**Mechanistic Insights into the Impact of Air Pollution on Pneumococcal Pathogenesis and Transmission**

Daan Beentjes, Rebecca K. Shears, Neil French, Daniel R. Neill, and Aras Kadioglu

## Abstract

*Streptococcus pneumoniae* (the pneumococcus) is the leading cause of pneumonia and bacterial meningitis. A number of recent studies indicate an association between the incidence of pneumococcal disease and exposure to air pollution. Although the epidemiological evidence is substantial, the underlying mechanisms by which the various components of air pollution (particulate matter and gases such as $NO_2$ and $SO_2$) can increase susceptibility to pneumococcal infection are less well understood. In this review, we summarize the various effects air pollution components have on pneumococcal pathogenesis and transmission; exposure to air pollution can enhance host susceptibility to pneumococcal colonization by impairing the mucociliary activity of the airway mucosa, reducing the function and production of key antimicrobial peptides, and upregulating an important pneumococcal adherence factor on respiratory epithelial cells. Air pollutant exposure can also impair the phagocytic killing ability of macrophages, permitting increased replication of *S. pneumoniae*. In addition, particulate matter has been shown to activate various extra- and intracellular receptors of airway epithelial cells, which may lead to increased proinflammatory cytokine production. This increases recruitment of innate immune cells, including macrophages and neutrophils. The inflammatory response that ensues may result in significant tissue damage, thereby increasing susceptibility to invasive disease, because it allows *S. pneumoniae* access to the underlying tissues and blood. This review provides an in-depth understanding of the interaction between air pollution and the pneumococcus, which has the potential to aid the development of novel treatments or alternative strategies to prevent disease, especially in areas with high concentrations of air pollution.

**Keywords:** $PM_{2.5}$, $PM_{10}$, particulate matter, pneumonia, pneumococcal infections

Asymptomatic colonization of the nasopharynx is the primary lifestyle of the pneumococcus and the principal reservoir for onward transmission (1, 2). Nasopharyngeal carriage also plays a key role in the development of pneumonia and invasive pneumococcal diseases, such as septicemia and meningitis (3–7). It is estimated that 91% of people worldwide are exposed to air pollution concentrations that exceed World Health Organization guideline limits, and those living in low- to middle-income countries are exposed to the highest concentrations (8). These populations also have the greatest burden of lower respiratory infections (LRIs) (9). Exposure to air pollutants is one of the major risk factors for mortality caused by LRIs, particularly for children under 5, in whom it is second only to childhood wasting (9). A multicenter international study showed that *Streptococcus pneumoniae* was responsible for 50% of LRI fatalities globally in 2016, with more than 1.18 million deaths (9). Exposure to air pollution has been identified as a risk factor for pneumococcal carriage (10–13) and is associated with a higher incidence of pneumococcal pneumonia and invasive pneumococcal disease (14–23). These studies indicate a strong association of air pollution exposure and pneumococcal infections. The underlying mechanisms are not fully elucidated, however, and thus form the basis of this review.

Air pollution typically contains a mixture of particulate matter (PM) and gaseous components such as ozone ($O_3$), volatile organic compounds, nitrogen oxides, sulfur dioxide ($SO_2$), and carbon monoxide (24). PM can be split into three categories based on aerodynamic diameter: coarse material ($PM_{2.5–10}$; $\leqslant$10 µm but >2.5 µm), fine PM ($PM_{2.5}$; $\leqslant$2.5 µm), and ultrafine PM ($\leqslant$0.1 µm) (25).

Particles larger than $PM_{10}$ are typically retained in the nose and upper respiratory tract; however, both $PM_{10}$ and $PM_{2.5}$ are able to filter into the lungs (24, 25). This review summarizes the effects that these gaseous and particulate components of air pollution have on the host and how this may contribute to pneumococcal pathogenesis and transmission. We begin by describing the impact of air

pollution on pneumococcal colonization and survival in the respiratory tract, followed by explaining the mechanisms by which air pollution may increase the severity of pneumococcal infections.

**Increased Susceptibility to Pneumococcal Colonization**

Colonization of the nasopharynx is a prerequisite for the development of pneumococcal disease and plays an important role in transmission (1, 2, 26). In addition, pneumococci that disseminate from the upper to the lower respiratory tract need to find a suitable niche for growth and survival. In this section, we discuss the most vital host responses that protect against pneumococcal colonization in the respiratory tract and how inhaled air pollution particles may aid the pneumococcus in evading these defenses (27–29). Figure 1 shows a summary of the main findings.

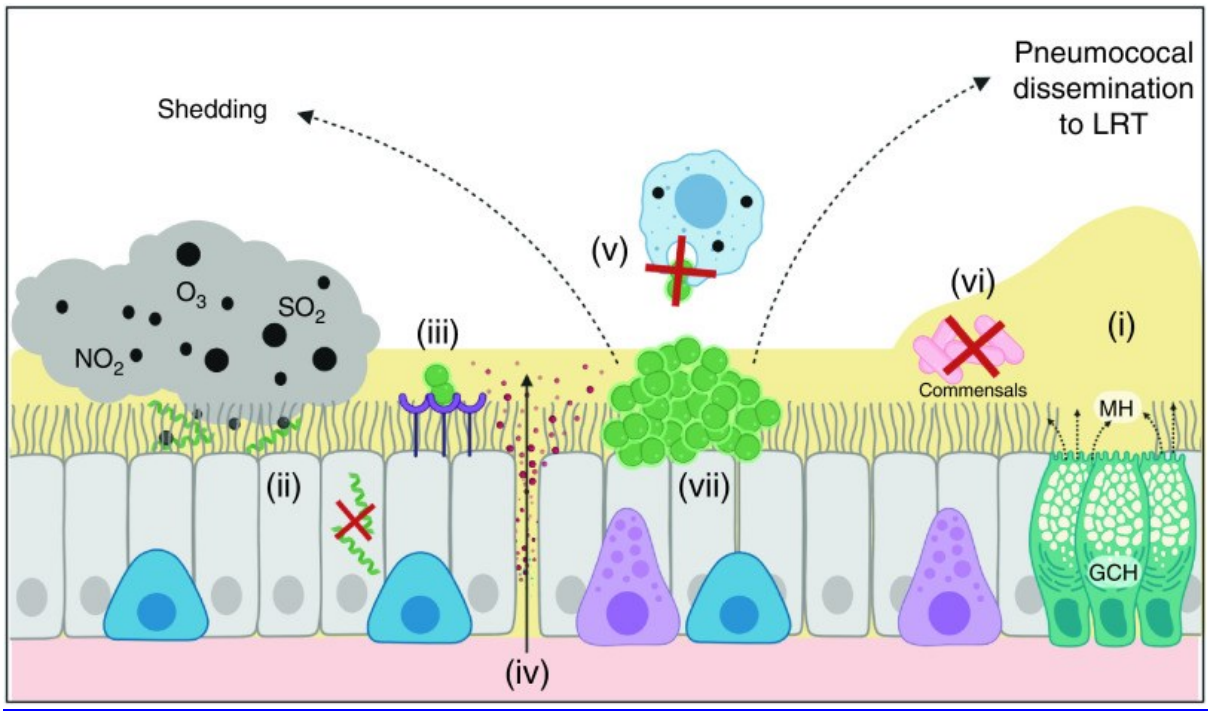


Figure 1.

Air pollution increases susceptibility to pneumococcal colonization. Inhaled air pollution particles, including particulate matter (PM), sand, dust, and ash (black dots) and gases $NO_2$, O3, and $SO_2$ (gray cloud) can enhance pneumococcal colonization through various mechanisms. (*i*) Reduced mucociliary

clearance as a result of impaired ciliary activity, goblet cell hyperplasia, and mucus hypersecretion. (*ii*) Inactivation of antimicrobial peptides and attenuated production by epithelial cells. (*iii*) Upregulation of an important pneumococcal adhesion factor, platelet-activating factor receptor on respiratory epithelial cells. (*iv*) Influx of nutrients into the airway lumen by increasing the permeability of the epithelial layer. (*v*) Reduced phagocytotic ability of macrophages. (*vi*) Microbiota dysbiosis. (*vii*) Impaired host responses enabling the pneumococcus to proliferate to higher densities in the upper respiratory tract, which is associated with increased susceptibility to the development of disease and enhanced shedding from the host. Increased proinflammatory responses in the respiratory tract observed after PM exposure can result in higher shedding events. GCH = goblet cell hyperplasia; LRT = lower respiratory tract; MH = mucus hyperproduction. Created with BioRender.com.

**Decreased Mucociliary Clearance and Improved Adhesion to Airway Epithelium**

The mucosal surfaces of the upper and lower respiratory tract are the first host cells that respiratory pathogens encounter. The mucus layer that covers these surfaces is key for trapping debris and pathogens, including *S. pneumoniae*, and forms an important barrier between the outside world and the host (30, 31). Contained bacteria are cleared by the mucociliary activity of ciliated epithelial cells, found on various parts of the respiratory tract (32, 33). The importance of a functional mucosal surface in preventing pneumococcal diseases is highlighted by research on primary ciliary dyskinesia, a disease that affects ciliary beating (32, 34). These studies show that *S. pneumoniae* is commonly found in the respiratory tract of patients with primary ciliary dyskinesia. In addition, in chronic obstructive pulmonary disease, mucociliary defects are common (35) and associated with a high incidence of pneumococcal infections (36, 37). Various studies report that air pollution can contribute to a dysfunctional airway mucosa and could therefore aid pneumococcal colonization. For example, it has been observed that PM reduces ciliary beating and mucociliary transport (38). Decreased ciliary activity was also measured in rats and healthy volunteers after exposure to carbon

monoxide, $NO_2$, or $SO_2$ (39–41). In addition, exposure to urban PM can cause mucus hypersecretion and goblet cell hyperplasia (41–43). This has been shown in both respiratory epithelial cell cultures after PM exposure and murine exposure models (41–43). The overproduction of mucus that ensues may cause obstructions in the airways and impair mucociliary clearance, hence benefiting the colonization of various bacterial species (35, 44–47). Moreover, urban PM and desert sand or dust can cause acidification and an increased viscosity of the produced mucus (43, 48, 49), resulting in a more rigid mucus layer that is more difficult to clear from the respiratory tract (47, 50–52). Montgomery and colleagues measured gene expression in human nasal epithelial cell cultures exposed to an organic extract of $PM_{2.5}$ and showed an upregulation of several genes involved in mucus secretion (53). The authors also observed significantly decreased expression of *FOXJ1* and *MCIDAS* (53), two transcription factors that play a vital role in cilia formation (54). This altered gene expression in epithelial cells may provide an underlying mechanism behind the impaired mucociliary function that is observed after exposure to air pollution.

In addition to causing a dysfunctional airway mucosa, exposure to urban PM or toxic gases, such as welding fumes, can enhance pneumococcal adherence to epithelial cells (27, 55). The main mechanism behind this is an upregulation of the platelet-activating factor receptor (PAFR)—a key pneumococcal adherence factor—on respiratory epithelial cells that was observed after exposure to urban PM or welding fumes (27, 55). The impact of increased PAFR expression on pneumococcal infection is highlighted in a study on electronic cigarette (E-cigarette) vapor (56). Here compared with unexposed mice, mice exposed to nicotine-containing E-cigarette vapor showed increased PAFR expression on nasopharyngeal epithelial cells and higher pneumococcal densities in the nasopharynx (56). This study indicates that oxidative stress responses that are activated after exposure to E-cigarette vapor contribute to the upregulation of PAFR. Therefore, the authors suggest that redox-promoting metals (e.g., copper) present in vapor could play an important role in the upregulation of PAFR (56). However, further research is required to determine the impact of each individual component of E-cigarette vapor.

A number of studies also suggest a role of PAFR in the development of pneumococcal disease (57, 58). For example, Rijneveld and colleagues showed that PAFR-deficient ($PAFR^{-/-}$) mice have lower pneumococcal densities in their lungs and a higher survival rate after induction of pneumococcal pneumonia than a wild-type control group (57). Others observed decreased dissemination of *S. pneumoniae* from the lungs to the blood and the central nervous system in $PAFR^{-/-}$ mice compared with wild-type mice (58). These studies could provide an explanation for why welders have an increased susceptibility to invasive pneumococcal disease (59), because daily exposure to welding fumes may lead to an increased PAFR expression on epithelial cells (55).

**Impaired Antimicrobial Responses**

In addition to being a physical barrier, the respiratory mucosa also contains antimicrobial peptides and proteins, which contribute to the eradication of bacteria (60, 61). Antimicrobial compounds found in the respiratory tract and important in combating *S. pneumoniae* infections include (apo)lactoferrin, lysozymes, and the cationic antimicrobial peptides (CAMPs) such as LL37 and β-defensins (62–66). Several studies show that air pollution could affect the expression and bactericidal properties of these compounds, which may reduce their effectiveness against respiratory pathogens. For example, carbon black nanoparticles—an example of ultrafine PM—can induce structural changes in LL37, thereby impairing its antibacterial activity (67). Airway acidification by urban PM and desert dust, described earlier in this review, can affect the activity of CAMPs, such as β-defensins and LL37, because their activity is pH dependent (68). A different mechanism of action is observed in a study on coal fly ash. This ambient PM is negatively charged and can neutralize the electropositive antimicrobials and therefore reduce their activity (69). In addition, epithelial cells show a decreased expression of β-defensin after exposure to PM (70–72). A recent study found that the suppression of CAMPs by corticosteroids led to increased bacterial counts in the lungs of mice challenged with a pneumonia-inducing dose of *S. pneumoniae* (73). In addition, low β-defensin 2 plasma concentrations in patients with pneumonia, measured upon hospital admission, were associated

with 30-day adverse outcomes (74). These studies highlight the importance of sufficient CAMP concentrations in the context of pneumococcal infections, and air pollution could therefore play a substantial role in the progression of disease. However, further detailed investigations into the effects of air pollution and the production of CAMPs is necessary because Nam and colleagues found an enhanced β-defensin response in PM-exposed alveolar epithelial cells (75).

**Dysbiosis of the Airway Microbiota**

Within the airway mucosa, *S. pneumoniae* must compete for adhesion sites and nutrients with other bacterial pathogens and commensals. These residents (i.e., the airway microbiota) are able to sequester carbon sources (76) and produce a variety of antimicrobial peptides (77), which provides some protection against intruding pathogens (78). The microbiota of the respiratory tract is a highly dynamic community (79), and exposure to PM, ozone, $NO_2$, or $SO_2$ has been shown to cause a shift in its microbial composition (80–83). Although the specific impact of air pollution is understudied and discrepancies exist in the literature, exposure to air pollution generally reduces the abundance of commensals, including the genera *Flavobacterium*, *Prevotella*, *Fusobacterium*, and *Veillonella*, whereas pathogenic species, including streptococci, are more commonly found (80–84). A recent review looked into the role of air pollution in (airway) microbiota dysbiosis and proposed that an impaired immune response after air pollution exposure is one of the underlying mechanisms behind it (85). Li and colleagues also observed higher bacterial diversity (Chao 1 and phylogenetic diversity whole tree index) in the lungs of rats exposed to ambient PM (i.e., biomass fuel and motor vehicle exhaust) (81). According to an experimental human challenge study, volunteers with a more diverse nasopharyngeal microbiota (i.e., higher Shannon index) showed an increased susceptibility to pneumococcal acquisition, which could suggest that ambient PM may increase host susceptibility (86). Further investigation into the effect of air pollution on microbiota diversity is needed, however, because other studies observed no or opposite effects of air pollution (recently reviewed by Xue and colleagues [84]).

In addition, *S. pneumoniae* and other pathogenic species have been found attached to PM (87, 88). The diversity and abundance of bacterial species on PM depends on geographical location and air quality index, and they vary seasonally (88–90). Although mucociliary clearance will likely prevent the colonization of most PM-attached bacteria, the inhalation of air pollution particles may introduce pathogenic species into the respiratory tract, which could cause dysbiosis of the airway microbiota. Liu and colleagues observed that PM size has an impact on the diversity and abundance of bacterial species attached to PM (89). The authors measured a higher abundance of pathogenic bacterial species on $PM_{2.5}$ than on $PM_{10}$, which may suggest that the risk of introducing pathogenic species in the airways is relatively higher after inhalation of $PM_{2.5}$. Given that $PM_{2.5}$ can penetrate more deeply into the lungs than $PM_{10}$, PM size could also affect the location where pathogenic species are deposited within the airways (91). In addition, Shears and colleagues suggested that adherence of *S. pneumoniae* to PM causes upper airway colonized pneumococci to be dragged down from the nasopharynx to the lungs (92). Attachment of pneumococci to PM could therefore increase susceptibility to pneumonia (92).

**Improved Pneumococcal Survival**

A substantial problem for *S. pneumoniae* to overcome is the limited nutrient availability within the respiratory tract. Restricting nutrient availability is an important defense mechanism for the host against pathogens (93, 94), and *S. pneumoniae* must adapt to find new ways of acquiring suitable carbon sources (95). PM, such as diesel exhaust particles (DEPs), can aid nutrient acquisition for bacterial pathogens within the respiratory tract by increasing the permeability of the airway epithelial barrier (96, 97), causing an influx of essential nutrients such as glucose into the airway lumen (93). An impaired epithelial barrier is also observed in epithelial cell cultures and *in vivo* after exposure to $NO_2$ or ozone, respectively (98, 99). In addition, it has been observed that DEPs can serve as a carbon source for *S. pneumoniae* under nutrient-restricted conditions (92).

A recent study also described a direct effect of air pollution on pneumococcal phenotype. The authors observed improved pneumococcal competence after exposure to environmental dust (100). Competence is a tool used by *S. pneumoniae* to acquire new DNA through transformation, which is believed to be the main driver of pneumococcal evolution. New traits acquired through the addition of fresh genetic material aids adaptation to new environments or competition with other bacteria for nutrients and adhesion sites (101). Inhaled dust particles may therefore enhance pneumococcal colonization and survival in the airway mucosa.

**Reduction in Macrophage Phagocytic Killing**

One of the key roles of alveolar macrophages is the removal of pathogens, dead host cells, and debris (including PM) from the lungs (102). Rylance and colleagues observed carbon loading of macrophages isolated by BAL from Malawian adults using wood-burning stoves (103), whereas Shears and colleagues reported carbon loading of alveolar macrophages isolated from DEP-exposed mice (92). An observational study performed by Kulkarni and colleagues found a significant correlation between the amount of PM that children were exposed to on a daily basis and PM uptake by alveolar macrophages isolated by BAL, as well as an inverse relationship between carbon loading of macrophages and lung function (as measured by $FEV_1$ and FVC) (104). Reduced phagocytic killing function of PM congested macrophages is also well documented (21, 92, 103–105). PM loading of macrophages is associated with reduced phagocytic killing ability in a number of different PM types, including black carbon generated from wood burning in Malawi, concentrated ambient particles collected in Boston, DEPs, and desert sand, and appears to affect all types of macrophages, including monocyte-derived macrophages (MDMs), human sputum–derived macrophages, and murine J774.2 cells (a macrophage cell line) (21, 92, 103, 105). This defect in phagocytic killing appears to be a result of reduced internalization of bacteria rather than impaired intracellular killing (104, 106), although a lower oxidative burst capacity has been reported for highly congested MDMs (103). Shears and colleagues reported that the alveolar macrophages of mice exposed for a total of 3 days

to DEPs were still loaded with PM 2 weeks later (92). These data suggest that clearance of PM by airway macrophages is a slow process and that the impaired phagocytic killing of PM-loaded macrophages may be long-lasting (92).

**Exacerbation of Proinflammatory Responses**

Innate and adaptive immune responses are required to control bacterial growth in the airways. These processes begin with the production of proinflammatory cytokines and the recruitment of immune cells to the site of infection. However, an overactivated immune response may lead to tissue damage, thereby enhancing the dissemination of pathogens such as *S. pneumoniae* to underlying tissues and blood, a key step in the development of invasive pneumococcal disease (21, 92). Because air pollution exposure is associated with increased incidence of pneumococcal disease (14–22), we summarize the impact that air pollution has on the immune responses that play a key role in controlling pneumococcal infections. The main findings are summarized in Figure 2.

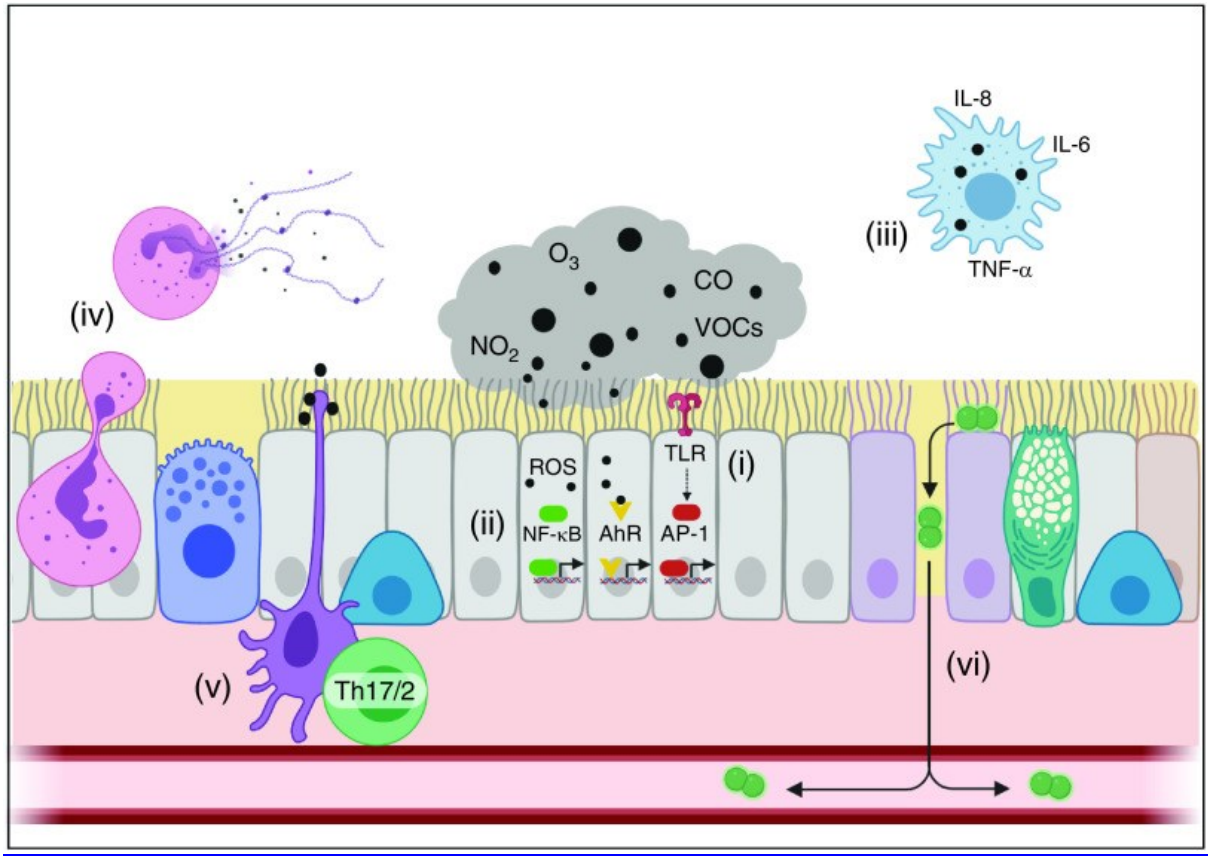


Figure 2.

Exacerbations of pneumococcal infections. The gaseous (gray cloud) and particulate matter components (black dots) of air pollution can reach the lower respiratory tract and enhance proinflammatory responses through various mechanisms. (*i*) Stimulation of Toll-like receptors (TLRs) on the surface of airway epithelial cells and intracellular aryl hydrocarbon receptor (AhR). (*ii*) Increased reactive oxygen species (ROS) production that indirectly activates proinflammatory signaling pathways. (*iii*) Increased proinflammatory cytokine production by macrophages. (*iv*) Enhanced neutrophil recruitment and NETosis. (*v*) Improved dendritic cell activation and T-cell priming (with T helper type 17/2 [Th17/Th2] responses favored). (*vi*) Epithelial damage as a result of uncontrolled immune responses could lead to increased dissemination of *S. pneumoniae* to the underlying tissues and systemic circulation. AP-1 = activation protein-1; NF-κB = nuclear factor-κB; TNF-α = tumor necrosis factor-α; VOC = volatile organic compound. Created with BioRender.com.

**Activation of Proinflammatory Pathways through Toll-Like Receptors, Aryl Hydrocarbon Receptor Signaling, and Oxidative Stress**

Stimulation of Toll-like receptors (TLRs), reactive oxygen species (ROS), and polycyclic aromatic hydrocarbon (PAH)-sensing pathways by components of air pollution can activate proinflammatory signaling, including through mitogen-activated protein kinase and nuclear factor-κB (NF-κB), leading to downstream inflammation (24, 107–109). PM containing LPSs and/or fungal spores is likely to be more immunogenic, because these are natural TLR ligands (110–112). PAHs found within PM, such as DEPs, are able to diffuse through cell membranes, where the PAHs are sensed by the aryl hydrocarbon receptor (AhR) (24, 113). Examples of PAHs that are abundant in air pollution include phenanthrene and pyrene (114–116). Binding of PAHs to the AhR allows the AhR to translocate to the nucleus, which leads to increased CYP1a1 (a cytochrome P450 family 1 member) expression and further generation of cytotoxic compounds (117). In fact, PAHs have been described as the most genotoxic components of air pollution (118). Others report that lipophilic components of DEPs are able to stimulate the AhR in endothelial cells, leading to increased IL-1α, IL-1β, COX2, and matrix metalloprotein 1 gene expression (119).

Induction of oxidative stress is thought to be due to both the heavy metal (e.g., copper) and organic components of PM (24). Kim and colleagues showed that mice have increased inflammatory responses and cell injury in the lungs after inhalation of copper particles (120). These copper-exposed mice also showed decreased bacterial clearance in the lungs when infected with *Klebsiella pneumoniae*, which highlights the negative impact of heavy metal exposure in the context of bacterial infections. Other metals that can be found attached to PM, such as iron, can catalyze the production of highly reactive hydroxyl ions from $H_2O_2$, which can react very quickly with proteins, DNA, and other biomolecules, resulting in tissue damage (113). Metals such as cobalt, chromium, and vanadium can undergo redox cycling, whereas cadmium, lead, mercury, and nickel deplete glutathione (an antioxidant) and protein-bound thiol groups, leading to ROS generation (113). These

metals can be bound to the surface of PM, particularly $PM_{2.5}$, which has a larger surface area than the equivalent amount of $PM_{10}$ (121). NF-κB, Nrf2, and activation protein-1 (AP-1) pathways are all regulated by redox status. These pathways are involved in the transcription of a wide range of genes, including those involved in oxidative stress and inflammation (113). The nuclear redox status can affect histone acetylation, making certain regions of the genome more accessible to transcription factors, including NF-κB, a key transcription factor controlling expression of a wide range of proinflammatory cytokines (24, 113). There is also some evidence to suggest that ROS can interact with $Ca^{2+}$ channels, which may also impact NF-κB signaling, because $Ca^{2+}$ can act as a second messenger in this pathway (24, 122). Nrf2 controls a range of antioxidant genes and also interacts with NF-κB and mitogen-activated protein kinase pathway members (24). Expression of Nrf2 and its upstream regulators is decreased after PM exposure, which may contribute to the increased oxidative stress and altered immune responses observed (123). Induction of AP-1 signaling is required for transcription of γ-glutamyl cysteine synthetase, an enzyme involved in antioxidant glutathione synthesis (113).

In a human experimental study involving weekly 4-hour indoor exposures of 13 volunteers to wood smoke, the authors reported detection of the ROS species malondialdehyde in the breath of volunteers, demonstrating that exposure to wood smoke in a real-world setting can induce oxidative stress in the lungs (124). A recent *in vitro* study demonstrated that exposure of human small airway epithelial cells to biomass smoke activates the AP-1 and AhR sensing pathways, but not NF-κB, resulting in short-term increases in IL-8 and granulocyte-macrophage colony-stimulating factor (125).

In addition to activating the proinflammatory pathways described above, ROS can damage proteins and DNA within the cell, which activates an intracellular damage-associated molecular pattern sensing apparatus such as the NLRP3 (NLR family pyrin domain containing 3) inflammasome (112, 126). Hirota and colleagues demonstrated that $PM_{10}$-induced NLRP3 activation results in IL-1β and CCL20 production, dendritic cell (DC) activation, and lung neutrophilia (126). Elevated $CO_2$ in air

pollution may also trigger NLRP3 activation and IL-1β production by neutrophils (127). In addition, damage to lung tissue caused by oxidative stress attracts inflammatory cells from the circulation, which may further exacerbate the damage (128). Park and colleagues generated several forms of anthropogenic PM under controlled laboratory conditions and investigated the ability of these forms of PM to cause DNA damage and oxidative stress responses using *in vitro* exposure models (129). The authors showed that the toxicity differs between PM derived from different sources and that diesel engine exhaust particles are the most toxic compared with other forms of anthropogenic PM.

**Increased Cytokine Responses by Macrophages**

PM exposure has been shown to increase proinflammatory chemokine and cytokine production by macrophages (92, 103). Rylance and colleagues reported an increase in IL-6 and IL-8 from MDMs exposed to black carbon, demonstrating that black carbon itself has inflammatory properties (103). This is supported by the observation of elevated serum IL-6, IL-8, and MCP-1 in firefighters after smoke exposure (130). These inflammatory properties may be due partly to microbial components that are absorbed onto the surface of PM (110–112). However, Shears and colleagues found that bone marrow–derived macrophages exposed to endotoxin-depleted DEPs produced higher concentrations of tumor necrosis factor-α and IL-6 when stimulated with pneumococcal antigens compared with sham-exposed bone marrow–derived macrophages also stimulated with pneumococci (92). These findings suggest that the PM itself (without interference from endotoxic material that may be adsorbed on the surface) promotes inflammation in the context of microbial challenge. Two previous studies found that *in vitro* coculture of PM-exposed epithelial cells and macrophages resulted in greater production of proinflammatory cytokines than either cell type in isolation, suggesting that there may be an additive effect (131, 132).

**Neutrophilia and Neutrophil Extracellular Trap Formation**

Increased IL-8 in the lung and circulation after exposure to air pollution is a common finding across *in vitro*, murine, and human exposure models (103, 125, 130, 133). IL-8 is a key neutrophil

chemoattractant, and although early influx of neutrophils is critical for controlling bacterial infections in the lung, it is likely that PM-induced neutrophilia, in the absence of infection, might be detrimental, because uncontrolled neutrophil influx results in further release of proinflammatory cytokines, recruitment of additional immune cells, and tissue pathology (134). However, a recent human exposure model found that short-term exposure of healthy nonsmokers to diesel exhaust leads to increased lymphocytic but not neutrophilic inflammation (135). Instead, the authors reported increased neutrophil extracellular trap (NET) formation in the lungs, which may contribute to the pathophysiology of diesel exhaust (135). Another study found that $O_3$ increases lung neutrophilia and NET production, demonstrating that different components of air pollution may have different effects on neutrophil recruitment and function (136). NETs are composed of DNA, histones, proteases such as elastase, and antimicrobial molecules including myeloperoxidase (134). NETs are an important part of the neutrophil's antimicrobial armor; however, they can also cause significant collateral damage to respiratory tissues (134). Neutrophil-derived $NAD^+$ reduced oxidase and myeloperoxidase can generate superoxide anions and hypochlorous acid, which, coupled with transition metals absorbed onto the surface of PM, could catalyze further redox cycling, causing more oxidative stress and contributing air pollution–induced lung damage (24, 134).

**Effects on Adaptive Immunity**

Because exposure to air pollution drives inflammation, with influx of neutrophils, macrophages, eosinophils, and lymphocytes, and increased proinflammatory cytokine production by these cells, it is perhaps not surprising that there are alterations in the adaptive immune response, too. Matthews and colleagues reported an increase in DC maturation and T cell priming when DCs were exposed to DEPs or in response to DEP-exposed epithelial cells (137). In particular, the authors reported an increase in IFN-$\gamma^+$ IL-17A$^+$ CD4 T cells, as well as increased IFN-$\gamma^+$ CD8 T cells (138, 139). In contrast, an older report found that exposure of human T cells to DEPs can affect intracellular T cell signaling, leading to reduced T-bet (the key T helper type 1 [Th1] transcription factor) and Txk (a tyrosine

kinase that controls the transcription of IFN-γ) expression (140). This may cause Th2 polarization (24, 140), resulting in an increased Th2-induced cytokine response. Several studies show that increased or chronic Th2-induced inflammation in the respiratory tract is associated with an impaired immunity to pneumococcal infections (141, 142). Altered T cell signaling after DEP exposure may therefore increase the risk of pneumococcal infections.

In addition to its role in the production of proinflammatory cytokines, described above, the AhR can act as a regulator of T regulatory (Treg) and Th17 cell differentiation at epithelial sites (143). A recent report demonstrated that PAHs in urban dust promote Th17 differentiation of T cells and lead to increased IFN-γ$^{+}$ DCs through activating the AhR (144). A balance between Th17 and Treg responses is critical for controlling *S. pneumoniae* infections, where memory Th17 cells are required for pathogen clearance (145), whereas Treg cells are key for controlling inflammation and minimizing tissue damage (146). O'Driscoll and colleagues showed that not all PAHs drive AhR-induced Th17 responses to the same degree (147). The authors found that of the five sources of PM tested, barley smoke promoted the strongest Th17 response *in vitro*, followed by urban dust and fine and ultrafine DEPs, whereas pine wood smoke was the least potent inducer of IL-17 (147). In another report, DEPs were shown to stimulate production of the alarmins IL-33, IL-25, and thymic stromal lymphopoietin by primary bronchial epithelial cells through interactions with the AhR (148). These cytokines trigger downstream activation of Th2 immunity (149), which, as mentioned above, could increase the susceptibility to pneumococcal infections (141, 142).

**Summary: Implications for Transmission and Development of Pneumococcal Diseases**

Collectively, published research demonstrates that various forms of air pollution can impair the mucociliary function of the airway mucosa, disrupt innate immune responses, and cause microbiota dysbiosis. On the basis of ability to impair these primary defense mechanisms of the host (32, 34, 62, 150, 151), air pollution increases host susceptibility to pneumococcal colonization, which

would in turn increase transmission (Figure 1). In addition, enhanced colonization of the upper respiratory tract could increase the risk of LRI.

Air pollution can result in higher nutrient concentrations in the airway lumen and reduce innate immune responses by attenuating the activity of antimicrobial peptides and impairing the phagocytotic ability of macrophages. As a result, inhaled air pollution particles may enable *S. pneumoniae* to replicate to higher densities in the respiratory tract. A higher pneumococcal count in the nasopharynx is associated with a higher incidence of pneumococcal pneumonia (152, 153) and is a driving force behind pneumococcal shedding from a host (154). Air pollution may therefore play a role in transmission and in the development of pneumococcal disease (Figure 1). This idea is supported by the study of Jusot and colleagues (21), in which significantly higher densities of pneumococci were found in the nasopharynx of mice exposed to dust. These dust-exposed mice also showed a higher susceptibility to develop pneumonia than an unexposed control group. In addition to the mechanisms described above, Shears and colleagues described an additional role of PM in the development of pneumonia (92). The authors showed that *S. pneumoniae* can directly attach to DEPs, which suggests that inhalation of DEPs can act as a physical conduit, dragging down pneumococci from the nasopharynx to the lungs.

Various components of air pollution can cause oxidative stress responses and activate multiple inflammatory pathways in epithelial cells. This may lead to increased production of proinflammatory cytokines and recruitment of innate immune cells, such as macrophages and neutrophils. When exposed to air pollution, these macrophages and neutrophils show an increased production of inflammatory cytokines and NETs, respectively, which may further enhance inflammation of the respiratory tract. Increased inflammatory responses are likely to cause significant tissue damage, which, if severe enough, could grant *S. pneumoniae* access to the underlying tissues and the systemic circulation (21, 92). By exacerbating inflammatory responses during active pneumococcal infections, air pollution could therefore contribute to the development of invasive pneumococcal disease.

Adaptive immune responses, including those mediated through Th17 and Treg cells, are also stimulated by air pollution. Neill and colleagues showed that a balance between immune suppression by Treg responses and inflammatory responses are key in controlling *S. pneumoniae* growth in the airways and preventing tissue damage (146).

Inflammation of the respiratory tract is also one of the underlying mechanisms behind pneumococcal shedding (155). The increased inflammatory responses cause more mucus production, which increases nasal secretions (156). Increased mucus production, as described earlier in this review and elsewhere (41–43), might therefore have an impact on pneumococcal transmission. However, impaired mucociliary clearance that has been observed after air pollution exposure (38–41) may contain the pneumococci within the airways. This could limit pneumococcal shedding from a host and may therefore impair transmission. Air pollution is also associated with the exacerbation of rhinitis, a prevalent respiratory disease (157). Sneezing—a common rhinitis symptom—increases the expulsion of respiratory aerosols and droplets and has therefore been suggested to play a role in pneumococcal transmission (2, 158, 159). Increased sneezing induced by air pollution could therefore impact transmission. Other respiratory reflexes such as coughing may also have a role, especially given that influenza-like symptoms, which encompass coughing, are associated with higher prevalence of pneumococcal carriage (160). However, a recent meta-analysis showed no link between air pollution exposure and cough (161).

This review summarizes several host responses that are affected by air pollution and describes how these altered host responses could benefit pneumococcal colonization, pathogenesis, and transmission. There is substantial evidence that air pollution causes a dysfunctional airway mucosa, impairs macrophage function, and exacerbates proinflammatory immune responses, because this has been observed in several *in vitro* and *in vivo* (human) exposure models (38–42, 67, 69, 92, 103–105, 124–126, 130, 133, 136). However, discrepancies exist in the literature for other effects of air pollution, such as the production of antimicrobial peptides and microbiota dysbiosis. In addition, the

link between air pollution and nutrient concentrations in the respiratory tract and the impact on pneumococcal proliferation are suggestive and require further research. Only a few studies exist that directly assess the impact of air pollution exposure on the development of (invasive) pneumococcal disease, and, because pneumococcal transmission is a relatively understudied topic, the effect of air pollution, including the associated effects on the host, has not yet been investigated in pneumococcal transmission models.

Although the incidence of pneumococcal disease is higher in areas with high air pollution (14–18, 20–22), the association is confounded by the strong link between burden of disease and low socioeconomic status (162, 163). Living in a high-pollution area is also linked to low socioeconomic status, making it difficult to determine if other effects associated with low socioeconomic status, such as chronic lung disease and poor diet, may also play a role (162, 163). It is known that welders are at increased risk for invasive pneumococcal disease when compared with nonwelder groups with a similar socioeconomic status; however, further research is required to determine if this is a specific risk from welding fumes (19). To control for confounding variables and determine direct impacts of air pollution on pneumococcal disease, we rely on *in vitro* and *in vivo* exposure models.

Effective vaccines against *S. pneumoniae* have led to a global reduction in the number of deaths caused by this pathogen (by 7.24% since 1990) (9). Some studies suggest that vaccination might reduce the adverse effects of air pollution exposure. For example, a study of 6,740 Chinese children showed that influenza vaccination reduced the negative effects of air pollution on lung function (164). In addition, the risk of acute coronary syndrome in the elderly is associated with exposure to air pollutants, but this risk is lower in the elderly population that received yearly influenza vaccines (165). Further research is required to determine if pneumococcal vaccines can reduce the adverse effects of air pollution. Conversely, air pollution may have an impact on the efficacy of vaccines. For example, lower neutralizing antibody titers to an inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine were measured in pollutant-exposed individuals, and reduced

antibody responses to a candidate *Haemophilus influenzae* vaccine antigen were observed in mice exposed to cigarette smoke (166, 167). The impact of air pollution on the effectiveness of pneumococcal vaccines has yet to be investigated. The effect of air pollution is likely to be more relevant for the pneumococcal polysaccharide vaccine than for the pneumococcal conjugate vaccine (PCV), because pneumococcal conjugate vaccine is administered early in life, whereas the effects of air pollution accumulate over a lifetime.

Despite effective vaccine programs, *S. pneumoniae* was still responsible for approximately 1.18 million deaths globally in 2016 (14), highlighting the need for other strategies to reduce mortality. Given the important role of air pollution in host susceptibility and development of pneumococcal disease, reducing air pollution concentrations or preventing inhalation of air pollution would be an effective strategy to reduce respiratory disease burden (10, 11, 21). In addition, treating pollutant-induced effects (e.g., an overactive immune response) may aid the management of pneumococcal disease. For example, a systematic review by Corrales-Medina and Musher (168) showed that treatment with immunomodulatory compounds has the potential to reduce the morbidity of pneumonia. These strategies could be especially effective in regions with high air pollution concentrations. Although epidemiological data show a strong correlation between air pollution and respiratory infections, much less is known about the underlying mechanisms (14–23). We rely primarily on animal exposure models, but it is difficult to evaluate or summarize the impact of air pollution because studies use different exposure concentrations and different generation/sampling methods (129) In addition, it is often difficult to extrapolate these data to “real life.” This is partly because of the technical challenge of simulating the dose and duration of real-life exposure in a laboratory setting. To fully understand the effects of air pollution—and that of the various chemical and biological components—we are in need of better real-world data to help us improve our current exposure models.

**Footnotes**

Supported by a U.K. Medical Research Council program grant (MR/P011284/1) and by a joint University of Liverpool–National Institute for Biological Standards and Control PhD Studentship to D.B.

**References**

1. Ferreira DM, Jambo KC, Gordon SB. Experimental human pneumococcal carriage models for vaccine research. *Trends Microbiol .* 2011;19:464–470.

2. Weiser JN, Ferreira DM, Paton JC. *Streptococcus pneumoniae*: transmission, colonization and invasion. *Nat Rev Microbiol .* 2018;16:355–367.

3. Backhaus E, Berg S, Andersson R, Ockborn G, Malmström P, Dahl M, et al. Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. *BMC Infect Dis .* 2016;16:367.

4. Kadioglu A, Weiser JN, Paton JC, Andrew PW. The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. *Nat Rev Microbiol .* 2008;6:288–301.

5. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax .* 2001;56:296–301.

6. van Aalst M, Lötsch F, Spijker R, van der Meer JTM, Langendam MW, Goorhuis A, et al. Incidence of invasive pneumococcal disease in immunocompromised patients: a systematic review and meta-analysis. *Travel Med Infect Dis .* 2018;24:89–100.

7. Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. *Lancet .* 2006;368:1048–1050.

8. Prüss-Üstün A, Wolf J, Corvalán C, Bos R, Neira M. *Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks.* Geneva, Switzerland: World Health Organization; 2016.

9. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* . 2018;18:1191–1210.

10. Carrión D, Kaali S, Kinney PL, Owusu-Agyei S, Chillrud S, Yawson AK, et al. Examining the relationship between household air pollution and infant microbial nasal carriage in a Ghanaian cohort. *Environ Int* . 2019;133:105150.

11. Vanker A, Nduru PM, Barnett W, Dube FS, Sly PD, Gie RP, et al. Indoor air pollution and tobacco smoke exposure: impact on nasopharyngeal bacterial carriage in mothers and infants in an African birth cohort study. *ERJ Open Res* . 2019;5:00052-2018.

12. Mackenzie GA, Leach AJ, Carapetis JR, Fisher J, Morris PS. Epidemiology of nasopharyngeal carriage of respiratory bacterial pathogens in children and adults: cross-sectional surveys in a population with high rates of pneumococcal disease. *BMC Infect Dis* . 2010;10:304.

13. Dherani MK, Pope D, Tafatatha T, Heinsbroek E, Chartier R, Mwalukomo T, et al. Association between household air pollution and nasopharyngeal pneumococcal carriage in Malawian infants (MSCAPE): a nested, prospective, observational study. *Lancet Glob Health* . 2022;10:e246–e256.

14. GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* . 2017;17:1133–1161.

15. Almirall J, Bolíbar I, Serra-Prat M, Roig J, Hospital I, Carandell E, et al.Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J .* 2008;31:1274–1284.

16. Kim PE, Musher DM, Glezen WP, Rodriguez-Barradas MC, Nahm WK, Wright CE. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. *Clin Infect Dis .* 1996;22:100–106.

17. Koul PA, Chaudhari S, Chokhani R, Christopher D, Dhar R, Doshi K, et al. Pneumococcal disease burden from an Indian perspective: need for its prevention in pulmonology practice. *Lung India .* 2019;36:216–225.

18. Pearson AL, Kingham S, Mitchell P, Apparicio P. Exploring hotspots of pneumococcal pneumonia and potential impacts of ejecta dust exposure following the Christchurch earthquakes. *Spat Spatiotemporal Epidemiol .* 2013;7:1–9.

19. Torén K, Blanc PD, Naidoo RN, Murgia N, Qvarfordt I, Aspevall O, et al. Occupational exposure to dust and to fumes, work as a welder and invasive pneumococcal disease risk. *Occup Environ Med .* 2020;77:57–63

20. Zanobetti A, Woodhead M. Air pollution and pneumonia: the “old man” has a new “friend.” *Am J Respir Crit Care Med .* 2010;181:5–6.

21. Jusot JF, Neill DR, Waters EM, Bangert M, Collins M, Bricio Moreno L, et al. Airborne dust and high temperatures are risk factors for invasive bacterial disease. *J Allergy Clin Immunol .* 2017;139:977–986.e2.

22. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. *J Infect .* 2009;58:37–46.

23. Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, et al.Active Bacterial Core Surveillance Team Cigarette smoking and invasive pneumococcal disease. *N Engl J Med .* 2000;342:681–689.

24. Glencross DA, Ho TR, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med .* 2020;151:56–68.

25. Brugha R, Grigg J. Urban air pollution and respiratory infections. *Paediatr Respir Rev .* 2014;15:194–199.

26. Neill DR, Coward WR, Gritzfeld JF, Richards L, Garcia-Garcia FJ, Dotor J, et al. Density and duration of pneumococcal carriage is maintained by transforming growth factor β1 and T regulatory cells. *Am J Respir Crit Care Med .* 2014;189:1250–1259.

27. Mushtaq N, Ezzati M, Hall L, Dickson I, Kirwan M, Png KM, et al. Adhesion of *Streptococcus pneumoniae* to human airway epithelial cells exposed to urban particulate matter. *J Allergy Clin Immunol .* 2011;127:1236–42.e2.

28. Smit LAM, Boender GJ, de Steenhuijsen Piters WAA, Hagenaars TJ, Huijskens EGW, Rossen JWA, et al. Increased risk of pneumonia in residents living near poultry farms: does the upper respiratory tract microbiota play a role? *Pneumonia (Nathan) .* 2017;9:3.

29. Sigaud S, Goldsmith CA, Zhou H, Yang Z, Fedulov A, Imrich A, et al. Air pollution particles diminish bacterial clearance in the primed lungs of mice. *Toxicol Appl Pharmacol .* 2007;223:1–9.

30. Dhar P, Ng GZ, Dunne EM, Sutton P. Mucin 1 protects against severe *Streptococcus pneumoniae* infection. *Virulence .* 2017;8:1631–1642.

31. Roy MG, Livraghi-Butrico A, Fletcher AA, McElwee MM, Evans SE, Boerner RM, et al. Muc5b is required for airway defence. *Nature .* 2014;505:412–416.

32. Alanin MC, Nielsen KG, von Buchwald C, Skov M, Aanaes K, Høiby N, et al. A longitudinal study of lung bacterial pathogens in patients with primary ciliary dyskinesia. *Clin Microbiol Infect* . 2015;21:1093.e1–1093.e7.

33. Yin W, Livraghi-Butrico A, Sears PR, Rogers TD, Burns KA, Grubb BR, et al. Mice with a deletion of *Rsph1* exhibit a low level of mucociliary clearance and develop a primary ciliary dyskinesia phenotype. *Am J Respir Cell Mol Biol* . 2019;61:312–321.

34. Møller ME, Alanin MC, Grønhøj C, Aanaes K, Høiby N, von Buchwald C. Sinus bacteriology in patients with cystic fibrosis or primary ciliary dyskinesia: a systematic review. *Am J Rhinol Allergy* . 2017;31:293–298.

35. Ramos FL, Krahnke JS, Kim V. Clinical issues of mucus accumulation in COPD. *Int J Chron Obstruct Pulmon Dis* . 2014;9:139–150.

36. Simpson JL, Baines KJ, Horvat JC, Essilfie AT, Brown AC, Tooze M, et al. COPD is characterized by increased detection of *Haemophilus influenzae*, *Streptococcus pneumoniae* and a deficiency of *Bacillus* species. *Respirology* . 2016;21:697–704.

37. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* . 2015;70:984–989.

38. Carvalho-Oliveira R, Pires-Neto RC, Bustillos JO, Macchione M, Dolhnikoff M, Saldiva PH, et al. Chemical composition modulates the adverse effects of particles on the mucociliary epithelium. *Clinics (São Paulo)* . 2015;70:706–713.

39. Helleday R, Huberman D, Blomberg A, Stjernberg N, Sandström T. Nitrogen dioxide exposure impairs the frequency of the mucociliary activity in healthy subjects. *Eur Respir J* . 1995;8:1664–1668.

40. Kienast K, Riechelmann H, Knorst M, Schlegel J, Müller-Quernheim J, Schellenberg J, et al. An experimental model for the exposure of human ciliated cells to sulfur dioxide at different concentrations. *Clin Investig .* 1994;72:215–219.

41. Saldiva PH, King M, Delmonte VL, Macchione M, Parada MA, Daliberto ML, et al. Respiratory alterations due to urban air pollution: an experimental study in rats. *Environ Res .* 1992;57:19–33.

42. Xu F, Cao J, Luo M, Che L, Li W, Ying S, et al. Early growth response gene 1 is essential for urban particulate matter-induced inflammation and mucus hyperproduction in airway epithelium. *Toxicol Lett .* 2018;294:145–155.

43. Yoshizaki K, Brito JM, Toledo AC, Nakagawa NK, Piccin VS, Junqueira MS, et al. Subchronic effects of nasally instilled diesel exhaust particulates on the nasal and airway epithelia in mice. *Inhal Toxicol .* 2010;22:610–617.

44. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med .* 2010;363:2233–2247.

45. Nadel JA. Mucous hypersecretion and relationship to cough. *Pulm Pharmacol Ther .* 2013;26:510–513.

46. Bagheri Lankarani N, Kreis I, Griffiths DA. Air pollution effects on peak expiratory flow rate in children. *Iran J Allergy Asthma Immunol .* 2010;9:117–126.

47. Daviskas E, Anderson SD. Hyperosmolar agents and clearance of mucus in the diseased airway. *J Aerosol Med .* 2006;19:100–109.

48. Yoshizaki K, Fuziwara CS, Brito JM, Santos TMN, Kimura ET, Correia AT, et al. The effects of urban particulate matter on the nasal epithelium by gender: an experimental study in mice. *Environ Pollut .* 2016;213:359–369.

49. Penconek A, Michalczuk U, Sienkiewicz A, Moskal A. The effect of desert dust particles on rheological properties of saliva and mucus. *Environ Sci Pollut Res Int .* 2019;26:12150–12157.

50. Demouveaux B, Gouyer V, Gottrand F, Narita T, Desseyn JL. Gel-forming mucin interactome drives mucus viscoelasticity. *Adv Colloid Interface Sci .* 2018;252:69–82.

51. Holma B. Effects of inhaled acids on airway mucus and its consequences for health. *Environ Health Perspect .* 1989;79:109–113.

52. Tang XX, Ostedgaard LS, Hoegger MJ, Moninger TO, Karp PH, McMenimen JD, et al. Acidic pH increases airway surface liquid viscosity in cystic fibrosis. *J Clin Invest .* 2016;126:879–891

53. Montgomery MT, Sajuthi SP, Cho SH, Everman JL, Rios CL, Goldfarbmuren KC, et al. Genome-wide analysis reveals mucociliary remodeling of the nasal airway epithelium induced by urban $PM_{2.5}$. *Am J Respir Cell Mol Biol .* 2020;63:172–184.

54. Lewis M, Stracker TH. Transcriptional regulation of multiciliated cell differentiation. *Semin Cell Dev Biol .* 2021;110:51–60.

55. Suri R, Periselneris J, Lanone S, Zeidler-Erdely PC, Melton G, Palmer KT, et al. Exposure to welding fumes and lower airway infection with *Streptococcus pneumoniae*. *J Allergy Clin Immunol .* 2016;137:527–534.e7.

56. Miyashita L, Suri R, Dearing E, Mudway I, Dove RE, Neill DR, et al. E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells. *Eur Respir J .* 2018;51:1701592.

57. Rijneveld AW, Weijer S, Florquin S, Speelman P, Shimizu T, Ishii S, et al. Improved host defense against pneumococcal pneumonia in platelet-activating factor receptor-deficient mice. *J Infect Dis .* 2004;189:711–716.

58. Radin JN, Orihuela CJ, Murti G, Guglielmo C, Murray PJ, Tuomanen EI. β-Arrestin 1 participates in platelet-activating factor receptor-mediated endocytosis of *Streptococcus pneumoniae*. *Infect Immun .* 2005;73:7827–7835.

59. Wong A, Marrie TJ, Garg S, Kellner JD, Tyrrell GJ, SPAT Group Welders are at increased risk for invasive pneumococcal disease. *Int J Infect Dis .* 2010;14:e796–e799.

60. Beisswenger C, Bals R. Antimicrobial peptides in lung inflammation. *Chem Immunol Allergy .* 2005;86:55–71.

61. Tjabringa GS, Rabe KF, Hiemstra PS. The human cathelicidin LL-37: a multifunctional peptide involved in infection and inflammation in the lung. *Pulm Pharmacol Ther .* 2005;18:321–327.

62. André GO, Politano WR, Mirza S, Converso TR, Ferraz LF, Leite LC, et al. Combined effects of lactoferrin and lysozyme on *Streptococcus pneumoniae* killing. *Microb Pathog .* 2015;89:7–17.

63. Hiemstra PS, Amatngalim GD, van der Does AM, Taube C. Antimicrobial peptides and innate lung defenses: role in infectious and noninfectious lung diseases and therapeutic applications. *Chest .* 2016;149:545–551.

64. Mirza S, Wilson L, Benjamin WH, Jr, Novak J, Barnes S, Hollingshead SK, et al. Serine protease PrtA from *Streptococcus pneumoniae* plays a role in the killing of *S. pneumoniae* by apolactoferrin. *Infect Immun .* 2011;79:2440–2450.

65. Mücke PA, Maaß S, Kohler TP, Hammerschmidt S, Becher D. Proteomic adaptation of *Streptococcus pneumoniae* to the human antimicrobial peptide LL-37. *Microorganisms .* 2020;8:413.

66. Scharf S, Zahlten J, Szymanski K, Hippenstiel S, Suttorp N, N'Guessan PD. *Streptococcus pneumoniae* induces human β-defensin-2 and -3 in human lung epithelium. *Exp Lung Res .* 2012;38:100–110.

67. Findlay F, Pohl J, Svoboda P, Shakamuri P, McLean K, Inglis NF, et al. Carbon nanoparticles inhibit the antimicrobial activities of the human cathelicidin LL-37 through structural alteration. *J Immunol .* 2017;199:2483–2490.

68. Simonin J, Bille E, Crambert G, Noel S, Dreano E, Edwards A, et al. Airway surface liquid acidification initiates host defense abnormalities in Cystic Fibrosis. *Sci Rep* . 2019;9:6516.

69. Vargas Buonfiglio LG, Mudunkotuwa IA, Abou Alaiwa MH, Vanegas Calderón OG, Borcherding JA, Gerke AK, et al. Effects of coal fly ash particulate matter on the antimicrobial activity of airway surface liquid. *Environ Health Perspect* . 2017;125:077003.

70. Rivas-Santiago CE, Sarkar S, Cantarella P, IV, Osornio-Vargas Á, Quintana-Belmares R, Meng Q, et al. Air pollution particulate matter alters antimycobacterial respiratory epithelium innate immunity. *Infect Immun* . 2015;83:2507–2517.

71. Zarcone MC, Duistermaat E, Alblas MJ, van Schadewijk A, Ninaber DK, Clarijs V, et al. Effect of diesel exhaust generated by a city bus engine on stress responses and innate immunity in primary bronchial epithelial cell cultures. *Toxicol In Vitro* . 2018;48:221–231.

72. Chen X, Liu J, Zhou J, Wang J, Chen C, Song Y, et al. Urban particulate matter (PM) suppresses airway antibacterial defence. *Respir Res* . 2018;19:5.

73. Singanayagam A, Glanville N, Cuthbertson L, Bartlett NW, Finney LJ, Turek E, et al. Inhaled corticosteroid suppression of cathelicidin drives dysbiosis and bacterial infection in chronic obstructive pulmonary disease. *Sci Transl Med* . 2019;11:eaav3879

74. Liu S, He LR, Wang W, Wang GH, He ZY. Prognostic value of plasma human β-defensin 2 level on short-term clinical outcomes in patients with community-acquired pneumonia: a preliminary study. *Respir Care* . 2013;58:655–661.

75. Nam HY, Ahn EK, Kim HJ, Lim Y, Lee CB, Lee KY, et al. Diesel exhaust particles increase IL-1β-induced human β-defensin expression via NF-κB-mediated pathway in human lung epithelial cells. *Part Fibre Toxicol* . 2006;3:9.

76. Armstrong SK. Bacterial metabolism in the host environment: pathogen growth and nutrient assimilation in the mammalian upper respiratory tract. *Microbiol Spectr* . 2015;3(3)

77. Zheng J, Gänzle MG, Lin XB, Ruan L, Sun M. Diversity and dynamics of bacteriocins from human microbiome. *Environ Microbiol .* 2015;17:2133–2143.

78. Brown RL, Sequeira RP, Clarke TB. The microbiota protects against respiratory infection via GM-CSF signaling. *Nat Commun .* 2017;8:1512.

79. Salter SJ, Turner C, Watthanaworawit W, de Goffau MC, Wagner J, Parkhill J, et al. A longitudinal study of the infant nasopharyngeal microbiota: the effects of age, illness and antibiotic use in a cohort of South East Asian children. *PLoS Negl Trop Dis .* 2017;11:e0005975

80. Gisler A, Korten I, de Hoogh K, Vienneau D, Frey U, Decrue F, et al.BILD study group Associations of air pollution and greenness with the nasal microbiota of healthy infants: a longitudinal study. *Environ Res .* 2021;202:111633.

81. Li N, He F, Liao B, Zhou Y, Li B, Ran P. Exposure to ambient particulate matter alters the microbial composition and induces immune changes in rat lung. *Respir Res .* 2017;18:143.

82. Li X, Sun Y, An Y, Wang R, Lin H, Liu M, et al. Air pollution during the winter period and respiratory tract microbial imbalance in a healthy young population in Northeastern China. *Environ Pollut .* 2019;246:972–979.

83. Mariani J, Favero C, Spinazzè A, Cavallo DM, Carugno M, Motta V, et al. Short-term particulate matter exposure influences nasal microbiota in a population of healthy subjects. *Environ Res .* 2018;162:119–126.

84. Xue Y, Chu J, Li Y, Kong X. The influence of air pollution on respiratory microbiome: a link to respiratory disease. *Toxicol Lett .* 2020;334:14–20.

85. Mousavi SE, Delgado-Saborit JM, Adivi A, Pauwels S, Godderis L. Air pollution and endocrine disruptors induce human microbiome imbalances: a systematic review of recent evidence and possible biological mechanisms. *Sci Total Environ .* 2022;816:151654.

86. Cremers AJ, Zomer AL, Gritzfeld JF, Ferwerda G, van Hijum SA, Ferreira DM, et al. The adult nasopharyngeal microbiome as a determinant of pneumococcal acquisition. *Microbiome .* 2014;2:44.

87. Cao C, Jiang W, Wang B, Fang J, Lang J, Tian G, et al. Inhalable microorganisms in Beijing's $PM_{2.5}$ and $PM_{10}$ pollutants during a severe smog event. *Environ Sci Technol .* 2014;48:1499–1507.

88. Fan XY, Gao JF, Pan KL, Li DC, Dai HH, Li X. More obvious air pollution impacts on variations in bacteria than fungi and their co-occurrences with ammonia-oxidizing microorganisms in $PM_{2.5}$. *Environ Pollut .* 2019;251:668–680.

89. Liu H, Zhang X, Zhang H, Yao X, Zhou M, Wang J, et al. Effect of air pollution on the total bacteria and pathogenic bacteria in different sizes of particulate matter. *Environ Pollut .* 2018;233:483–493.

90. Moelling K, Broecker F. Air microbiome and pollution: composition and potential effects on human health, including SARS coronavirus infection. *J Environ Public Health .* 2020;2020:1646943.

91. Falcon-Rodriguez CI, Osornio-Vargas AR, Sada-Ovalle I, Segura-Medina P. Aeroparticles, composition, and lung diseases. *Front Immunol .* 2016;7:3.

92. Shears RK, Jacques LC, Naylor G, Miyashita L, Khandaker S, Lebre F, et al. Exposure to diesel exhaust particles increases susceptibility to invasive pneumococcal disease. *J Allergy Clin Immunol .* 2020;145:1272–1284.e6.

93. Baker EH, Baines DL. Airway glucose homeostasis: a new target in the prevention and treatment of pulmonary infection. *Chest .* 2018;153:507–514.

94. Garnett JP, Braun D, McCarthy AJ, Farrant MR, Baker EH, Lindsay JA, et al. Fructose transport-deficient Staphylococcus aureus reveals important role of epithelial glucose transporters in limiting sugar-driven bacterial growth in airway surface liquid. *Cell Mol Life Sci .* 2014;71:4665–4673.

95. Paixão L, Caldas J, Kloosterman TG, Kuipers OP, Vinga S, Neves AR. Transcriptional and metabolic effects of glucose on *Streptococcus pneumoniae* sugar metabolism. *Front Microbiol .* 2015;6:1041.

96. Kim N, Han DH, Suh MW, Lee JH, Oh SH, Park MK. Effect of lipopolysaccharide on diesel exhaust particle-induced junctional dysfunction in primary human nasal epithelial cells. *Environ Pollut .* 2019;248:736–742

97. Liu J, Chen X, Dou M, He H, Ju M, Ji S, et al. Particulate matter disrupts airway epithelial barrier via oxidative stress to promote *Pseudomonas aeruginosa* infection. *J Thorac Dis .* 2019;11:2617–2627.

98. Robison TW, Kim KJ. Dual effect of nitrogen dioxide on barrier properties of guinea pig tracheobronchial epithelial monolayers cultured in an air interface. *J Toxicol Environ Health .* 1995;44:57–71.

99. Tovar A, Smith GJ, Thomas JM, Crouse WL, Harkema JR, Kelada SNP. Transcriptional profiling of the murine airway response to acute ozone exposure. *Toxicol Sci .* 2020;173:114–130.

100. Oliveira JD. Macedo CF. Guarnieri JPO. Theizen TH. Machado D. Lancellotti M. Influence of environmental dust in transformation capacity of *Streptococcus pneumoniae*. *Genet Mol Biol .* 2020;44:e20200028.

101. Salvadori G, Junges R, Morrison DA, Petersen FC. Competence in *Streptococcus pneumoniae* and close commensal relatives: mechanisms and implications. *Front Cell Infect Microbiol .* 2019;9:94.

102. Ley K, Pramod AB, Croft M, Ravichandran KS, Ting JP. How mouse macrophages sense what is going on. *Front Immunol .* 2016;7:204.

103. Rylance J, Chimpini C, Semple S, Russell DG, Jackson MJ, Heyderman RS, et al. Chronic household air pollution exposure is associated with impaired alveolar macrophage function in Malawian non-smokers. *PLoS One .* 2015;10:e0138762.

104. Kulkarni N, Pierse N, Rushton L, Grigg J. Carbon in airway macrophages and lung function in children. *N Engl J Med .* 2006;355:21–30.

105. Zhou H, Kobzik L. Effect of concentrated ambient particles on macrophage phagocytosis and killing of *Streptococcus pneumoniae*. *Am J Respir Cell Mol Biol .* 2007;36:460–465.

106. Zhou HM, Brust-Mascher I, Scholey JM.Direct visualization of the movement of the monomeric kinesin, UNC-104, in neurons of living *C. elegans* [abstract] *Mol Biol Cell* 20001181A.

107. Yan Z, Jin Y, An Z, Liu Y, Samet JM, Wu W. Inflammatory cell signaling following exposures to particulate matter and ozone. *Biochim Biophys Acta .* 2016;1860:2826–2834.

108. Lawal AO. Air particulate matter induced oxidative stress and inflammation in cardiovascular disease and atherosclerosis: the role of Nrf2 and AhR-mediated pathways. *Toxicol Lett .* 2017;270:88–95.

109. Pardo M, Qiu X, Zimmermann R, Rudich Y. Particulate matter toxicity is Nrf2 and mitochondria dependent: the roles of metals and polycyclic aromatic hydrocarbons. *Chem Res Toxicol .* 2020;33:1110–1120.

110. Shoenfelt J, Mitkus RJ, Zeisler R, Spatz RO, Powell J, Fenton MJ, et al. Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter. *J Leukoc Biol .* 2009;86:303–312.

111. Becker S, Dailey L, Soukup JM, Silbajoris R, Devlin RB. TLR-2 is involved in airway epithelial cell response to air pollution particles. *Toxicol Appl Pharmacol .* 2005;203:45–52.

112. Cevallos VM, Díaz V, Sirois CM. Particulate matter air pollution from the city of Quito, Ecuador, activates inflammatory signaling pathways in vitro. *Innate Immun .* 2017;23:392–400.

113. Leikauf GD, Kim SH, Jang AS. Mechanisms of ultrafine particle-induced respiratory health effects. *Exp Mol Med .* 2020;52:329–337.

114. Boström CE, Gerde P, Hanberg A, Jernström B, Johansson C, Kyrklund T, et al. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environ Health Perspect .* 2002;110:451–488.

115. Låg M, Øvrevik J, Refsnes M, Holme JA. Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases. *Respir Res .* 2020;21:299.

116. Marris CR, Kompella SN, Miller MR, Incardona JP, Brette F, Hancox JC, et al. Polyaromatic hydrocarbons in pollution: a heart-breaking matter. *J Physiol .* 2020;598:227–247.

117. den Hartigh LJ, Lamé MW, Ham W, Kleeman MJ, Tablin F, Wilson DW. Endotoxin and polycyclic aromatic hydrocarbons in ambient fine particulate matter from Fresno, California initiate human monocyte inflammatory responses mediated by reactive oxygen species. *Toxicol In Vitro .* 2010;24:1993–2002.

118. Kowalska M, Wegierek-Ciuk A, Brzoska K, Wojewodzka M, Meczynska-Wielgosz S, Gromadzka-Ostrowska J, et al. Genotoxic potential of diesel exhaust particles from the combustion of first- and second-generation biodiesel fuels—the FuelHealth project. *Environ Sci Pollut Res Int .* 2017;24:24223–24234.

119. Brinchmann BC, Skuland T, Rambøl MH, Szoke K, Brinchmann JE, Gutleb AC, et al. Lipophilic components of diesel exhaust particles induce pro-inflammatory responses in human endothelial cells through AhR dependent pathway(s) *Part Fibre Toxicol .* 2018;15:21.

120. Kim JS, Adamcakova-Dodd A, O'Shaughnessy PT, Grassian VH, Thorne PS. Effects of copper nanoparticle exposure on host defense in a murine pulmonary infection model. *Part Fibre Toxicol .* 2011;8:29.

121. Chow JC, Watson JG, Mauderly JL, Costa DL, Wyzga RE, Vedal S, et al. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc .* 2006;56:1368–1380.

122. Kourie JI. Interaction of reactive oxygen species with ion transport mechanisms. *Am J Physiol* . 1998;275:C1–C24.

123. Radan M, Dianat M, Badavi M, Mard SA, Bayati V, Goudarzi G. In vivo and in vitro evidence for the involvement of Nrf2-antioxidant response element signaling pathway in the inflammation and oxidative stress induced by particulate matter ($PM_{10}$): the effective role of gallic acid. *Free Radic Res* . 2019;53:210–225.

124. Barregard L, Sällsten G, Andersson L, Almstrand AC, Gustafson P, Andersson M, et al. Experimental exposure to wood smoke: effects on airway inflammation and oxidative stress. *Occup Environ Med* . 2008;65:319–324.

125. McCarthy CE, Duffney PF, Gelein R, Thatcher TH, Elder A, Phipps RP, et al. Dung biomass smoke activates inflammatory signaling pathways in human small airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* . 2016;311:L1222–L1233.

126. Hirota JA, Hirota SA, Warner SM, Stefanowicz D, Shaheen F, Beck PL, et al. The airway epithelium nucleotide-binding domain and leucine-rich repeat protein 3 inflammasome is activated by urban particulate matter. *J Allergy Clin Immunol* . 2012;129:1116–25.e6.

127. Thom SR, Bhopale VM, Hu J, Yang M. Increased carbon dioxide levels stimulate neutrophils to produce microparticles and activate the nucleotide-binding domain-like receptor 3 inflammasome. *Free Radic Biol Med* . 2017;106:406–416.

128. Yang J, Chen Y, Yu Z, Ding H, Ma Z. The influence of $PM_{2.5}$ on lung injury and cytokines in mice. *Exp Ther Med* . 2019;18:2503–2511.

129. Park M, Joo HS, Lee K, Jang M, Kim SD, Kim I, et al. Differential toxicities of fine particulate matters from various sources. *Sci Rep* . 2018;8:17007.

130. Swiston JR, Davidson W, Attridge S, Li GT, Brauer M, van Eeden SF. Wood smoke exposure induces a pulmonary and systemic inflammatory response in firefighters. *Eur Respir J .* 2008;32:129–138.

131. Fujii T, Hayashi S, Hogg JC, Mukae H, Suwa T, Goto Y, et al. Interaction of alveolar macrophages and airway epithelial cells following exposure to particulate matter produces mediators that stimulate the bone marrow. *Am J Respir Cell Mol Biol .* 2002;27:34–41.

132. Ishii H, Hayashi S, Hogg JC, Fujii T, Goto Y, Sakamoto N, et al. Alveolar macrophage-epithelial cell interaction following exposure to atmospheric particles induces the release of mediators involved in monocyte mobilization and recruitment. *Respir Res .* 2005;6:87

133. Mehra D, Geraghty PM, Hardigan AA, Foronjy R. A comparison of the inflammatory and proteolytic effects of dung biomass and cigarette smoke exposure in the lung. *PLoS One .* 2012;7:e52889.

134. Liew PX, Kubes P. The neutrophil's role during health and disease. *Physiol Rev .* 2019;99:1223–1248.

135. Wooding DJ, Ryu MH, Li H, Alexis NE, Pena O, Carlsten C, Canadian Respiratory Research Network Acute air pollution exposure alters neutrophils in never-smokers and at-risk humans. *Eur Respir J .* 2020;55:1901495.

136. Rocks N, Vanwinge C, Radermecker C, Blacher S, Gilles C, Marée R, et al. Ozone-primed neutrophils promote early steps of tumour cell metastasis to lungs by enhancing their NET production. *Thorax .* 2019;74:768–779.

137. Matthews NC, Faith A, Pfeffer P, Lu H, Kelly FJ, Hawrylowicz CM, et al. Urban particulate matter suppresses priming of T helper type 1 cells by granulocyte/macrophage colony-stimulating factor-activated human dendritic cells. *Am J Respir Cell Mol Biol .* 2014;50:281–291.

138. Matthews NC, Pfeffer PE, Mann EH, Kelly FJ, Corrigan CJ, Hawrylowicz CM, et al. Urban particulate matter-activated human dendritic cells induce the expansion of potent inflammatory Th1, Th2, and Th17 effector cells. *Am J Respir Cell Mol Biol .* 2016;54:250–262.

139. Pfeffer PE, Ho TR, Mann EH, Kelly FJ, Sehlstedt M, Pourazar J, et al. Urban particulate matter stimulation of human dendritic cells enhances priming of naive CD8 T lymphocytes. *Immunology .* 2018;153:502–512.

140. Sasaki Y, Ohtani T, Ito Y, Mizuashi M, Nakagawa S, Furukawa T, et al. Molecular events in human T cells treated with diesel exhaust particles or formaldehyde that underlie their diminished interferon-γ and interleukin-10 production. *Int Arch Allergy Immunol .* 2009;148:239–250.

141. Kasetty G, Bhongir RKV, Papareddy P, Tufvesson E, Stenberg H, Bjermer L, et al. Osteopontin protects against pneumococcal infection in a murine model of allergic airway inflammation. *Allergy .* 2019;74:663–674.

142. Knippenberg S, Brumshagen C, Aschenbrenner F, Welte T, Maus UA. Arginase 1 activity worsens lung-protective immunity against *Streptococcus pneumoniae* infection. *Eur J Immunol .* 2015;45:1716–1726.

143. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of $T_{reg}$ and $T_H17$ cell differentiation by the aryl hydrocarbon receptor. *Nature .* 2008;453:65–71.

144. O'Driscoll CA, Gallo ME, Hoffmann EJ, Fechner JH, Schauer JJ, Bradfield CA, et al. Polycyclic aromatic hydrocarbons (PAHs) present in ambient urban dust drive proinflammatory T cell and dendritic cell responses via the aryl hydrocarbon receptor (AHR) in vitro. *PLoS One .* 2018;13:e0209690.

145. Wang Y, Jiang B, Guo Y, Li W, Tian Y, Sonnenberg GF, et al. Cross-protective mucosal immunity mediated by memory Th17 cells against *Streptococcus pneumoniae* lung infection. *Mucosal Immunol .* 2017;10:250–259.

146. Neill DR, Fernandes VE, Wisby L, Haynes AR, Ferreira DM, Laher A, et al. T regulatory cells control susceptibility to invasive pneumococcal pneumonia in mice. *PLoS Pathog .* 2012;8:e1002660.

147. O'Driscoll CA, Gallo ME, Fechner JH, Schauer JJ, Mezrich JD. Real-world PM extracts differentially enhance Th17 differentiation and activate the aryl hydrocarbon receptor (AHR) *Toxicology .* 2019;414:14–26.

148. Weng CM, Wang CH, Lee MJ, He JR, Huang HY, Chao MW, et al. Aryl hydrocarbon receptor activation by diesel exhaust particles mediates epithelium-derived cytokines expression in severe allergic asthma. *Allergy .* 2018;73:2192–2204.

149. Wang W, Li Y, Lv Z, Chen Y, Li Y, Huang K, et al. Bronchial allergen challenge of patients with atopic asthma triggers an alarmin (IL-33, TSLP, and IL-25) response in the airways epithelium and submucosa. *J Immunol .* 2018;201:2221–2231.

150. Biesbroek G, Tsivtsivadze E, Sanders EA, Montijn R, Veenhoven RH, Keijser BJ, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *Am J Respir Crit Care Med .* 2014;190:1283–1292.

151. de Steenhuijsen Piters WA, Bogaert D. Unraveling the molecular mechanisms underlying the nasopharyngeal bacterial community structure. *mBio .* 2016;7:e00009–e00016.

152. Fan RR, Howard LM, Griffin MR, Edwards KM, Zhu Y, Williams JV, et al. Nasopharyngeal pneumococcal density and evolution of acute respiratory illnesses in young children, Peru, 2009-2011. *Emerg Infect Dis .* 2016;22:1996–1999.

153. Baggett HC, Watson NL, Deloria Knoll M, Brooks WA, Feikin DR, Hammitt LL, et al.PERCH Study Group Density of upper respiratory colonization with *Streptococcus pneumoniae* and its role in the diagnosis of pneumococcal pneumonia among children aged <5 years in the PERCH study. *Clin Infect Dis .* 2017;64(Suppl 3):S317–S327.

154. Short KR, Reading PC, Wang N, Diavatopoulos DA, Wijburg OL. Increased nasopharyngeal bacterial titers and local inflammation facilitate transmission of *Streptococcus pneumoniae*. *mBio .* 2012;3:e00255-12.

155. Zafar MA, Wang Y, Hamaguchi S, Weiser JN. Host-to-host transmission of *Streptococcus pneumoniae* is driven by its inflammatory toxin, pneumolysin. *Cell Host Microbe .* 2017;21:73–83.

156. Murakami D, Kono M, Nanushaj D, Kaneko F, Zangari T, Muragaki Y, et al. Exposure to cigarette smoke enhances pneumococcal transmission among littermates in an infant mouse model. *Front Cell Infect Microbiol .* 2021;11:651495.

157. Burte E, Leynaert B, Marcon A, Bousquet J, Benmerad M, Bono R, et al. Long-term air pollution exposure is associated with increased severity of rhinitis in 2 European cohorts. *J Allergy Clin Immunol .* 2020;145:834–842.e6.

158. Rodrigues F, Foster D, Nicoli E, Trotter C, Vipond B, Muir P, et al. Relationships between rhinitis symptoms, respiratory viral infections and nasopharyngeal colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* in children attending daycare. *Pediatr Infect Dis J .* 2013;32:227–232.

159. Morimura A, Hamaguchi S, Akeda Y, Tomono K. Mechanisms underlying pneumococcal transmission and factors influencing host-pneumococcus interaction: a review. *Front Cell Infect Microbiol .* 2021;11:639450.

160. Miellet WR, van Veldhuizen J, Nicolaie MA, Mariman R, Bootsma HJ, Bosch T, et al. Influenza-like illness exacerbates pneumococcal carriage in older adults. *Clin Infect Dis .* 2021;73:e2680–e2689.

161. Zhang J, Perret JL, Chang AB, Idrose NS, Bui DS, Lowe AJ, et al. Risk factors for chronic cough in adults: a systematic review and meta-analysis. *Respirology .* 2022;27:36–47.

162. Chapman KE, Wilson D, Gorton R. Invasive pneumococcal disease and socioeconomic deprivation: a population study from the North East of England. *J Public Health (Oxf) .* 2013;35:558–569.

163. Soto K, Petit S, Hadler JL. Changing disparities in invasive pneumococcal disease by socioeconomic status and race/ethnicity in Connecticut, 1998-2008. *Public Health Rep .* 2011;126(Suppl 3):81–88.

164. Liu K, Yang BY, Guo Y, Bloom MS, Dharmage SC, Knibbs LD, et al. The role of influenza vaccination in mitigating the adverse impact of ambient air pollution on lung function in children: new insights from the Seven Northeastern Cities Study in China. *Environ Res .* 2020;187:109624.

165. Huang CH, Chao DY, Wu CC, Hsu SY, Soon MS, Chang CC, et al. Influenza vaccination and the endurance against air pollution among elderly with acute coronary syndrome. *Vaccine .* 2016;34:6316–6322.

166. Zhang S, Chen S, Xiao G, Zhao M, Li J, Dong W, et al. The associations between air pollutant exposure and neutralizing antibody titers of an inactivated SARS-CoV-2 vaccine. *Environ Sci Pollut Res Int .* 2022;29:13720–13728.

167. Bhat TA, Kalathil SG, Bogner PN, Miller A, Lehmann PV, Thatcher TH, et al. Secondhand smoke induces inflammation and impairs immunity to respiratory infections. *J Immunol .* 2018;200:2927–2940.

168. Corrales-Medina VF, Musher DM. Immunomodulatory agents in the treatment of community-acquired pneumonia: a systematic review. *J Infect .* 2011;63:187–199.