A Pandemic Lesson for Global Lung Diseases: Exacerbations are Preventable

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Abstract

A dramatic global reduction in the incidence of common seasonal respiratory viral infections has resulted from measures to limit the transmission of SARS2-Cov-19 during the pandemic . This has been accompanied by falls reaching 50% internationally in the incidence of acute exacerbations of pre-existing chronic respiratory diseases that include asthma, Chronic Obstructive Pulmonary Disease (COPD) and Cystic Fibrosis (CF). At the same time, the incidence of acute bacterial pneumonia and sepsis has fallen steeply world-wide. Such findings demonstrate the profound impact of common respiratory viruses on the course of these global illnesses. Reduced transmission of common respiratory bacterial pathogens and their interactions with viruses appear also as central factors. This review summarises pandemic changes in exacerbation rates of asthma, COPD, Cystic Fibrosis (CF) and pneumonia. We draw attention to the substantial body of knowledge about respiratory virus infections in these conditions, and that it has not yet translated into clinical practice. Now the large-scale of benefits that could be gained by managing these pathogens is unmistakable, we suggest the field merits substantial academic and industrial investment. We consider how pandemic-inspired measures for prevention and treatment of common infections should become a cornerstone for managing respiratory diseases.

Key words

SARS2-Cov-19 pandemic, non-pharmaceutical interventions, rhinovirus, pathobionts, asthma, COPD, pneumonia

Importance of the proposed topic to clinical practice

The widespread introduction of non-pharmaceutical interventions (NPIs) such as social distancing, household lockdowns, school closures, restricted travel and mask wearing for SARS2-Cov-19 has greatly reduced the circulation of all known respiratory viruses. Unexpectedly, this has almost halved internationally the incidence of acute exacerbations of asthma, COPD, and bacterial pneumonia. The association of viral infections, particularly human rhinovirus (HRV), with exacerbations of airway disease is well known. Despite this, preventing or treating such infections is not currently a standard component of clinical care. Between a third and a half of the multiple billion-dollar costs of treating asthma and COPD arise from acute episodes, providing a strong incentive to bring to clinical practice post-pandemic insights into preventing and treating virus infections.

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Introduction

Approximately 545 million people worldwide have a chronic respiratory disease, an increase of 40% from 1990 to 2017 (1). The annual costs of healthcare and lost productivity due to COPD and asthma are €48.4 billion and €33.9 billion respectively in the European Community: half of this is attributable to exacerbations for both diseases (https://www.erswhitebook.org/). In the US the total cost of asthma, including absenteeism and mortality, was $81.9 billion in 2013 (2); 37% of medical costs were attributable to acute episodes. The annual cost of COPD to the US economy was $38.8 billion in 2005 (3). As a consequence, preventing exacerbations of these most common respiratory conditions is of global importance.

Circulation of respiratory viruses during the pandemic

During the SARS2-Cov-19 pandemic there has been widespread introduction in both the Northern and Southern hemispheres of non-pharmaceutical interventions (NPIs) that included enforced lockdowns, social distancing, border restrictions, school closures, and tracing and isolation of symptomatic individuals (4). Within-season influenza activity has been at historically low levels since 2020 (WHO Influenza Update N° 398, (5)) and circulations of human metapneumovirus (hMPV), enterovirus, adenovirus, respiratory syncytial virus (RSV), and human rhinovirus (HRV) have all been substantially reduced (6). In the UK The emergence of SARS-CoV-2 was associated with substantial reductions in the circulation of seasonal respiratory viruses and large differences in the characteristics of viral-associated disease (7).

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Pandemic effects on exacerbations

Asthma

Unexpectedly marked changes in the incidence of acute asthma attacks during the SARS2-CoV-19 pandemic have been observed internationally. In the US a study of 3959 children and adolescents with diagnosed asthma found all-cause healthcare encounters decreased significantly during the pandemic compared with the preceding year. This included well-child visits (48.1% during the pandemic vs. 66.6% in the prior year; $P<0.01$), emergency department visits (9.7% vs. 21.0%; $P<0.01$), and inpatient admissions (1.6% vs. 2.5%; $P<0.01$), despite a 100-fold increase in telehealth encounters (8). Asthma exacerbations that required treatment with systemic steroids also decreased (127 vs. 504 exacerbations; $P<0.01$) (8). A Harvard-led multi-centre study found a significant decrease in asthma exacerbations from Q1 to Q2 of 2020 compared with 2019 (–0.47 exacerbations per year (95% confidence interval (95% CI) –0.76 to –0.19; $P=0.001$), a relative reduction of 41%) (9)

In a large UK NHS Trust hospital a significant reduction in all-cause and exacerbation-related asthma and COPD admissions (~ 30% and 40% respectively) was observed, although patients also reported a subjective decline in disease control and a negative impact on their mental health (10). Also in the UK, a study of a primary care database of 9,949,387 patients containing 100,165 patients with asthma found a significant reduction in attendance to primary care for asthma exacerbations during the pandemic in all age groups, both sexes and across most regions in England (11).

During pandemic measures, a Japanese survey of 10,226 in-patient cases diagnosed with asthma exacerbations in 83 hospitals between October 2018 and September 2020 found a >70% decrease in paediatric patients with asthma exacerbations requiring hospital admission (12).

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In Guangzhou China, strict countermeasures undertaken for the pandemic were associated with a decreased frequency of infectious respiratory diseases and severe asthma exacerbations among urban children (13). The authors speculated that this may be due to reduced pollution as well as a reduction in the transmission of viral respiratory infections (13). An increase in the frequency of mild asthma exacerbations was attributed to overlap of symptoms associated with COVID-19 and a general fear of development of COVID-19 (13).

In Singapore, a sustained reduction in asthma admissions with PCR-proven respiratory viral infections coincided with the widespread adoption of public health measures (14). The total number of asthma admissions per month dropped from a mean of 64.7 (SD±9.1) pre-pandemic to 39.2±7.5 during the pandemic (P<0.001). During the pandemic, only 11.5% (33/288) of asthma admissions had a concurrent PCR-proven respiratory viral infection (RVI), while one-half (53.5%, 348/651) of asthma admissions had a positive result pre-pandemic (OR 0.11, 95% CI 0.08–0.17; P<0.001). Notably, over a 5-month period from May to September 2020 onwards, zero asthma admissions had concomitant RVIs.

A study from Jordan of 1,207 paediatric asthma exacerbations found that with non-pharmacological interventions in place there was a decrease in exacerbations measured by admissions and emergency room visits (15). During the lockdown (22 March to 1 May 2020), the mean weekly admissions (2.6 ± 1.4)) were significantly lower than that before the lockdown (8.6 ± 2.0) and after the lockdown (5.2 ± 2.0), and significantly lower than the same weeks in 2019 and 2018 (15).

In Holland a study of 67 patients with severe and uncontrolled asthma enrolled in a clinical trial (the BREATHE study) showed a significantly reduced (~70%) asthma exacerbation frequency during COVID-19 social distancing measures, compared with previous years (16). Anxiety towards acquiring COVID-19 infection was increased in these subjects (16).

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COPD

Equally impressive decreases in exacerbation rates have been reported internationally for patients with COPD. Within the UK an interrupted time series analysis of the entire populations of Scotland and Wales (approximately 5.5 and 3.2 million people respectively) showed a 48% pooled reduction in acute exacerbations of COPD requiring hospital admission (17). Within Wales, emergency room attendance for exacerbations was reduced by 46%, and primary care consultations were reduced by 39% below a five year average (17). Interestingly, the authors did not find a rebound in events following the release of lockdown but instead a gradual increase in healthcare utilisation (17).

In the USA, data involving 4422 COPD admissions to a large multicenter health care system in Maryland demonstrated a season-matched 53% decline in COPD admissions during the SARS2-Cov-19 pandemic. The demographics and co-morbidity profile of those who did attend were similar to those who attended in non-pandemic circumstances. The decline correlated to community viral burden (r = 0.73; 95% CI, 0.67-0.78) (18).

The number of exacerbations of COPD in Hong Kong fell by 44% in the first three months of 2020 compared with the same interval in four previous years, which was attributed to increased masking and social distancing (19). In Malta a 54.2% drop in acute exacerbation COPD admissions was seen in 2020 (n = 119 vs. n = 259 in 2019). There were no significant differences in patient demographics or medical comorbidities (20).

Studies from the Singapore General Hospital showed that acute COPD admissions per month decreased by more than 50% (average 36, standard deviation (SD) 6) during February–July 2020 compared to 92 (SD 18) pre-pandemic) (21). Within admitted patients the rate of positive respiratory viral PCR tests fell from 30% to 10.6%, despite increased PCR testing from 60% of patients pre-pandemic to 98% (21) .

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Cystic Fibrosis, Bronchiectasis and Interstitial Lung Disease.

Exacerbations also cause progressive declines in lung function in patients with CF and bronchiectasis. A comparison of exacerbation rates at the CF Centre in Indianapolis USA in the first months of 2019 (pre pandemic) and 2020 reported a 50% fall that was attributed to restrictions on social interaction and reduced exposure to respiratory viral infections (22). In a prospective UK study of bronchiectasis the proportion of patients experiencing a hospitalization due to severe exacerbation was 8.8% between March 2020 and March 2021 compared to 14.3% and 16.3% in the two previous years (23).

Interstitial Lung Disease (ILD) is another chronic respiratory disease with poorly understood episodes of exacerbation. A questionnaire survey of 134 hospitals in Japan of acute exacerbations of interstitial lung disease (AE-ILD) early in the COVID-19 epidemic found no clear trends in exacerbation frequencies (24). This mitigates against an infective element in ILD exacerbations.

Confounding factors

Factors other than infections may have added to the decline in attendances of exacerbations of airway disease. The recognition that COVID infection is associated with worse outcomes in asthmatics (25) and patients with COPD (26) may have affected patient behaviour, and data from the UK suggest that the reduction in asthma exacerbations may be related to reductions in primary care contacts (27). However, another UK study reported that the fall in primary care attendance for exacerbations for asthma was not seen in attendance numbers to the emergency room, implying people were struggling to access primary care, or that they were preferentially attending the emergency room or waiting at home until they became severe enough to attend at hospital (11). Others have suggested that the SARS-Cov-2 pandemic may have been an opportunity for patients to take more control over their healthcare, becoming more adherent to their medications and shielding advice (28).

Air pollution is another factor for consideration. Lockdown events reduced the population-weighted concentration of nitrogen dioxide and particulate matter levels by about 60% and 31% in 34 countries, with mixed effects on ozone (29), possibly affecting asthma and COPD exacerbation rates.

Nevertheless, while marked decreases have been reported in admissions for disorders of the respiratory system in the UK, no changes in admissions for surgery or accidental injury have been observed (30). It is difficult to discount that the declines in exacerbation rates are remarkably consistent internationally and are from comprehensive studies across a wide range of different healthcare systems and environments.

Acute bacterial infections

Lower respiratory bacterial infections are leading causes of global morbidity and mortality, especially in children and older adults (31). During 2016 *Streptococcus pneumoniae* was estimated to have caused approximately 1·1 million deaths worldwide, with *Haemophilus influenzae* also of global importance (31). In common with *Neisseria meningitidis*, which causes meningitis and sepsis, these WHO priority pathogens are transmitted by the respiratory route and are commonly carried in the oropharynx of healthy individuals.

The international Invasive Respiratory Infection Surveillance (IRIS) initiative prospectively analysed the incidence of invasive disease due to *S. pneumoniae, H. influenzae*, and *N. meningitidis* from laboratories in 26 countries and territories across six continents (32). Numbers of weekly cases in 2020 were compared with corresponding data for 2018 and 2019. All countries and territories had experienced a significant and sustained reduction in invasive diseases due to *S. pneumoniae, H. influenzae*, and *N. meningitidis* in early 2020 (Jan 1 to May 31, 2020), coinciding with the introduction of COVID-19 containment measures in each country.

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Overall, social changes caused by the SARS2-Cov-19 pandemic were accompanied by a 38% decrease in the incidence of reported *S. pneumoniae* invasive infections (incidence rate ratio [IRR] 0·62 [95% CI 0·54–0·70]). Similar steep decreases were seen for *H. influenzae* and *N. meningitidis* infections (32). The authors estimated population mobility changes from mobile phone data, and using time series analysis showed a decrease in reported *S. pneumoniae* infections of 68% at 4 weeks (IRR 0·32 [95% CI 0·27–0·37]) and 82% at 8 weeks (0·18 [0·14–0·23]) following the week when movement changes were first observed (32). By contrast, the incidence of disease due to *Streptococcus agalactiae*, a non-respiratory pathogen, did not change during the pandemic.

In the UK Prospective National Cohort Study the incidence of invasive pneumococcal disease in all of England fell by 30% in 2019/2020 compared with 2018/2019 (IRR, 0.70; 95% CI, 0.18–2.67), with large reductions observed across all age groups during March–June 2020 (33). Week by week contrasts during the 'Circuit Breaker' partial lockdown in Singapore against the preceding 10 years showed the mean number of positive urinary streptococcal antigen tests in 2020 to have fallen to by 50% compared to 2010 to 2019 (34).

In Taiwan, invasive pneumococcal disease (IPD) is a notifiable condition for which reporting is mandatory. A comparison of the case number of patients with IPD from Taiwan's CDC between January and August found 162 IPD cases were reported during the first 8 months in 2020, compared to a monthly range of 282 to 400 cases over the previous four years (35). In Guangzhou China "Strict childhood Pneumonia" cases fell from >600 over each of the past 3 years to 172 in 2020 (13); In Holland a study of three hospitals found that the first COVID-19 wave in March, April, and May 2020 was marked by 13 adults hospitalised with pneumococcal bacteraemia, compared to 32 ± 6 (mean ± SD) cases during the corresponding months in the preceding five years (36).

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Post pandemic return of common viral illnesses

The relaxation of the most stringent public health interventions in many countries has been followed by a rapid resurgence in rates of seasonal respiratory viral infections. For example, the CDC have reported that reduced transmission of common respiratory viruses in the United States during 2020 was followed by increased respiratory syncytial virus activity from April 2021, and increased rates of infection with coronaviruses, parainfluenza viruses, and respiratory adenoviruses from January or February 2021. By contrast, HRV and enteroviruses began to increase in June 2020 (37). An early resurgence of HRV has also been observed in German National data (38).

Data from approximately 260 hospitals and clinics in Tokyo has numbered paediatrician-diagnosed weekly cases of RSV infection since 2003 (39). No outbreaks of RSV were reported in 2020, but in 2021 the largest annual increase in cases since monitoring began was observed. Following relaxation of physical distancing recommendations in Australia, RSV activity increased well beyond median yearly peaks in 2021 (40). Both in Japan and in Australia the median age of patients with RSV was significantly higher during resurgence than previous years (39, 40), suggesting that an accumulation of susceptible persons during the pandemic may have contributed to this subsequent large outbreak.

The unusual timing and magnitude of the resurgent viral infections raises complex clinically relevant questions about the contribution of birth cohort effects, natural immunity, and interventions (37).

Known roles of viral exacerbations in common respiratory diseases

Exacerbations of childhood asthma have long been recognised to be precipitated by infections with common respiratory viruses, among which human rhinovirus (HRV) is by far the most important

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pathogen (41, 42). Adult asthma exacerbations show a similarly close relationship to HRV infection (43).

COPD exacerbations too are triggered by viral infections (44, 45). For example, in a longitudinal UK study 40% of COPD exacerbations were associated with viral infections (46) and HRV was found in 58% of viral exacerbations. Other viruses included coronavirus (11% of virus exacerbations), influenza A and B (16%), and occasional parainfluenza and adenovirus detections. Respiratory syncytial virus (RSV) was detected in approximately 29% of exacerbations, although RSV was also found in a significant number of patients in the stable state (46). Exacerbations were more severe objectively and symptomatically when viruses were present (46).

In normal circumstances, different viruses circulate in populations at different times, and this is reflected in the age of patients and the nature of their exacerbations. In the northern hemisphere childhood asthma exacerbations peak following school return after the summer vacation and are predominantly associated with HRV (47). In older subjects, exacerbations of both COPD and adult asthma, with increasing risk with age, are at their highest average annual levels during Christmas. This appears to be independent of the timing of levels of influenza, RSV, parainfluenza, or adenovirus detections (47). The role of HRV during the winter peak of both diseases has not been clarified, and transmission of bacterial pathogens to patients with COPD (discussed below) is also a factor.

In CF patients the frequency of viral respiratory infections also closely associates with pulmonary deterioration (48). In children with CF 46% of exacerbations have been associated with respiratory viruses, compared to asymptomatic carriage in 17% (49). Viral infections are recognised in 33% of adult CF exacerbations (50) and are most commonly due to HRV (51). It has been suggested that respiratory viruses may represent an under-exploited target in the battle to control CF symptoms and progression (52). Respiratory viruses, most frequently HRV-A, are similarly commonly detected during pulmonary exacerbations of bronchiectasis in children (53).

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Bacterial transmission and interactions with viruses

Pathobionts are normally resident bacteria that in some circumstances can cause disease (54). *S. pneumoniae, H. influenzae* (NTHi), *N. meningitidis* and *Moraxella catarrhalis* are classical pathobionts that are commonly found in normal airways. Transmission of *S. pneumoniae,* NTHi and *N. meningitidis* from healthy carriers is important in invasive bacterial diseases (55-57).

Recurrent exacerbations of COPD in individual patients are associated with the isolation of new strains of *S. pneumoniae, H. influenzae* (NTHi) and *M. catarrhalis* (58), supporting the causative role of bacteria and in the current context suggesting that their transmission may be suppressed to therapeutic advantage.

There is also strong evidence for bacterial pathogen engagement in asthmatic airway inflammation. Bisgaard *et al.* found by culture that neonatal nasopharyngeal colonisation with *S. pneumoniae*, *M. catarrhalis*, or *H. influenzae* foreshadowed the development of asthma (59). We subsequently discovered by bacterial sequencing that similar organisms were in excess in the lower airway microbiota of asthmatic children and adults (60). *Proteobacteria* excess has now consistently been found in asthmatic airways (60-62) (reviewed in (63)), as have *Streptococcus* spp. in severe disease (60, 64, 65). The neonatal study of Bisgaard *et al*. (59) and the presence of significant differences in wheezing-associated pathobiont frequencies in children who are naïve to the use of antibiotics and inhaled steroids (66) indicates that these changes are not secondary to asthma therapy.

Viral perturbations of the resident microbiome may be a general initiating factor of severe bacterial infections (67). Interactions between respiratory tract viruses and resident pathobionts are well recognised in upper respiratory tract infections (68). *H. influenzae* is the most common bacterial accompaniment of COPD exacerbations (69) and its presence during exacerbations with HRV is associated with poor outcomes (70). Similarly, the presence of pathogenic bacteria during HRV

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infection is associated with asthma exacerbations (71). Potential mechanisms for interactions are reviewed in (72).

Most deaths in the 1918-1919 influenza pandemic were attributable to secondary pneumonia caused by *S. pneumoniae* and *H. influenzae* (73), where the mass movement of troops and people contributed to bacterial as well as viral propagation. The recent pandemic-associated reduction in global rates of pneumonia (described above) was thought by the IRIS authors to follow reduced transmission of pathogenic bacteria (31), whilst recognising that respiratory viruses have a role in bacterial disease (5, 74).

Of interest in this regard is a prospective study from Israel of pneumococcal pneumonia in young children (75). The authors observed a steep decline in the incidence of community-acquired alveolar pneumonia (CAAP) and bacteraemic pneumococcal pneumonia during the pandemic (incidence rate ratios, 0·07 and 0·19, respectively). However, the prevalence of pneumococcal carriage prevalence was only slightly reduced, and the density of colonization and pneumococcal serotype distributions were similar to previous years. At the same time the pneumococcus-associated disease decline was associated with a suppression of RSV, influenza viruses, and hMPV, often implicated as co-pathogens with pneumococcus (75).

Ecology of airway microbial communities

The marked effects of social isolation during the SARS-Cov-2 pandemic encourage an overview of interactions between the population and airway pathogens (Figure 1). Respiratory viruses and bacterial pathobionts are in general circulation within the community and are transmitted over relatively short times scales between healthy and susceptible individuals (left side Figure 1). Commensal microbial communities at the airway mucosal barrier are conserved and highly ordered (76), reflecting symbiosis and co-evolution with human host factors (77). They play essential roles in resistance to pulmonary infections (62, 78, 79). Over longer periods (possibly generations) loss of commensal diversity in the wider population may reduce pathogen resistance (80). The clinical emphasis in asthma and in COPD has understandably been directed against inflammation (right side Figure 1) but the likely efficacy of left-sided interventions to prevent exacerbations are now clear.

Therapeutic implications

Modern biologic therapies in controlled clinical trials have successfully reduced exacerbations rates of moderate to severe asthma (81). By analogy, glucocorticoids and biologics are beneficial in the treatment of the inflammatory consequences of SARS-Cov-2 infection (82, 83). Nevertheless, nearly two-thirds of patients with severe asthma treated with biologics continue to experience uncontrolled disease (84). Although the importance of virus infections at the start of acute asthma exacerbations is very well understood, it may be fair to say that their prevention and treatment has before now been neglected. Indeed, a recent influential publication failed to mention infection at all in a review of potential of strategies to drive down the global burden of asthma (85).

The role of bacterial infections is accepted in patients with COPD, but viruses are not usually treated. Notwithstanding the known contribution of viruses, patients with recurrent COPD exacerbations typically are managed with repeated systemic antibiotic courses (86). However, microbiological diagnosis by culture of NHTi is demanding (79) and antibiotics are often given empirically. Acute infection accompanying COPD is one of the most common indications for adult antimicrobial therapy, and plays a substantial role in antimicrobial resistance (AMR) in the population (87). Consequently, sequence-based distinction of viral and bacterial components may better target management.

The efficacy of innovative responses to the SARS-Cov-19 pandemic demonstrates that several levels of strategy directed against microbial infection (Figure 2) are not only possible but also likely to be successful. For those approaches already developed, this review strengthens the case for their clinical

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implementation, but the opportunity is also clear for novel interventions. We consider preventive and therapeutic approaches below. We consider that most preventive therapies could be administered at times of high risk, such as autumn for childhood asthma in the winter months for patients with adult asthma and COPD.

Non-pharmaceutical interventions

The unexpected decreases in exacerbations of chronic respiratory diseases has resulted from a diverse array of different public health measures applied in different countries. Some measures such as social isolation and school lockdowns are not pragmatic on a long- term basis, and it remains unclear which interventions should be pursued in the post-pandemic era. Prospective research is therefore urgently required to assess the impact of individual interventions and should include objective measurements of viral transmission and kinetics in susceptible populations. In addition, the importance of public education should be highlighted regarding the risk that apparently trivial colds may pose to vulnerable individuals.

Access to safe air through sophisticated ventilation has potential in schools and workplaces (88), but a challenge exists to improve ventilation in the developing world. Hospitals are high-risk environments for patients and for staff. As a precedent, the transmission of respiratory bacterial pathogens between susceptible individuals is well recognised in hospitals (89) and in children attending clinics for cystic fibrosis (90-92). *Mycobacterium abscessus* is an exemplar for the international spread of dominant clones of an important lung pathogen (93). Knowledge of these risks to CF patients has led to aggressive measures to control transmission of MDR strains in hospitals and clinics (94). Nosocomial infections by HRV and common bacterial pathogens may also respond to such measures

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Bolstering mucosal resistance

The healthy airway microbiota are contained within a structured ecosystem, suggesting balanced relationships between the microbiome and human host factors (76). Although still poorly understood, this airway microbiome-mucosal complex (AMMC) is likely to exhibit cognate effects on pathogen activity and reactive immunity and is a rich area for future study and manipulation.

AMMC activities may be enhanced by non-specific “trained immunity” to a range of viral infections. BCG (bacille Calmette-Guérin) vaccination in children protects against a range of serious infections independently of tuberculosis prevention (95) and in elderly patients BCG vaccinations double the time to occurrence of respiratory tract infections of probable viral origin (96). Other non-specific approaches might include an oral bacterial extract (97), currently being investigated in a controlled clinical trial (the ORBEX study: NCT02148796) for the prevention of wheezing lower respiratory tract illness.

Binding inhibition

HRV gains access to airway epithelial cells by binding to surface receptors. Major group HRVs bind to intercellular adhesion molecule 1 (ICAM-1) (98) and minor group viruses bind the low density lipoprotein receptor (LDLR) (99) . HRV-C, which are associated with severe acute asthma attacks more frequently than other rhinoviruses (reviewed in (100)), binds to cadherin-3 CDHR3 (101). This limited range of receptors may permit strategies such as competitive inhibition (102) to prevent virus binding to airway epithelial cells. The initial site of infection is often nasal, providing the opportunity for topical therapies.

Most viral pathogens are membrane-enveloped viruses that require the fusion of viral and cell membranes for virus entry. Compounds that target the membrane fusion process represent new possibilities for broad-spectrum antiviral discovery (103)

It may be relevant that the most important genetic effect on asthma (the *ORMDL3/GSDMB* locus) (104) strongly mediates the risk of viral induced exacerbations (105) and provides potentially druggable targets in sphingolipid pathways that may influence HRV adhesion by modulating expression of ICAM1 (106). *CDHR3* is another susceptibility locus for early childhood asthma with severe exacerbations (107). The asthma-associated coding polymorphism (*CDHR3 C529Y*) exhibits enhanced cell-surface expression of protein and has shown 10-fold increases in HRV-C binding and virus progeny yields in a cellular model (108).

Vaccines

Vaccines against bacterial respiratory pathobionts can be highly effective and are administered internationally. The vaccine-related loss of capsular genes in NTHi and the widening number of circulating strains has however led to an urgent and ongoing search for alternative antigens (87).

Prevention of HRV infections by vaccination has also been difficult to achieve. HRV are made up of three genetically distinct groups, designated A, B, and C and containing more than 100 serotypes (109). Multiple virus types circulate simultaneously in families and HRV are frequently transmitted from children to other family members (110). HRV sequences show minimal common sites that might be antigen epitopes, so single vaccines have been problematic to design (111). Polyvalent vaccines may be useful (112), although development of a polyvalent vaccine for Dengue, an infection caused by four flaviviral serotypes (DENV1-4), has been hindered by antibody-dependent enhancement (ADE) of disease following mixed secondary infections (113).

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Despite these difficulties, the technological advances underpinning rapid development of vaccines for SARS-Cov-2 (114) should offer great hope for future efforts.

Small molecule

HRV infections are an obvious target for drug therapy, although major challenges have been recognised (115). Approaches used include Ribavirin, capsid binding inhibitors, 3C protease inhibitors, NO enhancers, and mammalian cathelicidins LL-37, protegrin-1, and SMAP-29 (reviewed in (115)). Molnupiravir, a novel antiviral recently identified as efficacious against SARS2-Cov-19 (116) is a prodrug for the ribonucleoside analog β-D-N4-hydroxycytidine (NHC) which has broad-spectrum antiviral activity against RNA viruses, including influenza (117). The macrolide antibiotic azithromycin (AZM) is effective in preventing exacerbations of COPD (118), and it is of interest that AZM reduces *in vitro* replication of several classes of viruses including rhinovirus, influenza A, and coronaviruses, via mechanisms that include enhanced expression of anti-viral pattern recognition receptors and induction of anti-viral type I and III interferon responses (119). These experiences and the potential size of the market encourage industry efforts to bring to the clinic small molecules to treat HRV.

Conclusions

Viral infections have long been recognised to precipitate attacks of asthma and COPD, but little of this knowledge has translated to improvements in healthcare. Bacterial pathobiont transmission plays also a significant but underestimated part. The SARS2-Cov-19 pandemic demonstrates how targeting of common respiratory pathogens could prevent 50% of exacerbations of COPD and asthma. The successful scientific response to SARS2-Cov-19 should encourage a reappraisal of means to prevent or mitigate other universal respiratory infections. The efficacy of pooling of resources during the

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pandemic into large, multiarm, multicentre, multicountry RCTs (120) suggests that similar efforts are justified for common respiratory pathogens.

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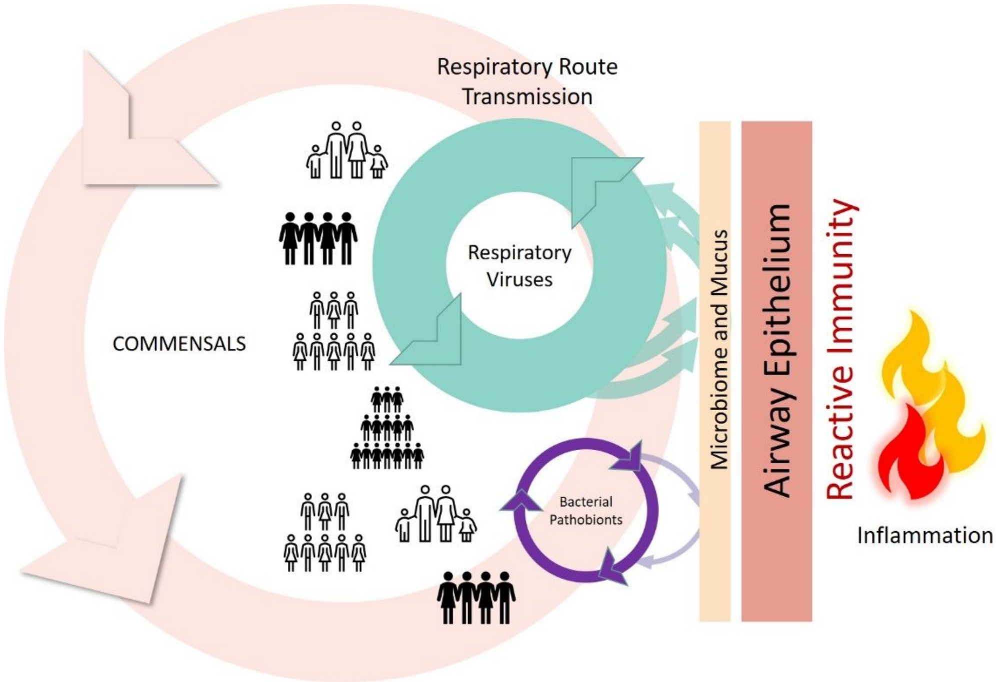
Figure 1: Major microbial factors in acute respiratory episodes



To the left of the figure, the circulation of multiple respiratory viruses in the population provides a continued source of mucosal insults. Circulation and adherence of common bacterial pathogens has the potential to cause invasive disease and sepsis as well as lower grade chronic damage. Airway commensals also circulate within the population, and their diversity is protective against infection. Viruses and bacteria interact positively and negatively within the mucous layer and the epithelium. The microbiota and epithelia induce reactive immunity to infection and consequent inflammation, shown on the right. Current therapies and research investment are directed to the right, but consequences of the SARS2-Cov-19 pandemic show the extraordinary potential of left-sided interventions.

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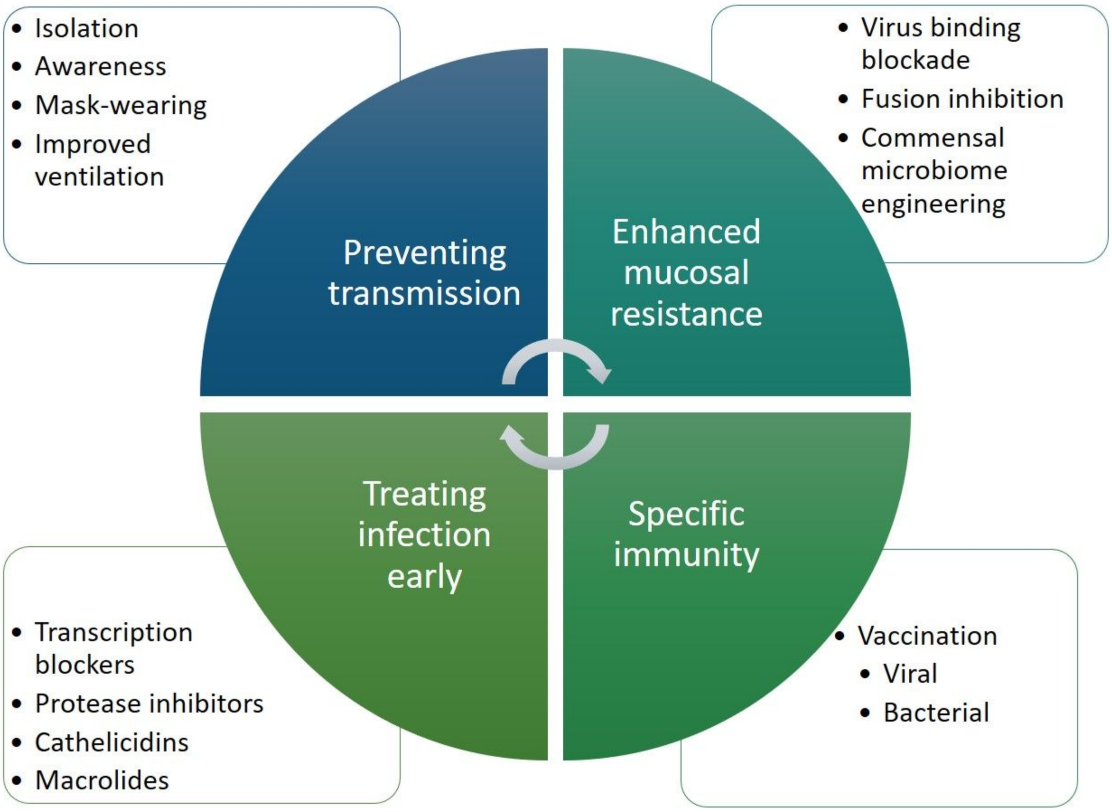
Figure 2. Prevention and treatment of viral-induced exacerbations



The figure illustrates potential ways of mitigating the effects of respiratory viral infections on exacerbations of COPD and asthma. Non-pharmaceutical interventions have been of proven efficacy in preventing transmission but may come at a significant societal cost. Novel methods to block viral adhesion and invasion of the mucosa have a high potential. Vaccination can provide effective immunity against severe infections, although it has so far proved difficult for important viral and bacterial pathogens. A range of drugs are already available for treating active viral infections, but strategies have yet to evolve for their early use.

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