FACT SHEET - Association between ambient air pollutants and virus infections of the respiratory tract

Background

In December 2019, the coronavirus Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), the pathogenic agent of COVID-19, was first described in a small cluster in Wuhan, China, and subsequently spread all over the world. In March 2020, the World Health Organization (WHO) declared it a pandemic (WHO 2020a). Early reports indicated that ambient air pollutants contribute to the number of cases and fatalities.

However, the publications which assess these relationships differ regarding study designs, study areas, exposures, outcomes, time frames and scientific quality. While the growing body of evidence from single studies has been summarised in a number of reviews (Ali and Islam 2020; Copat et al. 2020; Bourdrel et al. 2021; Domingo and Rovira 2020), up to now no meta-analysis is available. In addition, the included literature was qualitatively scanned for subgroup analyses to identify vulnerable populations.

This fact sheet summarizes the results of a scientific review of literature from 01 January 1980 to 27 October 2020 and a subsequent meta-analysis including not only SARS-CoV-2 but other viruses which can cause upper respiratory tract infections. It provides a first quantitative assessment of the association between air pollution and COVID-19. The included studies of the first SARS-CoV-2 wave cover a period where none or only few counter

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measures such as lock-downs, social distancing or obligations for wearing masks were in place. Therefore, publications from the first months of the COVID-19 pandemic are thought to give a clearer, unimpeded estimate of the true association.

**Possible reasons linking air pollution and COVID-1**

A number of possible biological mechanisms linking the exposure to ambient air pollution to COVID-19 morbidity and mortality has been proposed:

1. **High levels of ambient air pollution may weaken the immune defence** of the airways. Air pollution can impair the mucociliary epithelium lining the upper and lower respiratory tract, which constitutes the first line of defence of the airways against inhaled pollutants and pathogens (Cao et al. 2020). If these clearing mechanisms are weakened any viral load is more likely to reach the lower airways.

2. **Short-term (Rückerl et al. 2011) and long-term (Tsai et al. 2019) exposure to air pollution can lead to a low-level chronic inflammatory state.** Some COVID-19 patients show signs of a so called “cytokine storm” with an excessive and uncontrolled release of pro-inflammatory markers (Mehta et al. 2020). These cytokines are produced by a number of immune cells and comprise an essential part of the inflammatory process (Ragab et al. 2020). However, an uncontrolled increase can lead to multi-organ failure and even death. A cytokine storm can be caused by a number of infectious diseases including SARS-CoV-2, SARS-CoV-1 and influenza (Liu, Zhou, and Yang 2016; Wong et al. 2017).

3. **Exposure to ambient air pollution has been associated with (chronic) diseases such as cardiovascular disease (Rückerl et al. 2011) or diabetes (Lucht et al. 2020) which seem to make the human body more vulnerable to viruses.** The fact that COVID-19 mostly affects elderly people (Liu et al. 2020; Shahid et al. 2020) or patients with diabetes (Guo et al. 2020), hypertension, COPD or cardiovascular disease (Wang et al. 2020) supports this hypothesis.

4. **The association between increased ambient air pollutants and high infection rates and severity of COVID-19 might be explained by the overexpression of the angiotensin converting enzyme 2 (ACE-2) on epithelial cell surfaces of the respiratory tract.** This in turn could increase the risk of the virus attaching to the host epithelial cells along the respiratory tracts (Paital and Agrawal 2020). In addition, experimental evidence suggests that air pollutants such as O₃ and NO₂ increase protease activity and promote infections via protein cleavage of the spike protein and others.

**Methods**

We searched the publication servers “Pubmed”, “Web of Science” and the pre-print server “medRxiv” for epidemiological studies for “ambient air pollution”, “virus” and “virus-related diseases” published from 01/01/1980 to 27/10/2020. Studied conditions comprised virus-related disease incidence, severity, hospitalisation, mortality and symptoms of the respiratory tract caused by a virus. Risk of bias was assessed for each study included into the review according to the WHO risk of bias assessment instrument (WHO 2020b). The study was registered at PROSPERO (CRD42020199906).
Findings
The literature search yielded 1,294 studies for PubMed and Web of Science and 46 studies for MedRxiv of which 52 articles were reviewed in-depth and risk of bias assessed. A risk of bias assessment, also called "quality assessment" or "critical appraisal", is conducted to establish if the results of a particular study might be under- or overestimated. If a study has a risk of bias it might reflect a skewed picture. The review includes more than 65,000,000 cases and 264,000 deaths on five continents. Studies were divided into long-term exposure studies and short-term exposure studies. Long-term studies consider a cumulative exposure over a time period of at least three months. Short-term studies usually look at day-to-day changes in exposure.

The meta-analysis shows that past long-term exposure to both PM\textsubscript{2.5} and NO\textsubscript{2} was associated with SARS-CoV-2 related mortality (RR: 1.65; 95%CI: 1.09; 2.49 and RR: 1.19; 95%CI: 1.08; 1.30, respectively). NO\textsubscript{2} was also associated with the number of SARS-CoV-2 cases (RR: 1.24, 95%CI: 1.15; 1.32). Regarding the short-term studies, daily changes in exposure to NO\textsubscript{2} were associated with increases in SARS-CoV-2 and other respiratory virus infections. We observed smaller effect estimates for the association between NO\textsubscript{2} and influenza cases than for NO\textsubscript{2} and SARS-CoV-2. This might be due to the fact that influenza has shorter incubation time and is less lethal than SARS-CoV-2 (Lessler et al. 2009).

Special aspects
Confounders: It is important to consider adjustment for confounders in the studies included into the review. A confounder is associated with both, the exposure and the outcome, and inadequate adjustment for confounding may lead to biased results. Some authors investigated to what extent adjusting for potential confounders changed the results. Cox and colleagues (Cox and Popken 2020) found for COVID-19 mortality that the percentage of blacks, the average density of the population in the county, longitude, time since first case in the county, average temperature during the winter months and latitude had the strongest impact besides PM\textsubscript{2.5} concentration. In the publications of Wu and colleagues the reported increase of 15% in the COVID-19 death rate for 1 \( \mu g \)/m\textsuperscript{3} in PM2.5 was nearly halved (8%) after the authors adjusted for days since first COVID-19 case reported, population age distribution, and days since issuance of stay-at-home order. In the final published version, they reported an association of 11% (95% CI: 6%; 17%) (Wu et al. 2020).

Risk of bias and robustness of results: The results of this meta-analysis remained robust when excluding studies with higher risk of bias or uncertainty or such which did not adjust for socio-economic variables.

Vulnerable populations: People from lower socio-economic status (SES) and/or with chronic diseases seem to be disproportionately affected by the COVID-19 pandemic. Whether SES and chronic diseases are on the causal pathway between air pollution exposure or act as confounders is still unclear. The following routes have been proposed (O’Neill et al. 2003): a) air pollution exposure is differentially distributed by SES; b) low SES may directly increase susceptibility to air pollution related health consequences. Individuals from ethnic minority backgrounds
are more likely to live in larger household sizes comprised of multiple generations and to be employed as essential workers (Nguyen et al. 2020). c) Some health conditions and traits that cause vulnerability to air pollution are linked to SES and also represent risk factors for severe COVID-19 disease progression, including above all diseases of the cardiovascular system and the lung. O’Hearn and colleagues (O’Hearn et al. 2021) estimated that for more than 900,000 hospitalisations due to COVID-19 in the U.S. nearly two thirds (63.5%) were attributable to cardiometabolic conditions.

Implications
In light of the updated WHO Air Quality Guidelines, our evidence highlights the urgent need to protect respiratory health by reducing the air pollution in Europe and globally (Andersen et al. 2021). Moreover, it has been shown that people with chronic diseases and lower socio-economic status are disproportionately affected. Targeted approaches are needed to reach and protect especially these most vulnerable groups.

The findings substantiate the need to reduce ambient air pollution as it causes a large burden in non-communicable diseases and contributed thereby to the COVID-19 pandemic. The interventions which were put in place to hamper the spread of the pandemic such as country-wide lock-downs have resulted in transient decreases of ambient air pollution and this way demonstrated that reducing ambient concentrations is possible.
Definitions

**Respiratory viruses**

Respiratory viruses are a heterogeneous group of different virus families, affecting the human respiratory system. This includes infections of the upper respiratory tract like the sinuses or the throat as well as infections of the lower respiratory tract (windpipe and lung). Infections of the respiratory tract caused by viruses are among the most frequently occurring human diseases (Boncristiani, Criado, and Arruda 2009).

**SARS-CoV-1 (Severe acute respiratory syndrome coronavirus 1):** RNA virus from the coronavirus family. It was first described in November 2002 in Southeast Asia, and was the cause of a worldwide pandemic that lasted until 2004 (WHO 2004). Transmitted mainly via droplets and aerosols, the symptoms are fever and headache, combined with respiratory symptoms like cough and shortness of breath. Severe courses affect the lower respiratory tract in particular, and can range from pneumonia up to ARDS (acute respiratory stress disease) (Peiris et al. 2003) with a potentially fatal outcome.

**SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2):** The RNA virus from the coronavirus family is the pathological agent of COVID-19 (coronavirus disease 2019). After the first cases in Wuhan in December 2019, the virus caused an ongoing global pandemic. Transmission and symptoms are comparable to a SARS-CoV-1 infection. However, infectivity is considerably higher with SARS-CoV-2, but with a lower case fatality rate (Zhu et al. 2020).

**Influenza virus:** Large virus family, consisting of four different types of influenza virus. Influenza A and B viruses are the most common ones causing the seasonal influenza, influenza C mainly affects pigs and is extremely rare in humans (WHO 2018). While in temperate climates, the seasonal influenza viruses circulate mostly during winter, in tropical climate there are irregular outbreaks during the whole year. Transmission takes place mainly through droplets, but the viruses can also be transmitted via contact surfaces (e.g. hands). Symptoms are fever, headache and muscle pain next to respiratory symptoms like sore throat. Severe courses can lead to pneumonia, which is caused either by the virus itself or secondarily by bacteria. In addition, chronic pulmonary diseases may be exacerbated (Rothberg and Haessler 2010).

**Respiratory syncytial virus:** RNA virus that predominantly affects children and leads to an infection of the upper and lower respiratory tract (Black 2003). The seasonality of the virus is similar to that of seasonal influenza. Transmission is mainly via droplets, but hands or contaminated surfaces can also be carriers of infection. The disease begins with fever and an infection of the upper respiratory tract (cough, rhinitis, pharyngitis) and can spread to the lower respiratory tract in severe cases (pneumonia, bronchiolitis). In the presence of chronic pulmonary or cardiac pre-existing conditions, an infection can lead to a significant worsening of the symptoms (Tregoning and Schwarze 2010).
**Systematic Review and Meta-Analysis**

A *systematic review* is a review of scientific studies, that uses systematic methods for a predefined question of interest to synthesize the findings of the different included scientific studies (Page et al. 2021). This usually consists of a systematic literature search with in advance defined search terms. In a second step, the content is evaluated with regard to the research question and previously defined inclusion criteria, and the results are extracted. Finally, the results of the individual studies can be synthesised. Systematic literature reviews can provide new scientific insights and highlight gaps, conflicting results and under-examined areas of research.

A *meta-analysis* is a statistical method to synthesize the findings from a *systematic review* (Page et al. 2021). It uses the effect estimates from single studies in order to calculate an average effect to provide a quantitative summary of the results. It tests for heterogeneity of the single studies and their deviation from the overall mean.

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**Air pollutants**

*Particulate matter (PM)* is a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air. Usually, PM is defined by size: Particle mass with an aerodynamic diameter of \(<10\ \mu m\) is called \(PM_{10}\), particle mass with an aerodynamic diameter of \(<2.5\ \mu m\) is called \(PM_{2.5}\). The largest share of anthropogenic particle emissions originates from combustion processes such as motor vehicle traffic and building heating as well as production processes including bulk material handling. Particulate matter is not only emitted directly (primary particles) but also forms from gaseous pollutants (including sulphur dioxide, nitrogen oxide and ammonia) in the atmosphere (secondary particles).

*Nitrogen dioxide (NO\(_2\))* is an irritant gas that acts as a reactive oxidant. Due to its relatively low water solubility, it is not absorbed in the upper respiratory tract, but penetrates into deeper areas of the respiratory tract such as bronchioles and alveoli. NO\(_2\) is emitted by combustion engines when burning fossil fuels and formed as a secondary pollutant. Therefore, in densely populated urban areas, road traffic is one of the most significant sources of NO\(_2\).

*Ozone* is a colourless gas and a natural trace component of the air. It reacts easily with other substances. Ozone is very rarely emitted directly but is formed in the atmosphere mainly from precursor substances by UV radiation at higher temperatures via complex chemical reactions. The precursor substances include in particular hydrocarbons and nitrogen oxides. Ozone stems from natural and man-made (anthropogenic) sources of which motor vehicle traffic is in first place as internal combustion engines release large quantities of both nitrogen oxides and hydrocarbons.
**Epidemiological measures**

**Incidence**: The relative frequency of new events/diseases occurring in a population or group of people within a given time period.

**Mortality/mortality rate** denotes the number of deaths in relation to the total number of individuals in a given period of time.

**Case fatality/case fatality rate**: The case-fatality ratio/case fatality rate, is the proportion of people with a particular disease (cases) who die from that disease. The case-fatality ratio is a common statistical measure of the short-term severity of an acute illness and allows a direct assessment of the effectiveness of intervention measures. It is therefore used primarily for acute illnesses with a short duration of illness and less for chronic diseases.

**R0/ R(t)**: The reproduction number R describes how many people an infected person infects on average. At the beginning of a pandemic the initial value **R0** (basic reproduction number) describes how many people one infected person infects on average when the entire population is susceptible to the virus because there is no immunity in the population and no infection protection measures yet. **R0** is a quantity that is specific to a certain population at a certain point in time; there is no generally valid value. Infection control measures can reduce the reproduction number. This is known as the time-dependent reproduction number **R(t)**. If R is greater than 1, the number of new infections increases daily, if R equals 1, the number of daily new infections remains constant and if R is less than 1, the number of daily new infections decreases.
References
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