Viruses and chronic pulmonary disease: The role of immune modulation

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Introduction

Chronic diseases are the leading cause of death worldwide and the 3rd commonest group of chronic diseases are chronic pulmonary diseases that account for an estimated 4 million deaths annually[1]. The most prevalent diseases of the respiratory tract are chronic obstructive pulmonary disease (COPD), asthma, tuberculosis and lung cancer, and the most common genetic disease is cystic fibrosis (CF). COPD is estimated to be the 4th leading cause of mortality by 2030[2] and an estimated 300 million people suffer from asthma. COPD, asthma and cystic fibrosis are all chronic inflammatory conditions but their aetiology and pathogenesis differ markedly. The typical clinical course of these conditions is of chronic symptoms that are punctuated by periods of increased symptoms termed ‘acute exacerbations’. Acute exacerbations are now recognized to be significant events in the course of the disease and have enormous implications for patients, their carers and for healthcare providers. Exacerbations accelerate disease progression, impaired quality of life and significant morbidity for patients and are a major cause of mortality. In addition they are the major driver of excess healthcare costs as they often result in unscheduled healthcare visits, treatment costs and above all hospitalizations. Therefore preventing exacerbations is a major therapeutic goal in all three diseases and one that has not been achieved with currently available treatments. Despite the differences between COPD, asthma and CF, all three have in common that respiratory virus infections are a major trigger of acute exacerbations. The mechanisms underlying this may be impaired host immune responses to virus infection, and a better understanding of these mechanisms has the potential to lead to the development of new therapies that may be beneficial in different chronic pulmonary diseases. The aim of this article is to review the current knowledge regarding the role of viruses and
host immune responses in asthma, COPD and CF, and discuss avenues for future research and therapeutic implications.

Asthma

Asthma is the commonest chronic respiratory disease affecting up to 10% of adults and 30% of children in the western world[3]. The Global Initiative for Asthma (GINA) defines asthma as ‘a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment’. This definition refers to the key physiological marker of asthma – reversible airflow obstruction, and the key pathological characteristic – airways inflammation. The characteristic pattern of inflammation of allergic diseases is seen in asthma and typically involves eosinophils, mast cells and T helper 2 lymphocytes (Th2) and a wide range of inflammatory mediators. Asthma exacerbations are episodes characterized by progressive increase in shortness of breath, cough, wheezing and chest tightness, or some combination of these, and increased airflow obstruction that is manifested by reductions in measurements of lung function such as peak expiratory flow (PEF). Acute
Exacerbations are a common occurrence in asthma and the social and economic burden of asthma exacerbations is substantial, due to both the direct costs of healthcare utilization and the indirect costs associated with lost productivity. Current therapies for asthma consist of bronchodilator and anti-inflammatory medications, the mainstay of which are inhaled β₂-agonists and inhaled corticosteroids respectively. These are highly effective in relieving symptoms but much less so in preventing exacerbations and therefore treatment of acute exacerbations remain a major unmet clinical need in asthma.

**Viruses and asthma exacerbations**

It has long been recognized that viral respiratory tract infections are reported as triggers for exacerbations of asthma in both adults and children but early studies reported low detection rates of viruses in asthma exacerbations casting doubt on this association[4,5]. The development of highly sensitive and specific molecular diagnostic techniques using polymerase chain reaction (PCR) technology led to a reappraisal of the role of virus infections in asthma. Studies using PCR detected viruses in approximately 80-85% of asthma exacerbations in school-aged children and 60-80% of exacerbations in adults[6-9]. Therefore these studies suggest that the majority of asthma exacerbations are associated with respiratory virus infections and that the low detection rates in earlier studies were a consequence of diagnostic methods with a low sensitivity. The most common viruses detected in these studies were rhinoviruses. Rhinoviruses (RV) are members of the picornaviridae family and are the commonest cause for the common cold in both children and adults. More than 100 serotypes exist. Virus typing classified rhinoviruses into RV-A and RV-B groups based on susceptibility to anti-viral drugs, and on genetic sequence
similarity. More recently, a newly identified group termed RV-C has been identified based purely on sequencing data[10]. Other respiratory viruses have been detected in subjects with asthma exacerbations including influenza, respiratory syncytial virus (RSV), coronaviruses, human metapneumoviruses, parainfluenza (PIV) viruses and adenoviruses. However in a recent study in children the only virus type significantly associated with asthma exacerbations were rhinoviruses[11]. The risk of exacerbation following virus infection is influenced by other factors such as allergy and environmental pollution. Allergen sensitization, exposure to sensitizing allergens, and respiratory virus infection act in a synergistic manner to significantly increase the risk of hospitalization with acute asthma in both adults[12] and children[13]. The presence of high ambient levels of nitric oxide is also associated with an increased risk of exacerbation following rhinovirus infection[14].

**Mechanisms of virus-induced exacerbations**

Following discovery of the central role of rhinoviruses in asthma exacerbations research attention has focused on the mechanisms of susceptibility to virus infection in asthmatics. Rhinovirus infection in healthy individuals results in a predominantly upper respiratory symptom syndrome (‘common cold’), whereas in asthmatics infection results in lower respiratory symptoms and airflow obstruction (‘acute exacerbation’). A study of co-habiting partners discordant for the presence of asthma demonstrated that asthmatics do not have a higher frequency of rhinovirus infections but have greater lower respiratory symptoms and changes in airway physiology[15]. Similar results have been reported in experimental rhinovirus infection studies in asthmatics.
and non-asthmatic control subjects[16]. Therefore it would appear that the consequences of virus infection in asthmatics are more severe than in non-asthmatics. Understanding the mechanisms underlying increased disease severity is crucial to developing new strategies to treat virus-induced exacerbations.

**Biology of rhinovirus infection**

Most research into virus-induced asthma exacerbations has focused on rhinoviruses as these are the most common viruses detected in asthma exacerbations and well characterized models of rhinovirus exist both *in vitro* and *in vivo*. Rhinoviruses primarily enter and replicate in epithelial cells in the respiratory tract and trigger a cascade of immune and inflammatory responses. Following viral entry into a cell uncoating of the virus leads to the release of viral RNA that is recognised by pattern recognition receptors including toll-like receptors (TLR)-3, -7 and -8 - and the cytosolic RNA helicases, retinoic acid inducible gene I (RIG-I) and melanoma differentiation-associated protein-5 (MDA-5)[17,18]. The interactions between ligand and receptor trigger signalling cascades ultimately result in the activation of transcription factors such as interferon regulatory factor (IRF)-3 and-7, nuclear factor-κB (NF-κB), activating transcription factor 2 (ATF2) and c-Jun. These activated transcription factors translocate to the nucleus and induce transcription of the type I interferons (IFN-α and -β) and pro-inflammatory cytokines including IL-8/CXCL8, IL-6, epithelial-derived neutrophil-activating peptide 78 (ENA-78/CXCL5) and IFN-γ-induced protein 10 kDa (IP-10/CXCL10)[19-23]. IFN-α and β have both a direct antiviral effect through inhibition of viral replication in
cells, and an indirect effect through stimulation of innate and adaptive immune responses. The direct antiviral activity of type I IFNs is mediated by various mechanisms including blocking viral entry into cells, control of viral transcription, cleavage of RNA and blocking translation. These effects are mediated through the up-regulation of interferon stimulated genes (ISGs) and the production of antiviral proteins. The indirect antiviral effect is mediated through induction of natural killer cell cytotoxicity[24], up-regulation of the expression of MHC-I on cells and up-regulation of costimulatory molecules on antigen-presenting cells. Therefore a robust interferon response is central to effective antiviral responses and resolution of virus infections. Recently a novel class of interferons termed type III interferons, or interferon-lambda (IFN-λ) has been described. The type III IFNs consist of IFN-λ1, 2, 3 (respectively IL-29, IL-28A and IL-28B)[25]. IFN-λ utilizes a different receptor to IFN-α/β but appears to have functional similarities, however much more is known about the mechanism of action of IFN-α/β.

The pro-inflammatory mediators and cytokines induced by rhinovirus infection lead to chemoattraction of inflammatory cells such as neutrophils, lymphocytes and eosinophils. This inflammatory response contributes to virus clearance but is also responsible for the pathology induced by rhinovirus infections. The balance between antiviral and inflammatory responses following virus infection is likely to determine the clinical outcome of the infection. An effective antiviral response rapidly controls viral replication thus leading to a minimal inflammatory response and limited clinical illness. If viral responses are inadequate this is likely to result in uncontrolled viral replication, greater inflammatory response and more severe clinical illness (Figure 1). The evidence that clinical illness following virus infection is more severe in asthmatics has stimulated research into antiviral and inflammatory responses
In inflammatory and immune responses to virus infection in asthma

In 2005 Wark et al examined the kinetics of virus replication in bronchial epithelial cells obtained from asthmatics and reported that viral replication is increased compared to cells from non-asthmatic subjects[26]. This was the first report that indicated that the innate immune response to virus infection may be impaired in asthma. Furthermore the authors demonstrated that production of IFN-β was impaired in asthmatics and administration of exogenous IFN-β resulted in restoration of a normal antiviral response, and this was confirmed in a subsequent study[27]. Deficient IFN-λ production by epithelial cells and alveolar macrophages in asthmatics has also been reported and related to clinical outcomes following experimental rhinovirus infection[28]. Deficient IFN-β production by bronchial epithelial cells[29], as well as deficient IFN-α production by peripheral blood mononuclear cells[30-32] and dendritic cells[33] have also been reported in asthma and our group has also shown that IFN-α and IFN-β production by alveolar macrophages is impaired in asthmatics (manuscript submitted). However other groups have not reported deficient IFN induction in epithelial cells from asthmatics[34,35]. In experimental rhinovirus infections virus loads were higher and virus shedding prolonged in asthmatics but this was not statistically significant[16,36]. Therefore although interferon deficiency is an exciting new mechanism underlying increased severity of virus infection in asthma it has not been conclusively demonstrated to occur in all asthmatic subjects studied. The studies in question were small with different experimental conditions such as
Abnormalities of the acquired immune system in asthma have been well described with skewing of acquired immune responses towards a Th2 profile. As robust antiviral responses require a good Th1 response it is possible that in diseases such as asthma with predominant Th2 responses antiviral immunity is impaired. Impaired levels of the Th1 cytokines IL-12, -15, -18 and IFN-γ have all been reported in asthma[16,37-39]. In human experimental rhinovirus infection lower respiratory symptoms, bronchial hyperreactivity, reductions in blood total and CD8(+) lymphocytes and virus load are related to deficient IFN-γ, IL-12 or IL-15 responses or to augmented IL-4, IL-5, and IL-13 responses[16,37]. Sputum IFN-γ-to-IL-5 messenger RNA ratio following virus infection is inversely related to both peak cold symptoms and the time to viral clearance[40]. Therefore augmented Th2 and deficient Th1 immune responses are associated with greater clinical illness following rhinovirus infection in asthma.

**Inflammatory responses to virus infection in asthma**

*In vitro* infection of airway epithelial cells with rhinovirus induces the secretion of inflammatory mediators and this has also been reported *in vivo* in both experimental and naturally-acquired viral infections. Chemokines and cytokines such as interleukin (IL)-8, IL-6 and regulated on activation, normal T-
cell expressed and secreted (RANTES) have been detected during virus infections in asthmatic patients[9,41-44]. However it remains unclear whether the inflammatory response following virus infection differs quantitatively or qualitatively in asthmatic patients. One experimental rhinovirus infection study reported increased nasal lavage levels of IL-8 and IL-1β in asthmatics[42] but not in control subjects; however, another study reported no differences in IL-6, IL-8, IL-11, and granulocyte-monocyte-colony stimulating factor levels in either nasal lavage or sputum[41]. Increased levels of IL-10 but no differences in RANTES or IL-8 have been reported in sputum in asthmatics[9]. These conflicting results highlight the need for further studies evaluating the inflammatory profile (preferably in the lower airway) in well-characterized patients and non-asthmatic controls following virus infection.

In conclusion there is evidence that both innate and acquired immune responses in asthmatics are impaired and may underlie increased disease severity following virus infection. Further studies are needed to determine whether these deficiencies are common to all asthmatics or whether they represent a specific asthma phenotype.

**Chronic Obstructive Pulmonary Disease**

Chronic Obstructive Pulmonary Disease (COPD) is the most common chronic respiratory condition in adults. The Global Initiative for Obstructive Lung Disease (GOLD), a collaboration between the World Health Organization and the National Heart Lung and Blood Institute defines COPD as ‘a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is
characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious inhaled particles or gases'[45]. The main aetiological agents linked with COPD are cigarette smoking and biomass exposure and the inflammatory response consists of neutrophils, macrophages and CD8+ T cells and therefore differs from the allergic inflammation seen in asthma. Pulmonary inflammation is further amplified by oxidative stress and excess proteases released by inflammatory cells recruited to the lung. As in asthma acute exacerbations are a common occurrence in COPD and become more frequent as the disease progresses[46]. Exacerbations are a major cause of morbidity, mortality and healthcare costs in COPD and accelerate decline in lung function[47] and quality of life[48] in COPD patients. Historically bacterial infections have been considered the predominant infectious aetiology, however epidemiological data showing a greater frequency of exacerbations in the winter months[49], and frequent coryzal symptoms preceding exacerbations suggest a causal role for viruses[50]. Older studies using cell culture and serologic diagnostic tests detected viral infection in only ~10-20% of exacerbations[51,52]. However these diagnostic methods have low sensitivity for virus detection especially for rhinoviruses that are the commonest cause of upper respiratory tract infections. More recent studies using modern PCR-based techniques have allowed a re-evaluation of the importance of viruses in COPD exacerbations and these studies have shown presence of viruses in 47-56% of exacerbations[53-56]. A recent systematic review evaluated weighted mean prevalence of respiratory viruses detected by PCR in patients with acute exacerbations of COPD. Eight studies were included with an overall prevalence of 34.1%, with picornaviruses including rhinoviruses being the most frequently detected pathogen, followed by influenza,
parainfluenza, RSV and adenoviruses[57]. Although these studies have higher detection rates they are likely to have underestimated the role of viral infections in COPD exacerbation as they evaluated patients at the time of presentation to healthcare services which often occurs considerably later than the onset of exacerbation and by which time virus may no longer be detectable.

**Experimental infection studies in COPD**

Although viruses are frequently detected in COPD exacerbations, their presence during exacerbations does not prove a definite causative role. Experimental infection using rhinovirus provides a novel tool for investigating relationships between virus infection and exacerbations. Such studies have been previously conducted in asthma and yielded important insights into the mechanisms linking virus infection to exacerbations in asthma. A recent study from our group reported the first experimental infection study in COPD[58]. COPD patients and non-obstructed controls were infected with rhinovirus 16 with sequential measurement of symptoms, lung function, inflammatory markers and virus load. Following rhinovirus infection COPD subjects developed symptomatic colds followed by the typical lower respiratory symptoms of an acute exacerbation. Symptoms were accompanied by objective evidence of airflow limitation and airways inflammation and inflammatory markers correlated with virus load. Virus was detected in airway samples prior to the onset of symptoms and viral clearance was followed by symptom resolution and return of inflammatory markers to baseline levels. Therefore this study directly links respiratory virus infection to lower
respiratory symptoms, airflow obstruction and airways inflammation in COPD and provides novel evidence supporting a causative role for rhinovirus infection in COPD exacerbations.

**Mechanisms of virus-induced COPD exacerbations**

Much less is known regarding mechanisms of virus-induced exacerbations in COPD compared to asthma. In the experimental infection study, symptoms, airflow obstruction and airways inflammation were more severe in the COPD subjects compared to non-obstructed controls[58]. Therefore clinical illness following rhinovirus infection is more severe in COPD subjects but the mechanisms underlying this are poorly understood.

Binding of viruses to airway epithelial cells triggers signaling pathways through the activation of pathogen recognition receptors resulting in the production of pro-inflammatory cytokines and chemokines and recruitment of inflammatory cells. COPD exacerbations are associated with increased levels of inflammatory mediators including TNF-α[59], IL-8[59,60], IL-6[61], and leukotriene B4[62] and inflammatory cells such as neutrophils[53,60] and eosinophils[53]. However few studies have examined the inflammatory response specific to virus-induced exacerbations. High sputum levels of IL-6 have been associated with virus infection[63,64] and Papi et al reported that elevated sputum eosinophils were only seen in exacerbations in which a virus was present[53]. Others have reported that the presence of rhinovirus is not associated with significant airway inflammation[65] and that only exacerbations associated with purulent sputum (presumed bacterial infection) are associated with airways inflammation[62]. From the data available no clear conclusions can be
drawn regarding the inflammatory response to virus infection in COPD and there are no studies comparing the effects of naturally-occurring virus infections in COPD patients and non-COPD controls.

There is evidence from animal models that the inflammatory response to virus infection may be exaggerated in COPD. In a murine COPD model, infection with RV1B resulted in increased levels of pro-inflammatory cytokines TNF-α and IL-13 compared to wild-type controls[66]. This correlated with increased airway hyper-responsiveness and increased mucus production. Similarly, in the human COPD rhinovirus challenge study, increased levels of IL-8 and neutrophil elastase were reported in COPD subjects when compared to non-obstructed controls[58]. These studies suggest that COPD is associated with an exaggerated inflammatory response to viral infection and this may explain the increased severity and duration of symptoms seen in these patients.

*In vitro* studies have shown that cigarette smoke impairs release of IFN-β and IFN-α[67]. Bronchoalveolar lavage (BAL) cells from COPD patients infected *ex vivo* with rhinovirus, demonstrated deficient induction of IFN-β with similar trends for deficient induction of IFNs-α and -λ, associated with deficiency of the interferon stimulated gene CXCL10[58]. Similar findings have been reported in a mouse model where persistence of rhinovirus, increased airways inflammation and deficient induction of IFNs-α, β and -γ were reported in COPD mice compared to controls[66]. However *in vitro* rhinovirus infection of epithelial cells from COPD patients resulted in higher virus load and increased inflammatory mediators, but no differences in interferon production compared to cells from control subjects[68]. Further studies examining the role of interferon deficiency in viral exacerbations are required as this may lead to potential future therapeutic application of interferon therapy in reducing
exacerbation severity in COPD. Rhinoviruses bind to cells via ICAM-1 (major group rhinoviruses) or members of the low-density lipoprotein receptor family (minor group rhinoviruses). ICAM-1 is upregulated on the bronchial epithelium of patients with COPD[68,69] and therefore it is possible that increased ICAM-1 levels may permit greater virus binding and increased viral entry into epithelial cells in COPD patients.

**Virus infection and stable COPD**

The majority of studies have detected viruses at a greater frequency during acute exacerbations compared to stable state. One study indicated that RSV is detected at a similar frequency of around 25% in the stable state and during exacerbations[50]. This was followed by a similar study reporting detection of RSV in around 30% of sputum samples, with detection being related to greater airway inflammation and to a faster decline in lung function[70] but other studies have reported increased RSV detection during exacerbations[53,54]. A study comparing virus loads between infants with acute respiratory infections and adult COPD patients found that virus loads were 2000-fold higher in the infants, suggesting low-grade virus infection in COPD[71]. The disparity between these findings is likely to be due to a combination of factors including differing sensitivity of PCR techniques used, differences in severity of COPD patients included or differences in populations studied[72]. Latent infection by adenovirus has also been proposed to be involved in the pathogenesis of COPD. Lung tissue from COPD patients has been demonstrated to carry more group C adenoviral DNA than matched non-obstructed smokers[73]. Latent adenoviral infection in combination with cigarette smoke exposure in a guinea
pig model caused an increase in lung volumes, airspace volume and reduced surface to volume ratio compared to smoke exposure alone[74]. Additionally, adenovirus detection has been shown to be similar in exacerbated and stable COPD patients[75]. Some authors have postulated that the presence of RSV and adenovirus in stable COPD may contribute to the pathogenesis of the disease as there are some common pathologic features between respiratory viral infection and COPD including a predominance of CD8+ T lymphocytes. However, this remains a largely unproven hypothesis.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by a mutation in the gene for the cystic fibrosis transmembrane regulator (CFTR) protein. Defective CFTR function leads to abnormal transport of chloride and sodium across the pulmonary epithelium, resulting in viscous secretions in the lungs, recurrent bacterial infections and progressive loss of lung function. Pulmonary involvement is the most common manifestation of the disease and respiratory failure the commonest cause of death. Respiratory infections are the leading cause of morbidity, decline in lung function and hospitalizations due to acute exacerbations. The major cause of infectious complications in CF has always been considered to be bacterial infection, with Pseudomonas aeruginosa the most common organism detected. There has been relatively little research on the role of virus infections in CF but recent studies have suggested that viruses have a significant impact on the CF patient.

Viruses and CF exacerbations
The role of respiratory viruses in CF exacerbations is likely to have been under-appreciated in the past because older studies investigated only one virus type and the detection methods used were not sufficiently sensitive. Newer PCR techniques have helped to improve detection and it is now becoming clear that viruses are implicated in exacerbations in CF. Previous studies using serology, culture and immunofluorescence detected viruses in between 10-28% of exacerbations in CF patients[76-79]. In contrast studies using PCR for virus detection have reported detection rates of between 50-60%[80-82]. A number of different viruses have been detected in CF patients with the most common being rhinoviruses, influenza viruses and RSV. The incidence of viral infections in children with CF is not elevated in comparison to healthy children but the severity of clinical illness associated with infection is greater[83]. Viral infections are associated with deterioration in lung function and more severe clinical illness indicating that they contribute to disease progression thus demonstrating the clinical importance of research within this field[81,84].

**Mechanisms of virus infection in CF**

The mechanisms of viral-induced CF exacerbations and increased clinical illness are poorly understood with conflicting results from published studies. Some authors have reported increased production of pro-inflammatory cytokines and chemokines by epithelial cells obtained from CF patients compared to healthy controls[83,85]. However others have failed to detect any differences in cytokine production between CF and normal cells[86,87]. These differences may be due to different viruses used (rhinovirus, RSV, PIV) and differences in cell culture techniques, but it remains unclear whether the CF epithelium is intrinsically pro-inflammatory. Another mechanism that has been postulated is a deficiency in antiviral innate immune responses in CF cells. Increased
replication following PIV infection of CF cells has been reported and this was corrected by administration of interferon-α[83]. Interferon responses were not impaired but induction of nitric oxide synthase 2 (NOS2) was impaired in CF. NOS2 is required for production of nitric oxide (NO) that has potent antiviral effects and therefore impaired NO synthesis may be one mechanism of impaired antiviral host responses in CF. Our group has reported reduced IFN-β and IFN-λ production and reduced ISGs in CF epithelial cells and therefore IFN deficiency may be relevant to CF as in asthma and COPD (manuscript submitted). Holtzman has proposed that “hypersusceptibility” to virus infection, via defective interferon pathways, is a unifying pathway in asthma, COPD and now CF[88].

**Bacteria-virus interactions in pulmonary disease**

Both bacterial and virus infections are common in CF and COPD and therefore co-infections are likely to be common. There is now increasing evidence that both viral and bacterial infections can modulate host immune responses and increase susceptibility to subsequent infection. There is abundant evidence from both human studies and animal models that influenza infection impairs antibacterial immunity and this can result in secondary bacterial pneumonia[89,90]. However much less is known regarding the effect of other respiratory viruses, such as rhinoviruses, on susceptibility to bacterial infection. *In vitro* studies have reported that rhinovirus infection increases bacterial adhesion to epithelial cells[91-93] and impairs macrophage immune responses to bacterial products[94]. We have reported that experimental rhinovirus infection in COPD is followed by secondary bacterial infection in 60% of
patients, and this is related to deficiency of the antimicrobial peptides elafin and secretory leukoprotease inhibitor (SLPI) (submitted manuscript). There are also studies implicating virus-bacteria interactions influencing host immune responses in CF. Chattoraj et al reported that rhinovirus infection of CF cells liberates planktonic bacteria from biofilm[95]. Planktonic bacteria express virulence factors and stimulate inflammatory responses more readily compared with biofilm bacteria and this was manifested by increased cytokine responses. Evidence is also emerging that bacterial infection can increase susceptibility to viral infection. Infection of epithelial cells by *Haemophilus influenzae* (a common organism in COPD) increases susceptibility to infection by rhinovirus, possibly by up-regulation of ICAM-1[96]. CF cells infected with mucoid *P. aeruginosa* and then with rhinovirus produced less interferon and viral loads were higher compared to cells infected with the rhinovirus alone[97]. This effect was not seen in normal epithelial cells infected with *Pseudomonas* and was related to the inhibition of Akt phosphorylation and IRF-3 activation - both pre-requisites for the interferon response to rhinovirus infection.

It is widely acknowledged that the main infectious cause of asthma exacerbations is virus infection and that bacteria play only a minor role. However a recent study using culture-independent molecular methods for bacterial detection reported that the bacterial flora in the airways of asthmatics is closer to that of COPD patients rather than non-asthmatics[98]. The role of bacteria in asthma may need to be revisited and virus-bacteria interactions may also play a role in the pathogenesis of asthma and this is a fertile area for further research.

Therefore our knowledge of the interactions between respiratory viruses and
bacteria, and how these influence host immune responses in pulmonary diseases, is still at an early stage. Further research is required to better understand these complex relationships and explore the implications they may have for the development of new therapies.

**Conclusions**

There is now convincing data implicating respiratory viruses as a major cause of acute exacerbations in asthma, COPD and cystic fibrosis. In all these conditions there is evidence that host immune responses to virus infection are impaired, but whether this occurs through a common mechanism, or whether mechanisms differ between the different diseases is unclear. Further research is needed to elucidate the exact mechanisms of increased susceptibility to virus infection in pulmonary diseases and also the interactions between viruses and bacteria and how these impact on host immune responses. A better understanding of these mechanisms has the potential to lead to the development of novel therapies that will reduce the impact of acute exacerbations in chronic pulmonary diseases.

**Competing interests**

The authors have no competing interests to declare.

**Authors’ contributions**

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viruses as a shared mechanism for asthma, chronic obstructive pulmonary


Figure 1

**NORMALS**

- Minimal inflammation
- Short-lived, upper respiratory symptoms only

- Robust antiviral responses
- Minimal inflammatory response

- Up-regulation of interferon-stimulated genes

- Robust interferon responses

- Strong NK cell and Th1 cell responses

- Virus infection of epithelial cells

**ASTHMATICS**

**EXACERBATION**

- Cell necrosis
- Excessive inflammatory response

- Uncontrolled viral replication

- Impaired interferon responses

- Predominant Th2 cells

- Down-regulation of IFN-γ

- Virus infection of epithelial cells
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