



Review article

Pollen, respiratory viruses, and climate change: Synergistic effects on human health

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ABSTRACT

In recent years, evidence of the synergistic effects of pollen and viruses on respiratory health has begun to accumulate. Pollen exposure is a known risk factor for the incidence and severity of respiratory viral infections. However, recent evidence suggests that pollen exposure may also inhibit or weaken viral infections. A comprehensive summary has not been made and a consensus on the synergistic health effects has not been reached. It is highly possible that climate change will increase the significance of pollen exposure as a cause of respiratory problems and, at the same time, affect the risk of infectious disease outbreaks. It is important to accurately assess how these two factors affect human health separately and concurrently. In this review article, for the first time, the data from previous studies are combined and reviewed and potential research gaps concerning the synergistic effects of pollen and viral exposure are identified.

1. Introduction

Pollen is an important cause of seasonal allergies and contributes greatly to the worsening of asthmatic symptoms. It is estimated that 10–30% of the global population is afflicted by seasonal allergic rhinitis (hay fever) (World Allergy Organisation, 2013). Climate change increases the prevalence and severity of allergic disorders, as pollen seasons shift and the total time populations are exposed to different pollen is prolonged (Ziska and Caulfield, 2000). Higher intensity of pollen production and release (Anderegg et al., 2021; Kim et al., 2018), as well as the spread and adaptation of allergenic plants in new areas, will further affect respiratory health. Coupled with exposure to airborne pollen, humans can be co-exposed to respiratory viruses, another significant cause of respiratory problems at the population level. Similar to allergic disorders, climate change leads to an increase in the number and severity of viral pandemics (Pörtner et al., 2022). In recent years, evidence of the synergistic effects of these two inhalable exposures has begun to accumulate (Shah et al., 2021; Hoogveen et al., 2021; Wallace

and Wang, 2021; Damialis et al., 2021; Gilles et al., 2020; Choi et al., 2022). Co-exposure to pollen and respiratory viruses could induce immunological changes in the lungs and beyond, and thus affect the health status of the exposed individuals. As such, it is important to accurately assess how these two factors affect human health.

This review article is the first one to combine the data available from previous studies concerning the synergistic effects of pollen and viral exposure. Searches were conducted in PubMed and Scopus and articles of epidemiology and experimental studies which assessed associations between pollen and all relevant human respiratory viruses were retrieved. Keywords included allergen, allergy, antiviral, climate change, immune response, pollen, respiratory virus, viral infection. Articles published in English since 2000 were included. We also went through prior works that have been central or pivotal to this topic and included articles that could provide the reader with a comprehensive background for understanding the current knowledge. This review article aims to summarise the current knowledge and highlight the significance of new research.

Abbreviations: ACE2, Angiotensin-converting enzyme 2; AR, Allergic rhinitis; CCL, Chemokine (C–C motif) ligand; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HBE, Human bronchial epithelial cell line; HCMV, Human cytomegalovirus; HNEC, Primary human nasal epithelial cell; ICAM-1, Intercellular Adhesion Molecule 1; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; ILI, Influenza Like Illnesses; IP, Interferon gamma-induced protein; MCP, Monocyte chemoattractant protein; MDC, Macrophage-derived chemokine; MHC, Major histocompatibility complex; MIP, Macrophage Inflammatory Protein; PBEC, Primary bronchial epithelial cells; PBMC, Human peripheral blood mononuclear cells; RIG-I, Retinoic acid-inducible gene I; MDA5, Melanoma differentiation-associated protein 5; RSV, Respiratory syncytial virus; TER, Transepithelial/transendothelial electrical resistance; TLR, Toll-like receptor; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor.

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2. Pollen

During the pollen season, sensitized individuals may suffer from hay fever symptoms and the prevalence of the allergy and asthma-related emergency room visits and drug prescriptions increase subsequently (Saha et al., 2021; Neumann et al., 2019; Ito et al., 2015; Darrow et al., 2012). Interestingly, the threshold at which pollen counts can trigger symptoms varies by pollen species, the sensitivity of the population, and interactions with other atmospheric exposures (Dellavalle et al., 2013; Erbas et al., 2012). Pollen allergies can affect the quality of life of sensitized people by, for example, reducing the possibility of outdoor activities during periods of increased risk of exposure to pollen. However, high concentrations of pollen can also cause symptoms and discomfort in non-sensitized people (Muzalyova et al., 2019; Papapostolou et al., 2021). In addition to acute effects, exposure to pollen has been associated with changes in pulmonary function and inflammation, risk of childhood asthma, cardiovascular outcomes, and cognitive performance (Erbas et al., 2012; Bürgler et al., 2021). Altogether, pollen does not only induce allergy but exerts a broader impact on human health. The allergen-independent mechanisms are not yet well understood. The release of lipid mediators from pollen during contact with mucous membranes may be one potential initiator of the inflammation, potentially leading to the adverse health outcomes (Traidl-Hoffmann et al., 2003).

Although pollen is a major source of allergens, and one of the most important causes of allergy, pollen particles only tend to perform their natural function as part of the life cycle of a flowering plant. In general, pollen season in the northern hemisphere starts around March and lasts until the end of October, and production is typically initiated with trees and bushes, then grasses, and ends with weeds. The onset, duration, and intensity of the season vary as several different environmental factors (e.g., CO₂ levels, humidity, and temperature) affect pollen production (Rogers et al., 2006; Wayne et al., 2002) and release into the air (Ziello et al., 2012; Ziska et al., 2019). The length of the pollen season, and the health effects caused by pollen, are likely to be affected by climate change (Schmidt, 2016). Studies have already noticed an increasing trend in the yearly amounts of airborne pollen for many taxa in Europe, with the increase more pronounced in urban areas (Ziello et al., 2012). Not only the local pollen but also pollen transported from long-distance could be relevant for the health effects (de Weger et al., 2016; Menzel et al., 2021). The effect of climate change on flowering plants and pollen will be discussed in greater detail in a later section.

Symptoms, including runny nose, itchy eyes, and sneezing, which are caused by pollen and other allergens in sensitized people, are well-documented (Bastl et al., 2021). Immunological responses in allergy are more complex and include several cell types and soluble mediators. During the sensitization phase, antigen-presenting cells (macrophages and dendritic cells) capture and present allergens to other immune cells, such as T cells, which in turn interact with B cells. After this interaction B cells produce allergen-specific IgE antibodies. When the individual is exposed to the allergen again, IgE binds to mast cells and basophils and rapidly initiates an immune response via the release of histamine and other inflammatory components (Galli and Tsai, 2012; Salazar and Ghaemmaghami, 2013). It is still unclear why only a subset of those that are exposed to pollen develop allergies, or why those who have not previously responded to pollen may develop allergies later in life. The mechanisms and processes that are triggered by pollen in the airways have been explored through experimental research. Several studies have conducted nasal and lower respiratory tract challenges with pollen extracts in patients with asthma and allergies (Calus et al., 2015; Grainge et al., 2011; Orban et al., 2021). In allergic asthma, exposure to airborne allergens is known to result in inflammation, airway epithelial damage and remodeling. Studies have shown that the epithelium of healthy participants also responds to allergen exposure, however, this effect is not always similar to participants with allergies (Mattila et al., 2010; Gökkaya et al., 2020). In addition to the aforementioned studies, some *in*

vitro studies have been performed. Most of these studies have focused on the assessment of tight junction integrity and cytokine release. Table 1 highlights the effect of pollen on epithelial function, as well as how this effect may differ by pollen species. However, the moderately low number of studies, coupled with heterogeneity in study design and cell models, complicates the evaluation of the effects of pollen on the epithelium. In recent years, it has been observed that not only allergens but also other proteins and components in pollen, can contribute to the development of an immune response and subsequently, allergic sensitization (Aglas et al., 2018; Darnhofer et al., 2021; Gilles-Stein et al., 2016). This has been reviewed in detail by Pointner et al. (2020). Pollen proteases and airway epithelial dynamics have several roles in allergic disorders (Gaspar et al., 2020; Muhamad et al., 2021; Laulajainen-Hongisto et al., 2020).

3. Respiratory viruses

Respiratory viruses are the most common pathogens in humans, and they have a significant impact on morbidity and mortality worldwide. It is estimated that about 80% of acute respiratory diseases are due to viral infections (Zhang et al., 2020). Respiratory viral infections not only have severe adverse outcomes in children and in patients with established asthma and otherwise deficient lung function, but they have also been linked with the onset of asthma (Jartti and Gern, 2018; Rantala et al., 2011). The main viruses that cause respiratory infections include rhinovirus, influenza-, adeno-, respiratory syncytial viruses (RSV), and coronaviruses (Zhang et al., 2020). The agents, epidemiology, pathogenesis, clinical features, management, and control of the most important respiratory viruses have been reviewed elsewhere (Boncrisiani et al., 2009).

Like pollen, respiratory viruses also exhibit seasonal variation. In temperate regions, influenza virus, coronavirus, and RSV infections peak during the winter months (November to April), enteroviruses peak during summer months, and adenoviruses and rhinoviruses can be detected throughout the year (Moriyama et al., 2020). Despite the absence of a winter season, seasonal variation in infections has also been observed in the tropics. Furthermore, an increased incidence of respiratory viral infections has been observed in tropical rainy seasons (Paynter, 2015; Shek and Lee, 2003). A systematic analysis of the global monthly activity of the influenza virus, RSV, parainfluenza virus, and metapneumovirus has been reported by Li et al. (2019). Li et al. observed that lower temperatures were associated with higher influenza virus and RSV activity. Furthermore, when the temperature was lower than the annual average, higher relative humidity was also associated with increased RSV activity.

The lungs and respiratory epithelium are the first lines of defense against respiratory viruses. A successful antiviral response depends on both the physical barrier and several innate and adaptive immune responses. Upon viral recognition, airway epithelial cells secrete a variety of antiviral substances, such as interferons (IFNs), lactoferrin, β -defensins, nitric oxide, cytokines (for example, interleukin (IL)-1 β , IL-6, and TNF), and chemokines (for example, IL-8, MIP-1 α , MCP-1, and RANTES), which in turn lead to activation of several innate and adaptive immune cells. Viruses can damage epithelial repair mechanisms, disrupt epithelial integrity, and thus increase cellular permeability. Vareille et al. have comprehensively reviewed the role of airway epithelium in the fight against viral infections (Vareille et al., 2011). Co-exposure to several viruses and bacteria at the same time is also plausible, and it has been shown that prior or concomitant viral respiratory infection can predispose to secondary bacterial infection throughout the airways. Viruses damage the airways and dysregulate both innate and adaptive immune responses, which in turn affect bacterial growth, binding, and airway penetration (Bakaletz, 2017). Studies have also suggested that co-infection with two or more respiratory viruses results in increased disease severity (Stefanska et al., 2013). In contrast, cross-immunity/viral interference (infection by one virus strain

Table 1
Effects of pollen on the mucosal barrier function.

Pollen species	Cells/study material	Integrity of the physical barrier	Cytokine secretion		Reference
			Upregulation	Downregulation	
<i>P.pratense</i> , <i>A.artemisiifolia</i> , <i>A.vulgaris</i> , <i>B.alba</i> , <i>P.sylvestris</i>	16HBE	Increase in TER (all pollen species)	Secondary cell lines <i>P.pratense</i> : GM-CSF, IL-8, MIP-3α, TNF <i>P.sylvestris</i> : GM-CSF	–	Blume et al., 2015
<i>B.verrucosa</i> , <i>P. pratense</i>	16HBE14o ⁺	NA	–	<i>B.verrucosa</i> : IP-10 <i>P. pratense</i> : IP-10, MDC	Papazian et al., 2015
<i>O.europaea</i> , <i>D.glomerata</i> , <i>C.sempervirens</i> <i>P.sylvestris</i>	Calu-3	Increase in transepithelial permeability (all pollen species)	NA	NA	Vinhas et al., 2011
<i>A.trifida</i> , <i>P. pratensis</i> , <i>B. pendula</i> , <i>L.longifolium</i>	MDCK and Calu-3	Disruption of epithelial tight junctions (all pollen species)	NA	NA	Runswick et al., 2007
<i>P. Pratense</i>	NCI-H292	NA	Strong: IL-1 (RA), IL-6, IL-8 Moderate: IL-12,MIP-1β, MCP-1, GM-CSF, IFN-α Low: VEGF, IP-10	–	Röschmann et al., 2011
<i>B.pendula</i> , <i>P.pratense</i> , <i>A.artemisiifolia</i>	HNECs (healthy and allergic rhinitis (AR))	Healthy epithelium not affected, AR cells increase in TER (<i>P. pratense</i> , <i>A. artemisiifolia</i>)	Primary cells/in vivo <i>P. pratense</i> : IL-8 (non-AR),IL-18 (non-AR and AR)		Bergougnan et al., 2020
<i>P.pratense</i>	PBECs (healthy and asthmatic)	Not affected	IL-8 Only in asthmatics: MIP-3α, TNF, MDC	–	Blume et al., 2013
<i>B.pendula</i>	Nasal secretion (birch grass pollen allergy)	–	IL-8	–	Gilles-Stein et al., 2016

HBE: human bronchial epithelial cell line, HNEC: primary human nasal epithelial cell, PBEC: primary bronchial epithelial cells, TER: Transepithelial/transendothelial electrical resistance, AR: allergic rhinitis, GM-CSF: granulocyte-macrophage colony-stimulating factor, IL: interleukin, MIP: Macrophage Inflammatory Protein, TNF: Tumor necrosis factor, IP: Interferon gamma-induced protein, MDC: Macrophage-derived chemokine, MCP: Monocyte chemoattractant protein, VEGF: Vascular endothelial growth factor, IFN: Interferon gamma, CCL: chemokine (C–C motif) ligand.

activates immune responses that prevent or reduce infection by another virus strain) has also been observed (Laurie et al., 2018).

4. Co-exposure to pollen and respiratory viruses: immunological consequences

Currently, there are limited studies that explore the effect of co-exposure to pollen and respiratory viruses. Additionally, there is heterogeneity in study designs and thus conclusive interpretation of the literature is hindered. Epidemiological studies have shown conflicting results on the relationship between pollen and respiratory viruses. Some studies have found that high levels of airborne pollen lower the risk of respiratory infections at the population level (Shah et al., 2021; Hoo-geveen et al., 2021; Wallace and Wang, 2021; Hoo-geveen, 2020; Hoo-geveen and Hoo-geveen, 2021), but contradictory results have also been reported (Damialis et al., 2021; Choi et al., 2022). The results of scarce *in vitro* and *in vivo* studies are equally contradictory. Some studies have observed that pollen exposure can suppress or limit viral infections, while others have demonstrated that pollen exposure can induce harmful or undesired effects on virus-induced immune responses. Fig. 1 summarises epidemiological and experimental studies to date that have explored co-exposure of pollen with viruses. Throughout the coming sections, the current literature on the effects of co-exposures will be reviewed.

4.1. The evidence suggesting that pollen exposure increases the risk and severity of respiratory viral infections

Positive correlations between respiratory virus infection rates and pollen concentrations have been observed (Damialis et al., 2021; Choi et al., 2022). Choi et al. (2022) assessed the associations between spring and autumn pollen seasons and common viral infections in children. In spring, the number of virus-infected patients was strongly correlated with tree pollen concentration from the previous week. In autumn, the number of virus infections was correlated with weed pollen concentrations of that week. Lee et al. (2019) evaluated the effects of multiple outdoor environmental factors on the risk of asthma exacerbation and detected a possible causal association between tree pollen count and RSV detection rates. The study by Damialis et al. (2021) investigated relationships between SARS-CoV-2 infection rates and airborne pollen concentrations and considered day-to-day variations, the effect of lockdown, and population density in their analysis. Damialis et al. showed that pollen is a modulating factor in the overall progression of the SARS-CoV-2 infection, with the potential to add up to 30% to the infection rate. Interestingly, the effect of pollen on reported infection rates was less pronounced under lockdown. Unfortunately, the entire springtime pollen peak of the Northern Hemisphere was not included. Furthermore, Betsch and Sprengholz (2021) pointed out that allergic persons may be more likely to show symptoms that may be mistaken for those of COVID-19, and thus are more likely to get rapid antigen tests. A

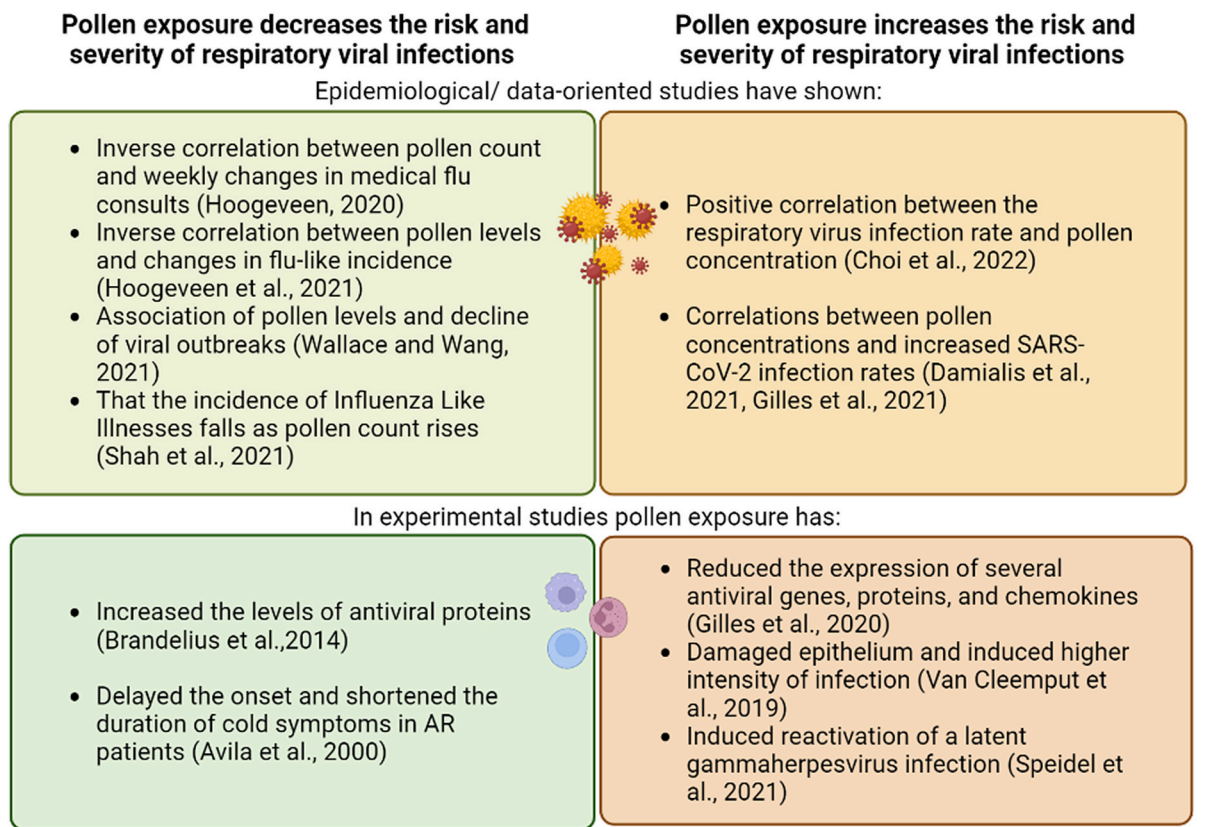


Fig. 1. Epidemiological and experimental data concerning co-exposure with pollen and viruses. Created with Biorender. References: (Shah et al., 2021; Hoo-geveen et al., 2021; Wallace and Wang, 2021; Damialis et al., 2021; Gilles et al., 2020, 2021; Choi et al., 2022; Hoo-geveen, 2020; Van Cleemput et al., 2019; Speidel et al., 2021; Brandelius et al., 2014; Avila et al., 2000). AR: allergic rhinitis.

follow-up study by Gilles et al. (2021), conducted from January to June 2021, demonstrated that the pollen effect was so strong that the lag effects or the coefficients of determination did not alter significantly, despite the testing frequency for SARS-CoV-2. The association between the concentration of total pollen and the cases of COVID-19, regardless of the allergic status, was not confirmed in a Spanish study conducted from March 2020 to February 2021 (Moral de Gregorio et al., 2022).

Few studies have assessed the effects of co-exposure *in vitro* or *in vivo*. In an *in vitro* and *in vivo* study conducted by Gilles et al. (2020), exposure to pollen impaired immunity against viruses. Primary human bronchial epithelial cells and nasal epithelial cells were first exposed to birch, timothy, or common ragweed pollen, and subsequently to human rhinovirus. Exposure to pollen increased the release of infective viruses and reduced the expression of several antiviral genes. Furthermore, exposure to pollen significantly decreased the release of several chemokines and increased levels of IL-1 β . A co-incubation of nasal cells with Poly I: C (viral mimic), and whole birch or grass pollen grains, significantly decreased the production of IFN- λ , which mediates antiviral protection. Pollen also modulated virus-induced TLR3, RIG-I, and MDA5 signaling in nasal epithelial cells. These pathways play an important role in the regulation of innate antiviral immune responses. Interestingly, downregulation of type I and -III interferons in nasal mucosa occurred in both pollen-allergic and non-allergic individuals, suggesting that the detected immunomodulatory effects of the pollen particles were independent of the sensitization. The same study also showed that pollen exposure diminishes the antiviral response in a mouse RSV infection model. In another *in vitro* study, conducted on horse epithelial cells, pollen proteases selectively and irreversibly damaged the integrity and anchorage of primary respiratory epithelial cells resulting in an

increased alphaherpesvirus infection intensity of the respiratory epithelium. Although alphaherpesviruses are not respiratory viruses, they often colonize new hosts through the respiratory mucosae. It was found that pollen extracts irreversibly affected epithelial morphology and the ciliated appearance of the respiratory epithelium was lost. Exposure to pollen also affected infection intensity (plaque latitude, percentage of infection, and virus titer) (Van Cleemput et al., 2019). Birch pollen extract has been shown to enhance human cytomegalovirus (HCMV) replication in monocyte-derived dendritic cells (Fneish et al., 2022). In the study, birch pollen extract induced changes in gene signatures and provided a favorable environment for HCMV infection and replication, despite an enhancement of pro-inflammatory cytokine responses. Furthermore, evidence that pollen grains and aqueous pollen extracts can induce reactivation of a latent gammaherpesvirus infection in mouse macrophages has been published (Speidel et al., 2021). The same study assessed whether stimulation with pollen grains or extracts led to polarization into "M1" or "M2" macrophages. Interestingly, treatment with alder pollen grains led to more M1-type polarization.

4.2. The evidence suggesting that pollen exposure decreases the risk and severity of respiratory viral infections

Epidemiological or data-oriented studies have shown inverse correlations between pollen levels and changes in flu-like incidence (Shah et al., 2021; Hoogeveen et al., 2021; Wallace and Wang, 2021; Hoogeveen, 2020). Hoogeveen et al. (Hoogeveen, 2020) reported an inverse correlation between pollen count and weekly changes in medical flu consults in the Netherlands. Unfortunately, the effects of meteorological and other factors that potentially affect the transmission of viral

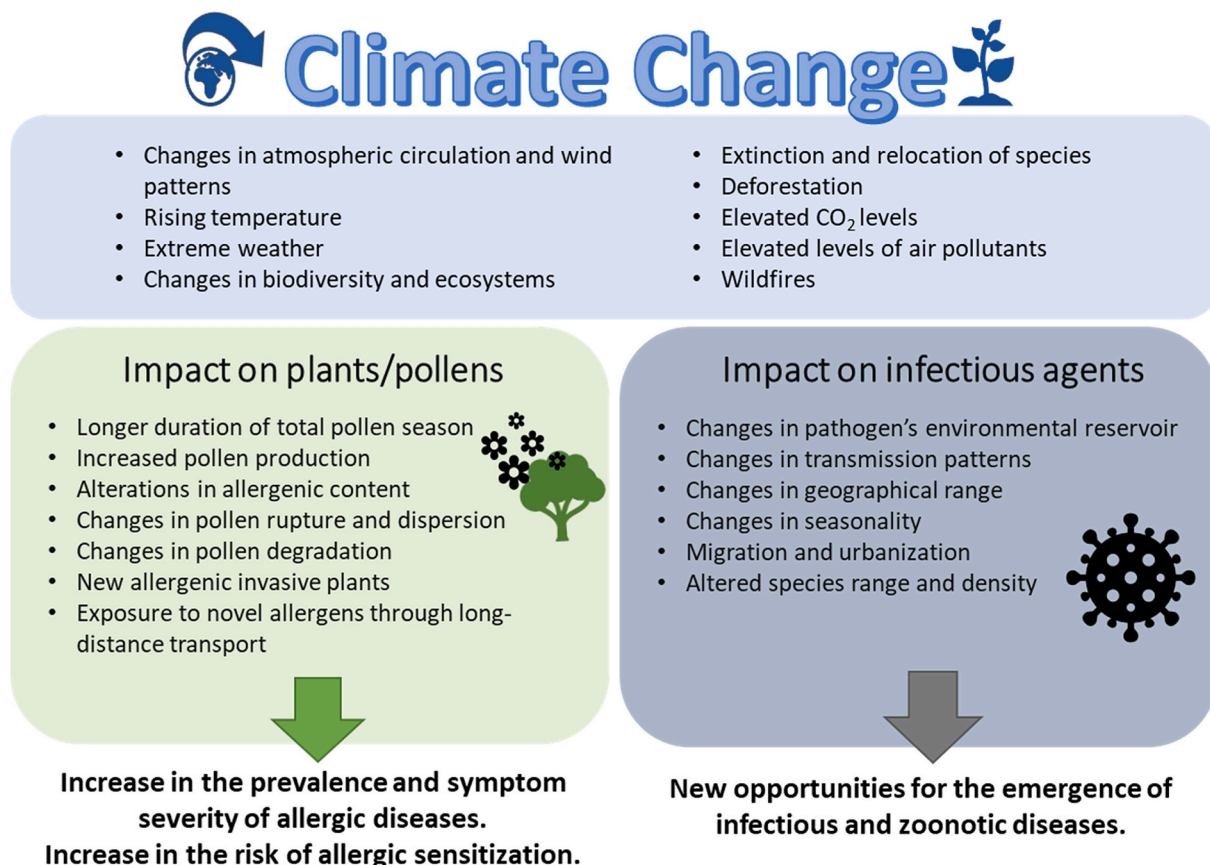


Fig. 2. Effects of climate change on pollen and infectious agents. References: Overall (Pörtner et al., 2022); Pollen; (Anderegg et al., 2021; Kim et al., 2018; Ziello et al., 2012; Ziska et al., 2019; Zhang and Steiner, 2022; D'Amato et al., 2020; Gentili et al., 2019; Choi et al., 2021; Liu et al., 2022; Ahlholm et al., 1998; Hjelmroos et al., 1995; Kralemann et al., 2018; Beck et al., 2013; Rauer et al., 2021; El Kelish et al., 2014; Stinson et al., 2017), Infectious agents (Baker et al., 2021; Mirsaeidi et al., 2016; Parmesan et al., 2022);

infections were not assessed in the same model. In a different study, Hoogveen et al. (2021) determined flu-like incidence as a WHO code “ILI” - Influenza Like Illnesses-incidence. In this study, weekly changes in medical flu-like incidence showed an inverse correlation with total pollen. Using a three-week moving average of changes in flu-like incidence, correlation coefficients became stronger. It could be argued that the use of the 3-week moving average might be too long to use in physiological correlation as the effects of pollen and the incubation period of several viral infections are usually shorter. The articles hypothesize that pollen exposure could activate immune responses and thus make it more difficult for flu-like viruses to penetrate the airway epithelium. Wallace and Wang (2021) found a negative association between pollen levels and viral outbreak episodes in both tropical and temperate climate regions. It should be noted that these regions have different pollen taxa and the amount of airborne pollen varies when compared to northern hemisphere. Thus, the results may not be applicable globally. Additionally, the analysis concerning the tropical region should be repeated as the occurrence of pollen was estimated using data from nearby location. It was hypothesized that IgEs might also target seasonal respiratory viruses. This hypothesis was based on the idea that pollen-induced IgE shares epitopes with other Ig types and, due to cross-reactivity, could protect from the development of respiratory infections. The concept that an IgE antibody could challenge viruses is not yet studied in detail. It should be noted that the presence of potential cross-reactive epitopes does not necessarily predict the outcome of immune responses, as regulatory, as well as effector responses, could be involved. Shah et al. (2021) have reported that the incidence of ILIs falls as pollen count rises. Their study focused on pollen measured between mid-March and mid-October. In their article they suggested that due to many types of pollen (and molds) having a surface texture reminiscent of those of influenza and SARS-CoV-2 viruses, they might compete for the same immune receptors, e.g., TLR4, and therefore limit viral engagement. Shah et al. have discussed this theory in detail in their article. Interestingly, the role of TLR4 in SARS-CoV-2 is under investigation as it could be that SARS-CoV-2 spike glycoprotein may bind and activate TLR4 signaling to increase the cell surface expression of Angiotensin-converting enzyme 2 (ACE2), thus facilitating viral entry (Aboudounya and Heads, 2021). In a novel *in silico* study, Balz et al. (2021) identified potentially cross-reactive allergen- and SARS-CoV-2-T cell epitopes and speculated that the similarity in epitopes could play a protective role. For example, it could prevent an overwhelming Th1 response or lead to a faster and more efficient memory response against heterologous SARS-CoV-2 epitopes. However, this similarity in epitopes could also lead to attenuated antiviral responses and inadequate virus clearance. Interestingly their study revealed the importance of MHC class I inhalant allergens in contrast to MHC II epitopes, usually thought to play a bigger role in allergic diseases. Balz et al. also demonstrated that epitopes of timothy grass (*Phleum pratense*) were recognized as one of the aeroallergens having high similarity to epitopes found in SARS-CoV-2-T cells. Unfortunately, they did not assess what phenotype the T cells that recognize these epitopes might have. The role of CD4⁺ cells in allergy and CD8⁺ cells in viral immunity has been long established, while the role of allergen-specific CD8⁺ T cells is under investigation. The same group has previously reported heterologous immune responses induced by influenza against allergens, which mediated protection from experimental allergic asthma. In this study, the protection could be attributed equally to CD4⁺ and CD8⁺ T memory cells (Skevaki et al., 2018).

Only a few experimental studies have investigated epithelium facing both environmental factors at the same time. In the study by Brandelius et al. (2014), nasal mucosa dsRNA challenges increased three antiviral proteins, IFN β , IFN λ 1, and IL-32 *in vivo* in individuals with allergies, but only during the pollen season. This suggests that patients with established symptomatic allergic processes in airway mucosa may not be as vulnerable to additional viral infections as atopic individuals without allergic symptoms. Interestingly, when subjects with allergic rhinitis

were first challenged with pollen and subsequently with rhinovirus, pollen exposure delayed the onset and shortened the duration of cold symptoms (Avila et al., 2000).

4.3. Allergic diseases and respiratory viruses

Immunological mechanisms activated in individuals with allergic rhinitis and/or asthma could help clear the viral load and prevent the cytokine storm and inflammation, thus contributing to the recovery from viral infections, as discussed in Section 4.2. Nasal epithelial cells of patients with allergic rhinitis display altered physical barrier responses when stimulated with pollen compared to healthy individuals (Bergougnan et al., 2020). However, it has also been reported that patients with allergies, asthma, or chronic rhinosinusitis have weaker antiviral immune responses (Hwang et al., 2019; Jackson and Johnston, 2012; Wark et al., 2005; Werder et al., 2017; Yamaya et al., 2016). Interestingly, a new study has demonstrated robust type I IFN responses to human rhinovirus infection in asthma, contrary to the *in vitro* findings and correlating with the virus copies and lower respiratory symptoms. This indicates that further investigation of the IFN responses early in infection is warranted (Farne et al., 2022). Wisgrill et al. (2022) observed that birch pollen stimulation of PBMCs induced activation in both innate and antiviral immune networks in birch-allergic children and adolescents. Viral infections, especially rhinovirus infection, but also RSV in younger patients, play an important role in the pathogenesis of asthma exacerbations (Nakagome and Nagata, 2022). Moreover, inhalant-allergen-sensitive children seem to be more susceptible to viral infections than others (Wang et al., 2020).

Generally, allergies increase the morbidity of respiratory infections. However, this might not be the case with COVID (Gao et al., 2021; Holt et al., 2021). For example, Holt et al. (2021) showed that atopic diseases were associated with a reduced risk of COVID-19, and a study by Ren et al. (2022) showed that allergic rhinitis was a major protective factor for COVID-19. Differences in responses may be due to different entry mechanisms. Rhinoviruses can enter the cell via an intercellular adhesion molecule 1 (ICAM-1) receptor, which has been observed to be elevated in patients with asthma (Nakagome and Nagata, 2022). In contrast, the ACE2 receptor is the key entry receptor for SARS-CoV-2, and the expression of this receptor is lower in individuals with allergies. This may be one factor that potentially reduces the risk of COVID-19 infections in this population (Jackson et al., 2020). Furthermore, allergen exposure has been shown to further decrease ACE2 expression in the airway epithelium of individuals with allergies. IL-13, a Th2 cytokine up-regulated in allergic asthma, might also play a role. In an *in vitro* study (Morrison et al., 2022), primary human airway epithelial cell cultures were infected with SARS-CoV-2 and treated with IL-13. Treatment led to reduced viral titers, viral messenger RNA, and cell shedding, and significantly diminished the number of infected cells. A review by Urrutia-Perreira et al. (Urrutia-Perreira et al., 2022) explored the effects of viral infections, including SARS-CoV-2, on asthma pathogenesis and its immunological mechanisms, and how different environmental exposures interact with COVID-19 and asthma.

4.4. Pollen as a viral carrier

It has also been suggested that airborne pollen grains could transport virus particles and thus affect morbidity (Dbouk and Drikakis, 2021), although contradictory results have also been reported (Dunker et al., 2021). The role of pollen as a viral carrier should be interpreted with caution due to the limited data available. While viral genetic information was found on pollen, it does not directly indicate that pollen could transport infectious viruses.

5. The effects of climate change on respiratory health

Climate change is a major threat to global health and affects many

different diseases, such as zoonoses, food-, water- and vector-borne diseases, and mental health issues. Climate change also affects respiratory health in several ways. For example, exposure to pollen and molds increases as the length and magnitude of the pollen emission season increases (Anderegg et al., 2021; Ziello et al., 2012; Ziska et al., 2019; Zhang and Steiner, 2022; D'Amato et al., 2020). Furthermore, co-exposure to air pollution (particulate matter, nitrogen dioxide, sulfur dioxide, and ozone) has been shown to induce respiratory problems and increase symptom severity in pollen-allergic individuals during pollen seasons (Berger et al., 2021). According to climate change scenarios, there will be an increase in the intensity and frequency of heavy rainfall episodes, including thunderstorms. This may increase the prevalence and severity of thunderstorm asthma (a form of asthma that is triggered by an uncommon combination of high pollen and a certain kind of thunderstorm) (D'Amato et al., 2014). Climate change will affect pollen and infectious agents in several ways (Fig. 2).

Global warming will prolong the growing and flowering seasons of plants, leading to an earlier start, longer duration, and increased intensity of the total pollen season. According to the worst-case climate scenario (SSP 585), the pollen season will start 10–40 days earlier for winter- and spring-flowering plants and will be delayed for 5–15 days, and extended for summer- and fall-flowering plants (Pörtner et al., 2022; Zhang and Steiner, 2022). This will differ across regions, species, and traits. In addition, factors related to climate change may influence the spread and adaptation of allergenic plants and their pollen production, release, degradation, and spread in the atmosphere (Kim et al., 2018; Ziska et al., 2019; Gentili et al., 2019; Choi et al., 2021; Beck et al., 2013; Rauer et al., 2021; El Kelish et al., 2014; Stinson et al., 2017). Observations of increased pollen allergenicity have also been made (Kim et al., 2018; Liu et al., 2022; Ahlholm et al., 1998; Hjelmoors et al., 1995). Furthermore, pollen grown under elevated carbon dioxide elicits stronger respiratory and immunological responses (Rauer et al., 2021). In addition to climate change factors, urbanization can also affect pollen production. For example, the flowering of *Betula pendula* was observed to start earlier during warmer years and at locations with higher urbanity (Kolek et al., 2021). Ziska et al. (2003) demonstrated that urban ragweed plants grew faster, flowered earlier, and produced more pollen than those grown outside the city. These changes might increase human exposure to pollen and thereby increase the prevalence and symptoms of allergic rhinitis and the risk of allergic sensitization. Interactions between pollen, air pollutants, and greenhouse gases also alter the allergen content of pollen and thereby alter its allergenicity and the severity of the symptoms it causes. In addition, the spread of new invasive species and their adaptation to a new residential area may affect the number and severity of allergies (Kralemann et al., 2018).

According to the climate change scenarios, it is likely that the outbreak and spread of viral infection will increase, leading to more prevalent and severe viral pandemics (Pörtner et al., 2022). Climate change will modify the geographical distribution and habitats of viral/pathogenic vectors. This, together with deforestation and urbanization, will increase inter-species contact leading to new opportunities for the emergence of infectious and zoonotic diseases. These factors also contribute to the possibility of pathogens coming into contact with humans. The reductions in biodiversity, caused by deforestation, could also lead to reduced inter-species contact. Altogether, all human actions that shape inter-species contacts are a subject of not only global but also local policies. Climate change also affects many environmental factors, including temperature, rainfall, and humidity, which affect viral transmission and can have a strong impact on other potentially harmful microorganisms, such as molds (Baker et al., 2021; Mirsaeidi et al., 2016; Parmesan et al., 2022).

6. Conclusions

In conclusion, conflicting results on the relationship between pollen and respiratory viruses have been reported. Studies assessing the effect

of pollen on the epithelium showed that exposure affects epithelial integrity and cytokine secretion in both healthy and allergic epithelium. The viral infection begins when the virus infiltrates the epithelium and if the epithelium is damaged due to pollen, proteases, or other components, the likelihood of a viral infection may increase. Could the observed adverse effects of pollen on viral infections come from epithelial degradation or disturbance of antiviral functions? Can pollen, on the other hand, contain components that strengthen the epithelium or elicit immune responses leading to a pre-modified immune activation (e.g., IgE, competing for access to receptors, activation of other immunological pathways) and thus reduce the chance or severity of infection?

The number of studies is still quite limited and not enough *in vivo* and *in vitro* data has been accumulated. Furthermore, heterogeneity in study designs complicates the comparison and interpretation of results. Thus, it is not yet possible to conclude whether pollen exposure protects against, or predisposes to, viral infections. Additionally, many studies do not distinguish between pollen allergies and others, such as multiple or perennial allergies. Apart from the common mechanisms (Th2, IgE), an immune response to grass pollen differs (at the level of epithelial signaling) from a response to e.g. birch or ragweed pollen. This suggests that some pollen types are also more relevant for crosstalk with viral infections. In our opinion, the synergistic effects of pollen and viruses are an important and relevant subject for public health, and thus further research is necessary.

Previous studies have mainly focused on how pollen exposure affects the immune responses against viruses. In the opposite direction, the impact of viral exposure on the subsequent exposure to pollen should also be assessed. Could it be that the viral exposure disrupts the respiratory epithelium and its tolerogenic mechanisms, allowing pollen to bypass the protective mechanisms and increase the possibility of sensitization?

More research should be conducted to better understand:

- Are there differences between pollen species in respect of their immunological or antiviral properties?
- Are the effects dependent on the allergenicity of the pollen?
- Whether these effects are due to allergens or other components of the pollen. If so, which components play a major role?
- Are the synergistic effects between pollen and virus dependent on the type of the virus?
- Is the exposure order and timing relevant (co-exposure vs consecutive exposure)?
- Whether pollen can act as a viral carrier and whether pollen that carries viral particles could transmit a viral infection?

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Statement of contribution

All authors approved the submitted version. Martikainen, Tossavainen, Hannukka, and Roponen conceptualized the scope of the article, decided on the headings, and wrote the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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