Respiratory Viral Infections in Chronic Lung Diseases

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KEYWORDS

• Chronic lung diseases • Respiratory viral infections • Chronic obstructive pulmonary disease • Cystic fibrosis • Interstitial lung diseases • Asthma

KEY POINTS

- Respiratory viruses remain to be important in the pathogenesis of chronic lung diseases.
- Respiratory viruses play an important role in chronic lung diseases, such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis, especially in disease exacerbations.
- There is not much evidence for the association of respiratory viruses with idiopathic pulmonary fibrosis or sarcoidosis.
- Preventive measures are needed to limit such viral infections, with good hand hygiene, avoidance of sick contacts, and viral vaccinations recommended for patients suffering from chronic lung diseases.

INTRODUCTION

Chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), and interstitial lung diseases (ILD), affect many individuals worldwide. Patients with these chronic lung diseases are susceptible to respiratory lung infections and some of these viral infections can contribute to disease pathogenesis. This review highlights the associations of lung infections and the respective chronic lung diseases and how infection in the different lung diseases affects disease exacerbation and progression.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is one of the leading causes of mortality and morbidity worldwide.[1,2] Among several risk factors, cigarette smoking is the most important one. However, smoking alone does not explain all the aspects of COPD. COPD can develop even in nonsmokers, especially in the context of biomass exposure in some parts of the world. More than half of smokers do not develop COPD. A subset of patients with COPD exhibits persistent inflammation despite smoking cessation.[3,4] In addition, accelerated loss of lung function may occur independent of smoking and occur with acute COPD exacerbations.[5] It is important to elucidate additional contributive factors besides smoking to control the disease. COPD is characterized by chronic inflammation of the small airways. Respiratory tract infection is an important cause of acute exacerbation and progression of the disease.[6]

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Common Viral Infections and Chronic Obstructive Pulmonary Disease Exacerbations

Historically, bacteria have been considered the main infectious cause of COPD exacerbations.[7] A growing body of evidence, however, implicates viral upper respiratory tract infections (URIs) as the predominant risk factor associated with exacerbations of COPD.[8] Approximately 40% to 60% of all COPD exacerbations are associated with upper respiratory infections (URIs) and viral infections have been suggested to be important contributors to COPD exacerbations.[9] In fact, it has been shown that respiratory viruses, including rhinovirus, influenza, and respiratory syncytial virus (RSV) cause COPD exacerbations.[10–12] These exacerbations are more severe, last longer, and are associated with more heightened airway and systemic inflammatory responses than exacerbations due to other nonviral causes.[13–15] These differences cannot be attributed solely to pulmonary structural alterations in patients with COPD because healthy smokers also experience exaggerated symptomatic responses after viral infections.[16–18]

Detection rates of virus in COPD exacerbation are variable between approximately 22% and 64%.[9,11,19–27] The detection rates depend on onset to presentation, type of samples, and season. The most commonly identified viruses in exacerbation of COPD include rhinovirus, influenza viruses, RSV, parainfluenza, adenovirus, metapneumovirus, and coronavirus. Among them, rhinovirus and metapneumovirus are the most common viral pathogens in studies using polymerase chain reaction (PCR).[12,13,25] In these studies, rhinovirus was detected in 8% to 44% in the events of COPD acute exacerbation. Influenza vaccination rate can also affect the prevalence. A Hong Kong study showed that influenza was the most common virus in hospitalized patients with COPD; meanwhile, a cohort from a London outpatient clinic showed low prevalence due to relatively high influenza vaccination rate (74%).[11,15] Many COPD exacerbations also include virus and bacteria coinfection. Approximately 25% of the hospitalized patients with COPD exacerbations showed coinfection. The clinical impact of coinfection is longer hospital stay and severe functional impairment.[28]

Symptoms of COPD exacerbation include cough, increased sputum volume and purulence, and dyspnea; however, it is not easy to differentiate viral and nonviral causes of COPD exacerbation by symptoms. Typical "common-cold" symptoms, including fever, nasal congestion, or rhinorrhea, are prevalent in patients with COPD when virus is detected, but those symptoms also can be noted in nonviral exacerbation, so their usefulness in diagnosis remains limited.[13,29] Sputum purulence has been suggested as evidence for bacterial infection in COPD exacerbation, but sputum also can be purulent due to neutrophilia irrespective of causal organism.[30] Furthermore, almost all COPD exacerbations can be marked with change in sputum characteristics.[31] Therefore, the sputum characteristics are not a useful marker to differentiate viral and bacterial infection. On the other hand, sputum purulence may be used to decide the usage of antibiotics.[32] Although neutrophils are the predominantly increased cell type in sputum during COPD exacerbations, one report showed increased eosinophilia during viral exacerbations.[28] Viral exacerbations also are associated with frequent exacerbations, severe exacerbations, and a prolonged time for symptom recovery.[13] Viruses also can be detected in stable COPD. Patients with RSV infection had higher plasma fibrinogen, serum interleukin (IL)-6, and hypercapnia in stable state.[13] This suggests that asymptomatic viral colonization can potentially have a role in chronic inflammation and disease progression of COPD. Another study that supports this showed a relationship between frequent RSV detection and accelerated lung function decline (101.4 mL/y vs 51.2 mL/y, $P = .01$).[33] It has been proposed that the alveolar epithelial cells of smokers and patients with severe emphysema are more frequently latently infected with adenovirus as compared with smokers without airflow obstruction.[34,35] They found COPD lung epithelial cells express adenoviral E1A protein, and that this was associated with specific lung inflammation. The investigators propose such adenoviral infections in patients with COPD contribute to the amplification of the lung inflammatory responses.

PCR of respiratory samples is the main tool to detect causal viruses. Before the widespread use of PCR technique, low virus-detection rates underestimated their role in COPD. The introduction of PCR helped revolutionize viral diagnostics; PCR is far more sensitive and equally specific to the traditional techniques that include culture, antigen-detection tests, and serology.[36,37] Rhinovirus is one of the most common viruses in COPD exacerbation, but it is difficult to culture and serology is not possible due to the presence of more than 100 serotypes. Without PCR, these viruses cannot be identified. As a result, early studies using other diagnostic methods underestimated the prevalence of rhinovirus.[15] Among various methods to obtain samples, such as nasal lavage, throat swab, or induced sputum, it is not yet evident which method is superior. Some viruses, especially RSV, can directly invade the

lower respiratory tract; therefore, obtaining a simultaneous lower respiratory tract sample can increase the sensitivity of these assays. The big challenge of this molecular diagnostic approach is that it cannot discriminate causative organisms from colonization.

Antiviral therapy is not necessary in most immunocompetent and asymptomatic patients with COPD. Antiviral therapy is not indicated solely on the basis of a known diagnosis of COPD. Most endemic viral infections are self-limiting, and pharmacologic management is not necessary. In the case of severe and progressive pandemic influenza virus, oseltamivir is indicated when the clinical diagnosis is made.[38] One of the difficult decisions is not to prescribe antibiotics when they are not necessary. When the causative organism is a virus, antibiotics are not usually necessary unless one is concerned about postviral secondary bacterial lung infections. Although sputum characteristics do not indicate the causative organisms, sputum purulence can be suggested to decide the usage of antibiotics.[32] Influenza vaccination is highly recommended in patients with COPD and other chronic lung diseases.

ASTHMA

Asthma is defined as reversible airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Asthma continues to be a serious global health problem for all age groups, and its prevalence is still increasing in many countries. Worldwide asthma affects approximately 300 million people, with an increased incidence in the developed world. Through the development of inhaled medications, hospitalization and mortality have decreased, but overall asthma control remains suboptimal. Many studies supported the evidence that viral infection has several important roles in disease development, exacerbation, and progression.

Virus Infection and Asthma Development

The "hygiene hypothesis" proposes that a lower incidence of infections in early childhood explains the rise in allergic diseases such as asthma.[39] The thought is that repeated exposures to infections are associated with a healthier immune system with protection against allergic and autoimmune diseases. Specifically, microbes encountered could elicit a more T-helper type 1 (T_H1) immune response that could downregulate the T-helper type 2 (T_H2) immune responses that favor asthma development. The hygiene hypothesis is focused on a lack of T_H1 stimulation that caused an overactive T_H2 response and could lead to a more allergic immune response. What role viruses play in the T_H2 response has been long debated and studied. Whether early viral infections set in motion a T_H2-driven immune response or whether a lack of a T_H1 response causes a more symptomatic response to viral infections has been unclear. Similarly, the debate over whether an asthma exacerbation is the result of an immune-deficient response or an exaggerated immune response continues. Many studies supported the evidence that viral infection has several important roles in disease development, exacerbation, and progression.

Common Viral Pathogens in Asthma

Viral infection is closely associated with wheezing episodes, which resembles the manifestations of asthma. Especially in younger groups, these episodes can be related to the later development of asthma. Among viruses causing respiratory infection, RSV and rhinovirus are well-documented to increase the risk of asthma though early adulthood. In an 18-year longitudinal study, severe early RSV bronchiolitis is associated with an increased prevalence of allergic asthma persisting into childhood, and even early adulthood.[40,41] Among viral wheezing illnesses in infancy and early childhood, those caused by RSV infections are the most significant predictors of the subsequent development of asthma.[42] Host factors may also affect the pathogenesis of asthma in connection with viruses. Children with wheezing illness with rhinovirus were associated with asthma development if they had certain variants at chromosome 17q21.[43]

Virus Infection and Exacerbation

Asthma exacerbations may be triggered by respiratory infections as well as by atmospheric and domiciliary environmental factors. Viral infections may cause a loss of asthma control, and most exacerbations, particularly in children with allergic asthma, coincide with respiratory viral infections. Studies of asthma exacerbation showed higher virus-detection rates than those of COPD. PCR showed the presence of viruses in 80% to 85% in children and 60% to 80% in adults.[44–46] The most common viruses included rhinovirus, influenza, RSV, and corona virus, although some seasonal variation is present. In patients with asthma, URI symptoms persisted longer and were more severe than in healthy controls. Like COPD, PCR for respiratory samples is the preferred diagnostic modality. Before the use of PCR technology, the etiology of respiratory

infections was established by viral cultures, which are difficult to perform. PCR showed a high sensitivity and specificity, although it may not be quantitative in all cases.

Many studies have attempted to find the pathologic immune response to viruses that cause exacerbations, but the mechanisms for exacerbations remain poorly understood. It is not clear if asthma exacerbations triggered by viruses are a manifestation of impaired or overactive immune responses. There is evidence that the T_H2 pathway causes downregulation of antiviral interferon (IFN)-β and IFN- λ and higher viral loads in vitro; however, this has not been reproducible in in vivo studies. On the other hand, there is evidence to suggest that increased T_H2 cytokines and chemokines produced in response to viral illnesses can activate an inflammatory cascade thought to be associated with asthma exacerbations.

Inhaled corticosteroids (ICS) are commonly used in the treatment of asthma, and this treatment should be continued in the case of viral infection. Pretreatment with the ICS was shown to improve airway hyperresponsiveness and eosinophilic inflammation in patients with atopic asthma experimentally infected with rhinovirus.[47] In acute exacerbation, oral or intravenous (IV) corticosteroids are usually indicated, and the immunosuppressive function of these medications does not preclude their use in viral infectious exacerbation. Most viral infection is self-limiting; therefore, antiviral medications are not necessary except during severe epidemic cases. Influenza vaccination is recommended because influenza can cause asthma exacerbation. However, the available evidence is not sufficient to assert that vaccination can reduce the frequency or severity of asthma exacerbations.[48]

CYSTIC FIBROSIS

CF is the most common fatal genetic disease in the United States, with 28,676 patients living with CF in the United States in 2014.[49] CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*) that lead to abnormalities in epithelial chloride transport, causing multiorgan dysfunction.[50–52] The lungs are particularly affected, with evidence of chronic inflammation, recurrent infections, impaired mucociliary clearance, and innate immune impairments that directly affect host defense against respiratory pathogens.[51,53–55] Pulmonary infections remain the greatest cause of morbidity and mortality leading to premature death in CF.[56]

Common Viral Pathogens in Cystic Fibrosis

Similar to individuals without CF, viral respiratory infections are common in CF. A variety of studies dating to 1981 reported variable incidences of common respiratory pathogens, including influenza A and B (12%–77%), RSV (9%–58%), parainfluenza virus (PIV), rhinovirus, metapneumovirus, coronavirus, and adenovirus.[57–64] In these studies, the incidence of specific viral isolates varied greatly from one study to the next due to multiple factors, including methodology, seasonal variation, geographic location, and different age groups. In a recent study of 100 adults with CF, followed prospectively for 12 months, rhinovirus accounted for 72.5% of confirmed viral infections, followed by metapneumovirus (13.2%), and adenovirus (4.1%). Unlike previous studies, influenza virus A and B, PIV, and RSV together accounted for only 10.6% of viral isolates.[65,66]

Previous studies have shown that individuals with CF are no more susceptible to viral infections than healthy controls. In a prospective study of school-aged individuals with CF compared with age-matched controls, there was no difference in the frequency of culture-documented and seropositive viral infections. Younger patients had a higher incidence of viral infections in both groups; however, this did not translate into accelerated lung function decline in the patients with CF.[59] A later study evaluating the impact of viral infections on pulmonary function in infants with CF similarly showed no difference in the incidence of viral infections. However, infants with CF had an increased frequency of respiratory symptoms. Whereas controls did not demonstrate an association between respiratory illness and lung function, infants with CF who suffered an RSV infection and developed respiratory symptoms had a reduction in lung function.[67] A prospective study examining the impact of RSV infection on lung function in a pediatric population demonstrated again that subjects with CF had an increased frequency of respiratory symptoms despite similar rates of viral isolation from cultures and serology in healthy controls. The investigators demonstrated clear associations between RSV infection and worsening clinical severity score, lung function measurements, and rates and duration of hospitalizations for respiratory exacerbations.[68]

Viruses, Exacerbations, and Clinical Deterioration in Cystic Fibrosis

CF respiratory exacerbations are acute clinical deteriorations in a patient's clinical condition characterized by increased respiratory symptoms and

sputum production, and declines in lung function. Exacerbations are commonly precipitated by acquisition of new organisms or changes in respiratory flora.[69–71] CF pulmonary exacerbation rates are increased during winter and have been linked to the influenza season.[72,73] The viruses most frequently implicated in causing respiratory symptoms in CF include rhinovirus, RSV, adenovirus, PIV, influenza A and B, and metapneumovirus.[57–61,66,67] Viral infections are frequently detected during CF exacerbations and viral detection has improved with significant leaps in diagnostic technologies. The implementation of quantitative real-time PCR studies for viral detection in the CF population achieved the highest detection rate of 46% compared with existing literature that previously relied on serologic testing or viral isolation.[61]

Identification of a respiratory virus during exacerbation purports clinical deterioration and increased duration of IV antibiotic compared with virus-negative exacerbations.[60] In a study of 103 children with CF respiratory exacerbations, 61.3% had a positive viral isolation.[74] Two studies in adult patients with CF reported viral isolation rates during exacerbation of 30.5% (n = 100) and 50% (n = 30).[66,75] Although virus-positive exacerbations were associated with higher respiratory symptom scores and serum biomarkers of inflammation, viral infection did not increase rates of lung function decline compared with virus-negative exacerbation. Similarly, there was no significant association between viral infection and accelerated lung function decline in long-term follow-up.[66] A recent study combining pediatric and adult populations reported even higher incidence of virus-positive exacerbations, with 68% in adults and 72% in children.[76]

RSV is the most common cause of lower respiratory tract infection in young children.[77] In children with CF, RSV and influenza have been shown to have the most significant effect in lung function. In infants with CF, RSV infection accounted for up to one-third of hospitalizations, respiratory failure, and chronic supplemental oxygen requirement when followed for more than 2 years.[78] In addition to RSV, influenza A and B infection has been detected in 12% to 23% of CF exacerbations.[61,79,80] Influenza also has been associated with acute and sustained declines in lung function, as well as respiratory failure, and subsequent supplemental oxygen requirement. In a study of 54 pediatric patients, those with an influenza virus–positive exacerbation had larger declines in lung function (26% vs 6% with other viruses). In addition, influenza infection was more frequently associated with larger drops in forced expiratory volume in 1 second (FEV_1) than the other viral infections.[81]

According to data from the European Cystic Fibrosis Society, the influenza A (H1N1) pandemic in 2009 had a severe impact on adult and pediatric patients with CF. The prevalence of infection among 25 centers in multiple countries ranged from 0% to 9.4%. Among the 110 cases reported, the incidence of exacerbations was 53%; 48% of these patients required hospitalization, and 31% required supplemental oxygen. There were 6 incidences of respiratory failure and 3 fatalities. Patients with advanced lung disease were more likely to suffer a severe clinical course. Interestingly, most of the patients recovered lung function to preinfection values.[82,83] Rhinovirus is increasingly reported as a significant pathogen in the CF population. Rhinovirus has now been associated with increased respiratory symptoms, lung function decline, and frequency of exacerbations.[66,74,76] This may be due to improvements in detection techniques and inclusion of a more recently detected species, rhinovirus C.[74]

Interactions Between Viruses and Bacteria

The clinical significance of viral infections in CF extends beyond their immediate morbidity, as viral infections have been proposed to play a role new bacterial acquisition and worsening clinical outcomes. The new acquisition of *Pseudomonas aeruginosa* in CF has been associated with the winter months, coinciding with the peak of respiratory viral infections.[84] Some have proposed that RSV could facilitate the initial infection of the CF airway by *P aeruginosa*[64]; however, a study of 35 adults with CF showed no change in sputum density of *P aeruginosa* when concurrent viral infection was present.[75] A retrospective study in older patients with chronic *P aeruginosa* infection reported an acute deterioration in clinical status in association with influenza A virus infection.[85] Punch and colleagues[86] used a multiplex reverse-transcriptase PCR (RT-PCR) assay combined with an enzyme-linked amplicon hybridization assay (ELAHA) for the identification of 7 common respiratory viruses in the sputum of 38 patients with CF. Fifty-three sputum samples were collected over 2 seasons and 12 (23%) samples from 12 patients were positive for a respiratory virus (4 for influenza B, 3 for parainfluenza type 1, 3 for influenza A, and 2 for RSV). There were no statistical associations between virus status and demographics, clinical variables, or isolation rates for *P aeruginosa*, *Staphylococcus aureus* or *Aspergillus fumigatus*. Retrospective study in older patients with chronic *P aeruginosa* infection reported an acute

deterioration in clinical status in association with influenza virus infection.[85]

PULMONARY FIBROSIS

Pulmonary fibrosis is the end stage of several diffuse parenchymal lung diseases characterized by excessive matrix deposition, lung parenchymal destruction, and progressive respiratory insufficiency.[87] Idiopathic pulmonary fibrosis (IPF) is a form of pulmonary fibrosis with overall poor survival rate and its etiology remains poorly understood. Several risk and predisposing factors of pulmonary fibrosis include environmental, tobacco smoking, viral infections, family history, and genetics. Pulmonary fibrosis is characterized by progressive lung decline over time, with many patients experiencing disease stability punctuated by episodes of acute worsening of clinical symptoms and radiographic changes on chest imaging.

Acute exacerbation of pulmonary fibrosis has been defined to be when no obvious identifiable cause is found for the pulmonary worsening.[88,89] Up to 10% of patients with IPF develop acute exacerbations each year with some resulting in deaths. However, it is unclear if these exacerbations truly accelerate the underlying fibrotic and proliferative process in pulmonary fibrosis or if it is due to complications such as infections, given IPF exacerbations are often accompanied by cough and fever. Initially it has been suspected that respiratory viruses are likely causes of IPF exacerbations. Compared with the strong association between viruses and exacerbations of obstructive lung diseases, such as asthma and COPD, there is currently very little research to suggest possible cause for exacerbations in IPF.

There have been several investigations on the role of pulmonary viruses in acute exacerbations that have resulted, however, in mixed results.[90] Gene expression analyses of stable IPF versus exacerbation in patients with IPF did find evidence of infectious or overwhelming inflammatory etiology. Although the antimicrobial peptide, alpha defensing, was found to be increased in the epithelium and the peripheral blood,[91] using multiplex PCR and pan-viral microarray discovery platform and next-generation deep sequencing to increase viral detection sensitivity, viral infection was not detected in most cases of acute IPF exacerbations. Four of 43 patients with IPF acute exacerbations had evidence of common respiratory viral infections (2 rhinovirus, 1 coronavirus, 1 parainfluenza), whereas no viruses were detected in bronchoalveolar lavage fluid from stable patients.[92] Interestingly, torque teno virus (TTV), a relatively new single-stranded DNA virus, was found to be more common in patients with acute exacerbations than in stable controls. However, TTV also can be detected in patients with acute respiratory distress syndrome, suggesting that this virus is not specific to IPF. Deep sequencing of the lungs from patients with acute exacerbation of IPF did not reveal any evidence for viral pathogens.

Whether viral infections truly have no major role in IPF pathogenesis remains unclear, although evidence suggests this is the case given the studies thus far. It is still possible viral associations have not been clearly proven due to the timing of sampling of IPF patients during their exacerbations or possible incorrect compartment sampling to identify viruses (bronchoalveolar fluid vs interstitial disease). Gene expression studies of lung tissues show suggestive of type II alveolar epithelial cell injury or proliferation, endothelial cell injury, and coagulation in patients with acute exacerbation of IPF that is distinct from patients with acute lung injury.[93] It is possible there are no major associations with conventional respiratory viruses with IPF. However, there have been reports of the presence of certain human herpesviruses, such as Epstein-Barr virus (EBV), in patients with IPF and animal models of fibrosis.[94] Another study showed patients with IPF who underwent lung transplantation were found to be positive for EBV (11/12) and human herpesvirus (HHV)-6B (10/12) compared with control lung samples that were positive for HHV-6B (3/10) and negative for EBV (0/10).[95] They suggest that herpesviruses could contribute to the lung epithelial injury that initiates profibrotic responses in IPF. Whether or not IPF acute exacerbation represents reactivation of latent herpesviruses remains unknown and requires further explorations.

It is interesting the evidence associating respiratory viruses with IPF is rather weak, whereas it is quite clear that respiratory viral infections are important in the pathogenesis of obstructive lung diseases, such as COPD and asthma. Is this difference in association of respiratory virus and chronic lung disease due to the involvement of different cell types in the lung, such as airway epithelium versus alveolar epithelium? Understanding the mechanism behind these differences will be important to determine.

SARCOIDOSIS

Sarcoidosis is a systemic inflammatory disease characterized by noncaseating epithelioid granulomatous inflammation in affected sites, including the lung.[96] Although many patients experience disease remission within the first few years, more

than 30% to 50% of patients develop chronic disease requiring treatment to prevent progression of organ dysfunction and fibrotic changes. Epidemiologic studies and basic research suggest that sarcoidosis represents an immune response to an exogenous agent in a genetically susceptible individual. A definitive exogenous agent responsible for sarcoidosis remains elusive. Some investigators have speculated that a transmissible or infectious agent may cause sarcoidosis.[97] There has been an increasing body of evidence to suggest a link between infection and sarcoidosis, especially with regard to *Mycobacteria* and *Propionibacteria*. The thought is that maybe persistent antigenic stimulation from microbial agents at sites of inflammation results in sarcoidosis. However, to date, identifying the etiology of sarcoidosis has remained elusive. A variety of viruses have been proposed as etiologic agents or triggers for sarcoidosis; yet, this association has been difficult to define. The viruses associated with sarcoidosis based on serology include EBV, cytomegalovirus, herpes simplex, HHV-6 and HHV-8, and coxsackie virus.[96,98] Data supporting an increased frequency of these viral respiratory infections in sarcoidosis have been lacking.

SUMMARY

Respiratory viruses remain to be important in the pathogenesis of chronic lung diseases. Recent data with the use of more sensitive nucleic acid–based viral diagnostics highlight the underappreciation of prevalence of respiratory viruses and their role in lung diseases. Evidence for their contribution in disease pathogenesis and exacerbation is more compelling in chronic lung diseases, such as COPD, asthma, and CF, in which viruses are commonly found and associated with disease exacerbations. There is much less compelling evidence for the association of viruses with IPF or sarcoidosis. Measures to better understand how respiratory viral infections contribute to disease pathogenesis of many of the chronic lung diseases are needed. Preventive measures to limit such viral infections with good hand hygiene, avoidance of sick contacts, and viral vaccinations are recommended for patients suffering from chronic lung diseases.

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