerbations, but further studies are needed for more definite conclusions. Since only a single study investigated the role of EBV in exacerbations of COPD, definitive conclusions regarding its role cannot be made [10]. Additionally, the risk of bias of this paper is relatively high (7/14 points), despite the high number of patients. The prevalence observed was high (47.79%) and it is surprising that none of the other included papers detected this particular virus and further research is necessary to elucidate the possible role of EBV in exacerbations of COPD.

The results of this systematic review should be interpreted with caution since it is subject to several limitations. First of all, there is the risk of publication bias as studies with negative results may not be reported. However, this is less likely as studies with a wide range of virus detection rates have been published and are included in this review. It was assumed that sputum was not contaminated with material from the URT. Since contamination cannot be ruled out, this assumption could generate wrong conclusions. Most respiratory viruses exhibit a strong winter predominance (e.g. RSV, influenza, parainfluenza, coronavirus), but the rhino-/enteroviruses circulate mainly in the autumn and spring [22,30,31]. Since not all studies were conducted in the same season(s), seasonal bias cannot be ruled out. Adding the seasonal bias to the criteria of quality assessment could offer a solution.

This systematic review demonstrates that respiratory viruses are commonly detected in both upper and lower respiratory samples in COPD exacerbations with rhino-/enteroviruses, RSV and influenza viruses as the most prevalent viruses. However, detection rates of individual viruses vary markedly between studies and further studies are needed to investigate the factors that influence the role of different viruses in COPD exacerbations.

Funding

There are no sources of funding for this manuscript.

Table 5
Studies investigating the prevalence of the influenza virus with the percentage vaccinated patients against influenza.

Study	Year	Prevalence influenza (%)	Vaccinated patients* (%)	Detection period
Zakharkina	2011	48.28	NA	Winter/spring
Rohde	2003	22.35	NA	All seasons
Aaron	2001	7.14	NA	NA
Kherad	2010	2.33	74.42	All seasons
Camargo	2008	3.95	87.00	Winter
Hutchinson	2007	2.03	87.00	All seasons
Seemungal	2001	1.19	74.00	All seasons
Papi	2006	10.94	100.00	All seasons
Ko	2007	9.54	41.80	All seasons
McManus	2008b	2.21	NA	All seasons
Dimopoulos	2012	11.00	44.50	All seasons
Beckham	2005	3.42	89.00	All seasons
Tan	2003	35.71	NA	All seasons
Perotin	2013	6.67	71.18	All seasons

* Vaccine against the influenza virus; NA = data not available.

Competing interests

None.

Ethical approval

Ethical approval was not required.

Acknowledgments

None.

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