Pollution and the spread of Covid-19
Pollution and the spread of Covid-19

Epidemiological studies of Covid-19 have, in most cases, provided inconclusive results to date regarding the role of air pollution in the transmission of the SARS-CoV-2 virus and the geographical spread of the disease, both regionally and globally.

The present review analysed just under 6 000 articles published up to 31 May 2021, looking at the role of pollution and air quality factors in the transmission of SARS-CoV-2 and in the geographical differences in Covid-19 propagation. A body of evidence shows that chronic and short-term exposure to different fractions of aerosols and types of air pollution exacerbates symptoms, affects comorbidities and increases mortality rates for respiratory diseases similar to Covid-19, as well as for Covid-19. Although other pathways can contribute, the airborne route is likely to be the dominant mode.

There is consistent and increasing evidence that SARS-CoV-2 spreads by airborne transmission, and it is possible that different variants have different environmental sensitivities. Safer indoor environments are required, not only to protect unvaccinated people and those for whom vaccines fail, but also to deter vaccine-resistant variants or novel airborne threats that may appear at any time.

The public health community, governments and health agencies should act accordingly, referring to this mode as the principal mode of transmission in their recommendations and statements, enhancing associated research and improving monitoring networks.
This study has been written by Xavier Rodó, ICREA Research Professor at the Barcelona Institute for Global Health (ISGlobal), at the request of the Panel for the Future of Science and Technology (STOA) and managed by the Scientific Foresight Unit, within the Directorate-General for Parliamentary Research Services (EPRS) of the Secretariat of the European Parliament.

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Executive summary

1. Introduction

Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) is the pathogenic agent of Covid-19, a disease first reported in a small cluster of people in Wuhan, Hubei Province, China, in December 2019, which subsequently spread worldwide. Due to its high infectiousness and aggressive course, the World Health Organization (WHO) soon declared Covid-19 a public health emergency of international concern. While the course of the disease is often mild, indistinguishable from common influenza, in a considerable number of cases, patients affected by SARS-CoV-2 infection experience serious complications. These include organ failure, septic shock, pulmonary oedema, severe pneumonia and acute respiratory stress syndrome, which proved fatal in many cases. In 2020, the most severe symptoms, requiring intensive care recovery, were generally observed in older people with previous comorbidities, including cardiovascular, endocrine, digestive and respiratory diseases. With the arrival of more transmissible variants in 2021 and the large-scale implementation of mass vaccination campaigns in developed countries, the burden of Covid-19 shifted to younger, unvaccinated populations as of June 2021.

However, due to the high variability in political and sanitary decisions taken by the different governments, data about incidence, lethality and mortality differ between countries and even between regions of the same country. From the end of February 2020, contagion spread rapidly in Italy and Covid-19 spread widely quickly thereafter to other European countries and continents, leading to restrictions and a global lockdown, with evident social and economic repercussions. Dissimilarities in the stages of the pandemic, cannot be explained by different health policies and systems alone.

Although knowledge concerning the aetiology of coronavirus-related disease has grown since the outbreak was first identified, considerable uncertainty remains concerning Covid-19’s pathogenesis, as well as the factors contributing to heterogeneity in disease severity around the globe. Environmental factors, such as urban air pollution or differences in air quality may play an important role in facilitating the spread and transmission of SARS-CoV-2. Similarly, these factors may have different effects on the pathology and prognosis of the infection (e.g. by increasing susceptibility to severe outcomes of Covid-19). Despite the impact of ambient air pollution on excess morbidity and mortality being well established for a suite of diseases and over several decades, precise mechanistic associations and clear attribution in the case of Covid-19 are still emerging. In particular, major ubiquitous ambient air pollutants, including fine particulate matter (PM2.5), nitrogen dioxide (NO2), and ozone (O3), may have both a direct and an indirect systemic impact on the human body by enhancing oxidative stress and inflammation, eventually leading to respiratory, cardiovascular and immune system dysfunction and deterioration.

Although epidemiological evidence remains limited, previous findings on the severe acute respiratory syndrome (SARS) outbreak, the most closely related human coronavirus disease to Covid-19, revealed associations between air pollution and the SARS case-fatality rate in the Chinese population. An analysis of 213 cities in China initially demonstrated that temporal variations in Covid-19 cases were associated with short-term variations in ambient air pollution. It is plausible therefore, that prolonged exposure to air pollution determinants may have a detrimental effect on the prognosis of patients infected with Covid-19. As is usual in the early literature on emerging hazards, questions remain concerning the generalisability and reproducibility of these findings, due to the lack of control in the epidemic stage of disease, population mobility, residual spatial correlation, and potential confounding by co-pollutants.

In this regard, only a few studies to date (mid-2021) have successfully resolved the current vast evidence gap on this topic. This review examines recent evidence.
2. Aim of the study

This study has four main objectives:

1. To establish the degree of knowledge on the role and nature of air pollution in the transmission of SARS-CoV-2, or in a potential increased burden of disease for Covid-19 patients, stemming from currently available peer-reviewed literature research.

2. To use the current literature to make a preliminary identification of the gaps of knowledge currently existing in uncovering any potential hazards for enhanced incidence, transmission and severity of Covid-19 associated with pollution, in particular with aerosol chemical composition.

3. To investigate the probability that Covid-19 might have had its more negative impact in more polluted cities or regions in Europe. Similarly, to look for existing evidence on the possibility that new surges of the infection, occurring in meat-processing factories, could be related to cooling conditions, which could facilitate the transmission of the disease in such premises.

4. To outline the general state of knowledge emerging from the research up to date, propose important lines of investigation that require further investigation, identify knowledge gaps in the current literature and issue essential recommendations on all these matters, as well as list and assess potential policy actions.

This report has the central objective of analysing all relevant knowledge and the evidence generated so far of a potential influence of air quality factors on facilitating both the geographical evolution of Covid-19 pandemic and SARS-CoV-2 transmission. It also aims to provide EU decision-makers and the general public with a rapid summary and policy actions to undertake in the light of this evidence.

3. Methodology

This report presents a summary of key findings to date, as informed by published peer-reviewed literature up to the end of May 2021. It is motivated both by the global relevance of the subject and by the staggering number of papers and pre-prints currently available, which emphasises the need for careful review and communication of the state of the science.

We emphasise that this report has also a number of constraints. First, it considers only peer-reviewed papers (not pre-prints) published by the end of May 2021. In this regard, this report is not a formal systematic review, but a summary of the most relevant state of the literature according to the author and other scientific reviewers. Second, the report focuses on outdoor air quality conditions and not on indoor air quality determinants. Although connections between outdoor and indoor environments are somehow considered, the report does not thoroughly address the details of indoor air circulation or climate control. Finally, links with climate and weather patterns are not considered at the same level of detail, as they were addressed elsewhere in full. They are introduced and discussed in this report in the supportive impact meteorology may have on the effects of air quality and pollution on both the SARS-CoV-2 virus and the geographical spread of the Covid-19 pandemic.

4. Results and conclusions

Epidemiological studies of Covid-19 have, in most cases, provided as yet inconclusive results regarding the role of air pollution on the geographical spread of the disease, both regionally and globally. Although some interesting research points towards AQ sensitivity of the virus and facilitated spread of the disease geographically, further study and more systematic research on the relationship between air pollution (sensu air quality) and Covid-19 should be encouraged and conducted.
To date, Covid-19 transmission dynamics appears to not have mainly been driven by air quality factors, despite airborne transmission appearing to have played a central role. Instead, public health interventions may have had a more prominent role in transmission and its geographical propagation. Other relevant drivers include changes in human behaviour, stringency in non-pharmacological interventions (NPI) and demographic structure of affected populations. In mid-2021, main effects can also be attributed to the dominance of new virus strains, in combination with the different vaccination strategies adopted by different countries with regard to age classes, vaccine types etc.

There is evidence that chronic and short-term exposure to different fractions of aerosols and air pollution (AP) exacerbates symptoms and increases mortality rates for respiratory diseases similar to Covid-19 and – albeit limited – for Covid-19. This is consistent with early studies of differences in Covid-19 mortality rates, but these results need to be further confirmed and consolidated by controlling for individual-level risk factors.

Mechanisms by which aerosols appear to have facilitated airborne transmission are well established for similar viruses to SARS-CoV-2 and both laboratory and field results are emerging in this case. These important results, particularly those informing on how the virus transmits from person-to-person, need to be fully complemented by curated epidemiological studies at the population level and by dedicated cohorts.

Governments and health leaders should heed the science and focus their efforts on airborne transmission and its implications. Safer indoor environments are required, not only to protect unvaccinated people and those for whom vaccines fail, but also to deter vaccine-resistant variants or novel airborne threats that may appear at any time. Updating regulations on indoor ventilation and air quality (AQ), particularly in healthcare, work and educational environments is urgently required, both in the face of new pandemic waves (i.e. new variants), and to better respond to new potential respiratory viruses and bacteria in the future.

Detailed high-resolution and quality-controlled datasets on both Covid-19 indicators as well as on weather and pollution measurements should be encouraged and be made free and openly accessible according to findability, accessibility, interoperability, and reusability (FAIR) standards to the research community at large.

Facilitated transmission in meat processing factories has repeatedly occurred in many countries in Europe, although a clear link either to contaminated food packages or to an enhanced airborne transmission inside those premises still needs to be established. Clear and active communication between researchers, the media, and decision-makers is required to ensure that scientific findings are promptly translated into actionable policy in an appropriate, objective and responsible manner.

5. Policy options

**Policy option 1. Increase the recognition of the airborne transmission of SARS-CoV-2**

There is consistent and increasing evidence that SARS-CoV-2 spreads by airborne transmission. Although other routes can also contribute to the spread, the airborne route is likely to be the dominant mode. The public health community and health agencies could act accordingly, referring to this as the principal mode of transmission in their recommendations and statements, and work to issue corresponding occupational guidelines.

**Policy option 2. Coordinate the development of early-warning systems for Covid-19**

Early-warning systems could be developed by research groups and companies, and quality-controlled comparison exercises could be stimulated and funded by international agencies and governing bodies. Results of such an initiative could be based on open-data and publicly accessible results. Process-based modelling studies at this time begin to anticipate that Covid-19 transmission
may become seasonal over time, suggesting that extrinsic climatic and environmental factors (also AP and AQ) may be relevant for disease prediction.

**Policy option 3. Upgrade the monitoring network of aerosols in Europe**

An improvement of the network of aerosol and AP monitoring stations in Europe could be encouraged. This new generation of AQ stations could supply a more recently updated portfolio of a wider variety of atmospheric chemicals (in addition to the few ones that are at present subject to mandatory EU regulation). This physical, chemical, but also biological determination of the aerosols we breathe could, whenever possible, be provided on a near-real time basis and for a broader range of AQ composition. The current EU regulatory legislation is very limited in this regard.

**Policy option 4. Investigate the links between AQ and Covid-19**

Research quantifying links between AQ factors and Covid-19 is urgently needed. It is critical that analytical and modelling studies are properly designed to accurately account for confounding factors, to consider both direct and indirect extrinsic environmental effects, to integrate limitations in the Covid-19 data record, and to make use of mathematical or statistical techniques in order to explicitly integrate data errors in models, report uncertainty ranges, evaluate predictive capacity properly (for out-of-fit data), and apply appropriate statistical or process-based modelling techniques. Further epidemiological studies are needed to better estimate the impact of AP on Covid-19.

**Policy option 5. Higher investment in epidemiological and laboratory research**

In vitro, in vivo, as well as epidemiological and modelling studies at the population level are also strongly needed, particularly to explore the particle–virus interaction more precisely in the air and in the person-to-person transmission, but also to precisely quantify any potential sensitivity and dose-response function of the virus. Hitherto, no studies exist on the specific effects that the chemical nature of aerosols may exert in facilitating or not SARS-CoV-2 transmission, or in conditioning human susceptibility (e.g. in enhancing inflammatory responses, promoting the cytokine cascade etc.).

These studies should be supported. Effects exerted by the aerosol chemistry that may explain geographical/spatial propagation in Covid-19 cases within and between populations are thus far contradictory, and deserve more investigation. Research on aerosol size and chemical composition with regard to the viability and infectivity of SARS-CoV-2 are also needed urgently. In parallel, better precision equipment and methodologies to monitor the presence of viruses – and other pathogens – could be developed.
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<th>Description</th>
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<tr>
<td>ACE-2</td>
<td>Angiotensin-converting enzyme-2</td>
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<tr>
<td>AQ</td>
<td>Air quality</td>
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<tr>
<td>AP</td>
<td>Urban air pollution</td>
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<tr>
<td>Covid-19</td>
<td>Coronavirus diseases</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CO</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>CAFO</td>
<td>Concentrated animal feeding operation</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>FAIR</td>
<td>Findability, accessibility, interoperability, and reusability principles</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care units</td>
</tr>
<tr>
<td>LSTM</td>
<td>Long short-term memory models</td>
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<tr>
<td>MERS-CoV</td>
<td>Middle East respiratory syndrome coronavirus</td>
</tr>
<tr>
<td>NLRP3</td>
<td>NLR family pyrin domain containing protein 3</td>
</tr>
<tr>
<td>NO2</td>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>NPI</td>
<td>Non-pharmacological interventions</td>
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<tr>
<td>NSTEMI</td>
<td>Non-ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>O3</td>
<td>Ozone</td>
</tr>
<tr>
<td>PM2.5</td>
<td>Fine particulate matter (2.5 micron size threshold)</td>
</tr>
<tr>
<td>PM10</td>
<td>Coarse particulate matter (10 micron size threshold)</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal protective equipment</td>
</tr>
<tr>
<td>QMRA</td>
<td>Quantitative microbial risk assessment</td>
</tr>
<tr>
<td>RT-qPCR</td>
<td>Reverse transcription quantitative real time polymerase chain reaction</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe Acute Respiratory Syndrome CoronaVirus 2</td>
</tr>
<tr>
<td>SO2</td>
<td>Sulphur dioxide</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet radiation</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. A brief introduction on health effects of air quality (AQ)

Air quality (AQ) and in particular in its reference to air pollution (AP) has been reported to be the biggest environmental threat to health in Europe, with more than 400,000 deaths annually attributed (EEA, 2019), affecting a diverse array of health outcomes (from ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer and respiratory infections to contributing to neurological disorders, asthma, diabetes and obesity). PM2.5 is widely known to have significant adverse effects on human health (US EPA 2009; Anderson et al., 2012; Kim and Kabir, 2015). Many studies and reports by agencies, institutions and governments have addressed AP effects on health in the past and keep regularly updating on the matter. I refer to those publications for a more exhaustive understanding of the topic, well beyond the scope of the current report. Being fine particles (less than 2.5 μm) where consensus is as the main AP contributors, their geographical differences could be also associated to locally harsher impacts of SARS-CoV-2 infections, should the two be demonstrated to have a connection.

This particular aspect will be explored in Section 3. Other constituents, such as nitrous oxides and ozone should be also carefully analysed, despite it is well-known that a diversity of APs are not customarily measured on a routine basis throughout the EU. Therefore, there is little margin to assess other APs effects on both the severity of Covid-19 or on the previous pre-conditioning towards more susceptibility by people living in areas with specific types of APs, a limitation that should be overcome and that is specifically addressed in the Policy recommendations. Epidemiological studies show evidence that PM2.5 long-term exposure is associated with enhanced mortality and morbidity (WHO, 2013), this evidence being weaker for PM10. There are also consistent relations between APs daily exposures and immediate mortality and morbidity during the next days. Repeated exposures in several days can result in health effects greater than single-day effects and the hazards of long-term exposure are known to be much greater than those observed for short-term exposure.

The former might suggest that the relation is not only with severity, but may also be due to the progression of the underlying diseases. There is also significant evidence from toxicological and clinical studies on the effects of combustion-derived particles that short-lived maximum exposures (ranging from less than an hour to a few hours) lead to immediate physiological changes [WHO, 2013]. The breathing of particulate matter carries these particles deep into lungs and the bloodstream, giving rise to respiratory and cardiovascular disease, or premature death. Inhaling PM2.5 induces the activation of the NLRP3 inflammasome and NLRP3 plays a central role in pulmonary inflammation-related diseases like chronic obstructive pulmonary disease, asthma, and acute respiratory distress syndrome.

PM2.5 has been implicated in a broad range of diseases, like Alzheimer’s disease, Prion diseases, type 2 diabetes, and some infectious diseases (Yang et al., 2013). Inflammasome activation by Covid-19 has been recently described by Conti et al. (2020), linked to an hyperinflammation status of poor prognosis Covid-19 patients. These patients show increased blood levels of Interleukin-1, Interleukin-6 and tumor necrosis factor-α (TNF-α). It is also known that chronic exposure to fine particulate matter (PM2.5) (Hassan et al., 2019; Kloog et al., 2012), ozone (Purvis et al., 1961; Yazdi et al., 2019), and nitrogen dioxide (Kulle and Clements, 1988) can lead to immune system dysregulation such as overexpression of inflammatory cytokines and chemokines (Bemstein et al., 2004; Fattorini and Regoli, 2020).

Exposure to ultrafine or nano sized particles from vehicle exhaust fumes is also of additional concern due to their bioreactivity, having the potential to penetrate every human organ, including the brain, and are heavily abundant in cities (Gonet & Maher, 2019). Under 5 % of Alzheimer’s cases, for example, are inherited, which indicates a strong likelihood that environmental factors may be
contributing factor to the fact that cases of Alzheimer’s disease are expected to double in the next two decades (Maher, 2019). As an example, iron bearing nanoparticles coming from industry, heating and vehicles could be of particular importance, because of the specific impacts of iron on health. While iron is essential for human health, its excessive accumulation in certain regions of the brain has been connected to a number of cardiovascular effects and neurodegenerative illnesses, including Alzheimer’s, Parkinson’s and Huntingdon’s. Externally produced magnetite particles were also recently identified in the brain’s frontal cortex (Gonet & Maher, 2019).

This research differed from previous studies which, while having shown a correlation between an abundance of magnetite and Alzheimer’s disease, had focused on magnetite as something endogenous, or in other words produced by the human body rather than coming from the external environment. Examination of human brain samples from Mexico City and Manchester found that the magnetites present in the brain tissue were extremely similar to magnetite ‘nanospheres’ formed by combustion (Maher et al., 2016). These externally generated iron-rich nanoparticles were increased in brain autopsies from older individuals from Manchester, and in younger people from Mexico City, including airborne magnetite, in urban environments alongside busy urban roads. (Maher et al, 2016; Maher, 2019). Similarly, ultrafine particles are seen to be able to penetrate deep in the alveolar tissue and the circulatory cascade, being found in cardiac tissue among many other organs (Chen et al., 2020), despite there is not yet a specific EU directive regulating ultrafine AP levels.

Some evidence has tightly linked ambient AP to occurrence of numerous respiratory diseases, such as Chronic obstructive pulmonary disease (COPD, Ling and van Eeden, 2009) and asthma (Gorai et al., 2016). Moreover, AP is also associated with infectious diseases transmission. For example, worse AQ has also been shown to increase SARS fatality (Cui et al., 2003) as well as to increase influenza incidence (Landguth et al., 2020). In laboratory conditions, van Doremalen et al. (2020) demonstrated a long viability of SARS-CoV-2 in ambient aerosols, which could be an important source of Covid-19 transmission (Luo et al., 2020). However, whether ambient air pollutants are associated with increased incidence of Covid-19 in realistic situations remains largely unknown.

Most policies targeting AP are based on mass concentrations of particulate matter (PM), while nanoscale particles, to which human bodies are most easily exposed, contribute little to mass measurements (Maher, 2019). Ultrafine particles could be a matter of particular concern because of their reactivity (high surface to volume ratio), potential toxicity (arising from their composition and/or surface charge), and their ability to gain access to any organ, cell, and organelle, including mitochondria.

Episodic acute AP, from both fine particulate matter and gases (ozone, nitrogen dioxide and sulfur dioxide) exposure can also lead to intensified respiratory infection symptoms, due to exacerbation of asthma and other inflammatory responses that can lead to acute respiratory distress (Guarnieri and Balmes, 2014). Ozone was found to disrupt the protease/antiprotease balance in the human airway, leading to an increased risk of influenza infection (Kesic et al., 2012). Other laboratory findings showed that ozone can effectively inactivate influenza virus (Hiroshi and Jp, 2009; Sooryanarain and Elankumaran, 2015). And even other evidence suggests that ozone might enhance pulmonary innate immunity, which promotes allergic responses in susceptible individuals (Ali et al., 2018), indicating that the various mechanisms by which inhaled oxidants might modulate viral pathogenesis are highly complex and still remain to be fully characterised (Kesic et al., 2012).
2. Methodology and bibliographic search strategy

The author used PRISMA guidelines for the selection of referenced studies to be included in this report (Page et al., 2021). The flowchart is presented below in Fig. 1.

Figure 1– PRISMA flowchart used in this review for the selection of articles to be included

*Databases: Scopus, Web of Science, PubMed and the National Center for Biotechnology Information (NCBI). **Reports excluded after personal assessment, as topic was different from sought.

For more information, visit: http://www.prisma-statement.org/

Since September 2020, the author performed a thorough review of available peer reviewed literature on Covid-19 and, as requested, when relevant, on other AQ-sensitive respiratory viruses. The text of the report represents an expert evaluation of this rapidly evolving literature and might
be subject to omissions. Only peer reviewed articles published by May 31st 2021 or those I was made aware of that have proof of acceptance at the time of closing this are cited in the report. The search strategy consisted of the following terms:

- (COVID OR SARS-COV-2) AND (POLLUTION OR AEROSOLS)
- (COVID OR SARS-COV-2) AND (CLIMATE OR WEATHER OR METEOROLOGY)

Searches were not aimed at being fully systematic as this lies beyond the scope of the present report. However, searches were very broad in scope and including other/additional keywords was found not to significantly influence the amount of results, as similar searches identified similar articles. Hyphenation (for example, ‘bio-aerosol’) also did not affect results.

This report has followed the PRISMA guidelines and reviewers have performed a check on the quality of the study according to ECBM. The total number of articles analysed in the present review of current evidence is 5,920, divided in the following way:


These articles –albeit being published- were additionally subject to an expert evaluation on their quality and reliability prior to being included in this report and by the assessment of expert reviewers. In this regard, I am aware that this post-publication assessment may reflect a certain bias by the author and reviewers, despite this process was made in a further aim for scientific quality at a time when many more publications than normal on a single topic (Covid-19) overload all scientific journals. This publication pressure (both from the side of authors as well as from publishers in order to keep public attention), might have resulted in (the risk of) a low-quality bias, as normal peer-review process would take more time and undergo stricter revisions.

The approach to the literature was to focus on those studies that were deemed to be most relevant to the report objectives. The report is not a systematic review, and does not attempt to be comprehensive in its treatment of the available literature. I also acknowledge that the fast pace of Covid-19 publication and the tendency for authors to disseminate their reports on pre-print servers prior to review has meant that the peer reviewed literature lagged publicly discussed research findings.

In addition of an oriented search made by the author of this report, a more exhaustive search was made every week of the titles and abstracts of databases of academic journal papers (Scopus, Web of Science, PubMed and the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM)) for evidence relating aerosols and their composition, pollution and Covid-19 health effects.
3. Results

This review is organized around five guiding questions that attempt to answer the aims described above. These five questions are listed below, namely:

3.1 Can the physical size and chemical nature of aerosols facilitate SARS-CoV-2 spread?
3.2 Can Covid-19 effects be exacerbated by AP and is there an enhanced effect in people with co-morbidities?
3.3 Is there higher risk of Covid-19 in more polluted cities?
3.4 Can Meteorological factors facilitate aerosol-mediated transmission of SARS-CoV-2?
3.5 Outbreaks in meat-processing factories: A real link with indoor air conditions?

Literature reviewed is therefore organised around these five topics, after which a conclusion section follows.

3.1. Can the physical (size) and chemical nature of aerosols facilitate SARS-CoV-2 spread?

Studies of the influence of AP on Covid-19 have addressed both the acute impacts that compromised AQ might have on transmission or on severity of Covid-19 symptoms and the influence that chronic exposure to AP can have on human susceptibility to Covid-19. Consistent with studies of other respiratory infections, early studies indicated that there is a positive relationship between prevailing AQ conditions (e.g. pollution, B. Wang et al., 2020; R. Wang et al., 2020; Yao et al., 2021), especially fine particulate matter (PM2.5), and Covid-19 mortality rates (Jiang and Xu, 2021; Wu et al., 2020; Yao et al., 2020b), as well as with total case counts (Borro et al., 2020). One global analysis concluded that long-term exposure to ambient fine particulate AP contributed to ~15 % (95 % confidence interval 7–33 %) of Covid-19 mortality worldwide, through the third week of April 2020, with higher rates in more polluted environments (Pozzer et al., 2020).

While a number of studies have found associations between AP and Covid-19 rates (Conticini et al., 2020; Dettori et al., 2020; Ogen, 2020; Petroni et al., 2020; Wu et al., 2020; Yao et al., 2021; Yongjian et al., 2020), concerns among the scientific community have arisen about methodological caveats in some of these studies (Heederik et al., 2020; Villeneuve and Goldberg, 2020). This includes studies of the impact of ozone on Covid-19 dynamics, which have yielded inconsistent results, demonstrating either positive or negative associations between ozone and Covid-19 risk (Adhikari and Yin, 2020; Ran et al., 2020; To et al., 2021).

In general, however, disentangling any independent effects of AP from effects of other causes related to Covid-19 outbreaks has been challenging, potentially resulting in an overestimation of the effects of AP on Covid-19 occurrence and severity (Brunekreef et al., 2021). Results therefore need to be further confirmed and consolidated by controlling for individual-level risk factors (Wu et al., 2020). To date, there has been no peer reviewed evidence of the direct influence that various air pollutants have on SARS-CoV-2 transmission. Indoor AP, caused by sources such as smoking, woodstoves and fireplaces, is another potentially important and understudied factor in SARS-CoV-2 transmission, given that people spend most of their time indoors (Brunekreef et al., 2021). Future large cohorts and administrative databases, enabling the inclusion of individual level data and high resolution spatiotemporal data, will provide opportunities to thoroughly investigate effects of AP on Covid-19 dynamics at the population level (Brunekreef et al., 2021).
To date, there is substantially less evidence regarding impacts of AQ on virus transmission arising from field studies and data. Aerosol transmission has been identified in other coronaviruses (Doremalen et al., 2020) together with infectious doses for other respiratory viruses (Karimzadeh et al., 2021), which offers reason to expect that it could be important for SARS-CoV-2 as well (Hou et al., 2020). Insomuch as particulate matter might serve as a transport medium for virus agents enhancing aerosol stability or virus survival on aerosols, it is reasonable to expect that it might similarly enhance transmission potential both directly as well as indirectly in high population density or poorly ventilated spaces, through deposition of viable virus on fomites, similarly defined as inanimate objects that, when contaminated, can transmit pathogens to new hosts.

In a commentary piece, Greenhalgh et al. (2021) reported consistent, strong evidence that the SARS-CoV-2 virus, is predominantly transmitted through the air and urged change in public health measures as they fail to treat the virus as predominantly airborne. Until recently, main international (and national) agencies have been downgrading/denying this transmission route. Recently also, evidence supporting large droplet transmission has been questioned as weak or almost non-existent. Lines of evidence to support the predominance of the airborne route for aerosols over droplets or direct contact, were cited as follows: Super-spreader events (i.e. the Skagit Choir outbreak, in which 53 people became infected from a single infected case, Lewis, 2021; Bahl, 2021), cannot be adequately explained by close contact or touching shared surfaces or objects. Also, transmission rates of SARS-CoV-2 are much higher indoors than outdoors, and transmission is greatly reduced by indoor ventilation. Silent (asymptomatic or pre-symptomatic) transmission of SARS-CoV-2 from people who are not coughing or sneezing accounts for at least 40 percent of all transmission (Greenhalgh et al., 2021). Albeit more specific research is needed, confirmation would urgently call for a change in mitigation policies and regulation towards contention of the airborne transmission.

Similarly, long-range transmission of the virus between people in adjacent rooms in hotels, who never was in each other presence, has been documented (Eichler et al., 2021). By contrast, in this review, Greenhalgh et al., 2021 found little to no evidence that the virus spreads easily via large droplets, not of contamination of surfaces. Implications for public health measures designed to mitigate the pandemic are important, namely, 'droplet measures' such as handwashing and surface cleaning, while not unimportant, should be given less emphasis than airborne measures, which deal with potential inhalation of infectious particles suspended in the air.

Airborne control measures (as an infected person exhales, speaks, shouts, sings, or sneezes), include ventilation, air filtration, reducing crowding and the amount of time people spend indoors, wearing masks whenever indoors (even if not within 6 feet or 2 metres of others), attention to mask quality and fit, and higher-grade personal protective equipment (PPE) for healthcare and other staff when working in contact with potentially infectious people. Greenhaulgh et al., 2021 see the widespread practice of unnecessary levels of cleaning to the detriment of public health, use of plexiglass indoors that is far from sufficiently protective and, depending on air flows, may even be contraindicated, instead of attention to ventilation and aerosol risks. According to Tang et al., 2021 study in the Lancet in April, also Covid-19 has redefined airborne transmission and authors stress on the relevance of indoor ventilation and AQ measures.

Controversy is to date still ongoing and possibly one of the reasons is the confusion emanated from different understandings of the terminology introduced about the concept of aerosols during the last century. This created poorly defined divisions between ‘droplet,’ ‘airborne,’ and ‘droplet nuclei’ transmission, leading to misunderstandings over the physical behaviour of these particles (Tellier et al., 2019). Essentially, if a person inhales particles—regardless of their size or name— this person is breathing in aerosols (Tang et al., 2021). People infected with SARS-CoV-2 produce many small respiratory particles laden with virus as they exhale, that other people can breathe, namely ‘short range’ distance (<1 m), while the remainder disperse over longer distances to be inhaled by others.
further away (>2 m). In essence, all are aerosols as can be inhaled directly from the air (Morawska and Milton, 2020).

On this regard, it is why ventilation is of the utmost importance because the tiniest suspended particles can remain airborne for hours, and these constitute an important route of transmission. Under these conditions, air replacement or air cleaning mechanisms become much more important (Morawska and Cao, 2020; Morawska et al. 2020). This aligns with opening windows or installing or upgrading heating, ventilation, and air conditioning systems, as outlined in a recent WHO document (2021).

In this context, where airborne transmission might be dominant, discussion arises on the quality of the mask for effective protection against inhaled aerosols, as both high filtration efficiency and a good fit are needed to enhance protection against aerosols (Fennelly, 2020, Drewnick et al., 2021). Aerosol scientists showed in the past that even talking and breathing are aerosol generating procedures (Asadi et al., 2019; Scheugh, 2020; Stadnytskyi et al., 2020).

In close range situations, people are much more likely to be exposed to the virus by inhaling it than by having it fly through the air in large droplets to land on their eyes, nostrils, or lips (Chen et al., 2020). Similarly, the transmission of SARS-CoV-2 after touching surfaces is now considered to be relatively minimal (Goldman, 2020; Haug et al., 2020; SAGE, 2020). Co-benefits of improved indoor AQ through better ventilation should also be considered (e.g. reduced sick leave for other respiratory viruses, allergies and sick building syndrome (Laumbach and Kipen, 2005; Sundell et al., 2011).

As we will see later for other airborne viruses, the enhancing role of PM in virus-to-person interaction has been highlighted. The former was argued when –albeit low-, presence of viral RNA on PM was reported associated to PM10 exceedances in Bergamo at February 2020 (Setti et al., 2020a-c), similar to what Qin et al (2020) reported in Beijing. The complexities associated to the potential binding of virus particulates to PM have been hypothesised on the basis of former studies with similar viruses, although clearly more research is needed in this direction (see Fig. 2; Duval et al., 2021). Understanding the role of coalescence processes for viral particulates in aerosols with PM of different sizes is clearly both controversial and an urgent topic of research. Also is uncovering the associated molecular properties favouring their persistence and viability or even facilitating infection. Association with meteorological and air quality factors is therefore an important derivative.
Figure 2 – Schematic overview of the processes that might be involved in the presence and interaction of SARS-CoV-2 particulates and aerosols, and in the routes of infection

As reported in some studies, asymptomatic or pre-symptomatic transmission of SARS-CoV-2 from people who are not coughing or sneezing is likely to account for at least a third, and perhaps up to 59%, of all transmission globally and is a key way SARS-CoV-2 has spread around the world (Johansson et al., 2021). This is supportive of a predominantly airborne mode of transmission. Direct measurements show that speaking produces thousands of aerosol particles and few large droplets (Chen et al., 2020), which also supports the airborne route. Indeed, transmission of SARS-CoV-2 is higher indoors than outdoors (Bulfone et al., 2021) and is substantially reduced by indoor ventilation. Both observations support a predominantly airborne route of transmission.

In addition, use of personal protective equipment (PPE) in health-care facilities, designed to protect against droplet but not aerosol exposure, has not prevented massive infections (Klompas et al., 2021). Viable SARS-CoV-2 has been detected in the air and in laboratory experiments, SARS-CoV-2 stayed infectious in the air for up to 3 h with a half-life of 1.1 h (Van Doremalen et al., 2020). Viable SARS-CoV-2 was identified in air samples from rooms occupied by Covid-19 patients in the absence of aerosol generating health-care procedures (Lednicky et al., 2020) and in air samples from an infected person’s car.

Although other studies have failed to capture viable SARS-CoV-2 in air samples, this is to be expected. Sampling of airborne virus is technically challenging for several reasons, including limited effectiveness of some sampling methods for collecting fine particles, viral dehydration during collection, viral damage due to impact forces (leading to loss of viability), re-aerosolisation of virus during collection, and viral retention in the sampling equipment. Measles and tuberculosis, two primarily airborne diseases, have never been cultivated from room air (Fennelly, 2020). SARS-CoV-2
has been identified in air filters and building ducts in hospitals with Covid-19 patients; such locations could be reached only by aerosols (Nissen et al., 2020).

Wide variation in respiratory viral load of SARS-CoV-2 counters arguments that SARS-CoV-2 cannot be airborne because the virus has a lower R0 (estimated at around 2.5, Petersen et al., 2020) than measles (estimated at around 15; Guerra et al., 2017). More so since R0, which is an average, does not account for the fact that only a minority of infectious individuals shed high amounts of virus. Overdispersion of R0 is well documented in Covid-19 (Endo et al., 2020). In addition, there is limited evidence to support other dominant routes of transmission—i.e., respiratory droplet or fomite (Chen et al., 2020; Goldman, 2020). Ease of infection between people in close proximity to each other has been cited as proof of respiratory droplet transmission of SARS-CoV-2. However, close-proximity transmission in most cases along with distant infection for a few when sharing air is more likely to be explained by dilution of exhaled aerosols with distance from an infected person.

The flawed assumption that transmission through close proximity implies large respiratory droplets or fomites was historically used for decades to deny the airborne transmission of tuberculosis and measles (Fennelly, 2020; Tang et al., 2021). Respiratory activities have been established to produce an overwhelming number of aerosols. This recognition and the proper definition of the boundary in particle size of 100 μm between aerosols and droplets, instead of the 5 μm, are of much relevance (Fennelly, 2020; Tang et al., 2021). In fact, it is sometimes argued that since respiratory droplets are larger than aerosols, they must contain more viruses. However, in diseases where pathogen concentrations have been quantified by particle size, smaller aerosols showed higher pathogen concentrations than droplets when both were measured (Fennelly, 2020).

One major argument, however, against airborne transmission in the case of SARS-CoV-2 is that as for other respiratory viruses, this transmission is difficult to demonstrate directly. Methodologies for extraction are not unified and mixed findings appear in the literature from studies that seek to detect viable pathogens in air samples (Pan et al., 2019). Counterarguments to this claim stress that if there are insufficient grounds for concluding that a pathogen is not airborne, this statement should not be used against this potential route of transmission (Greenhalgh et al., 2021).

An important point is that the infectious dose needed for transmission through aerosols needs to be determined. However, determining infectious doses for each particular virus is a difficult task, despite some attempts have been made that indicate it can be very low for other respiratory viruses (i.e. HuCoV-229E around 10 PFU; Karimzadeh et al., 2021). They propose that the infectious dose of SARS-CoV-2 may be a few hundred particles (despite it is not clear whether the authors refer to particles or PFU).

Instead, a meta-analysis performed on a systematic review aimed at developing a comprehensive dataset of respiratory viral loads (rVLs) of SARS-CoV-2, SARS-CoV-1 and influenza A(H1N1) pdm09 shed some light. It showed that for rVL there exists as an intrinsic virological factor facilitating greater over-dispersion for SARS-CoV-2 in the Covid-19 pandemic than A(H1N1) pdm09 in the 2009 influenza pandemic. A model of individual infectiousness by shedding viable virus via respiratory droplets and aerosols, indicates Covid-19 case heterogeneity is of maximal importance. The reason is that highly infectious individuals shed tens to thousands of SARS-CoV-2 virions/min via droplets and aerosols while breathing, talking and singing (Chen et al., 2021) This finding has important implications for disease control and occupational health regulations.

For instance, the dispersion of aerosols was studied experimentally in several concert halls to evaluate their airborne route and thus the risk of SARS-CoV-2 spreading (Schade et al., 2021). The former experiment was conducted with a dummy that emitted simulated human breath containing aerosols and aerosol and CO2 concentration profiles were mapped using sensors placed around the dummy. No substantial enrichment of aerosols and CO2 was found at adjacent seats, provided that (1) there were floor displacement outlets under each seat enabling a minimum local fresh air vertical
flow of $v = 0.05 \text{ m/s}$, (2) the air exchange rate was more than 3, and (3) the dummy wore a surgical face mask.

A second crucial implication of airborne spread is that the quality of the mask matters for effective protection against inhaled aerosols. Masks usually impede large droplets from landing on covered areas of the face, and most are at least partially effective against inhalation of aerosols. However, both high filtration efficiency and a good fit are needed to enhance protection against aerosols because tiny airborne particles can find their way around any gaps between mask and face (Philip et al., 2021). If the virus is transmitted only through larger particles (droplets) that fall to the ground within a metre or so after exhalation, then mask fit would be less of a concern (Tang et al., 2021). In this regard, inhalation as well as exhalation matters in occupational settings' regulations are to be improved (Philip et al., 2021).

As an example, healthcare workers wearing surgical masks have become infected without being involved in aerosol generating procedures (Fennelly, 2020; Drewnick et al., 2021; Goldberg et al., 2021). As airborne spread of SARS-CoV-2 is fully recognised, our understanding of activities that generate aerosols will require further definition. Aerosol scientists have shown that even talking and breathing are aerosol generating procedures (Asadi et al., 2019; Schleuch et al., 2020; Stadnytskyi et al., 2020). It is now clear that SARS-CoV-2 transmits mostly between people at close range through inhalation. This does not mean that transmission through contact with surfaces or that the longer range airborne route does not occur, but these routes of transmission are less important during brief everyday interactions over the usual 1-m conversational distance.

In addition, many studies have investigated the reduction in AP levels as a result of Covid-19 restrictions (Kumari and Toshniwal, 2020; Menut et al., 2020; Ordóñez et al., 2020; Saxena and Raj, 2021; Venter et al., 2020), which might result in beneficial health effects, e.g., short-term and long-term avoided mortality from exposure to PM2.5 (Giani et al., 2020). However, the entirety of lockdown-induced direct and indirect effects and changes such as delayed treatments for disease, mental health impacts and changes in physical activity should be considered. The former might offset or surpass the observed reductions in burden of disease due to improved AQ during Covid-19 lockdown periods (Brunekreef et al., 2021).

3.1.1. Epidemiological evidence from other respiratory viral diseases

While direct epidemiological evidence of AQ influence on Covid-19 is only beginning to emerge, there is more mature evidence from other respiratory viruses (Audi et al., 2020; Moriyama et al., 2020). This evidence contributes to the expectation that Covid-19 may also be sensitive to variations in AQ factors.

Asadi et al. (2020) provide evidence of a mode of transmission seldom considered for influenza: airborne virus transport on microscopic particles called 'aerosolised fomites.' In a guinea pig model used to test influenza virus transmission, a study convincingly demonstrated for influenza virus, that aerosolised fomites can be generated from inanimate objects. Complementary, air pollutants might also play a role in airborne transmission of viruses. It has been demonstrated that particulate matter can be a carrier of airborne pathogens (Cambra-López et al., 2010; Cao et al., 2014), and that aerosols can enhance the stability of some viruses, including Middle East respiratory syndrome coronavirus (MERS-CoV) (Van Doremalen et al., 2013). The importance of these pathways to infection risk relative to the influence that AP has on host resistance to infection is not yet well characterised.

In the case of influenza, airborne transmission may occur by two modes. First, by sprays of virus-laden respiratory droplets, such as from a cough or sneeze, impacting immediately onto the respiratory mucosa of a susceptible individual. Alternately, by the eventual inhalation of droplet nuclei, microscopic aerosol particles consisting of the residual solid cores of evaporated respiratory droplets (Killingley, B. & Nguyen-Van-Tam, 2020). The relative contribution of each of these
transmission modes remains unknown, and viral, host, or environmental factors may individually or in combination, affect which modes are favoured in different settings (Tellier et al., 2019; Roy and Milton, 2004; Erbelding et al., 2018). Of interest, Asadi et al. (2020) showed that the vast majority of airborne particulates emitted from a guinea pig cage are non-respiratory in origin and thus presumably have their origin in environmental dust (Fig. 3). These findings also suggested that guinea pigs emit expiratory particles with a size range comparable to that of humans, confirming that they could serve well as an analog animal model. It seemed established that if these dust particulates become contaminated with influenza virus they can serve as aerosolised fomites that carry the virus to a susceptible guinea pig through the air.

Finally, that same study showed that aerosolised fomites can be generated from inanimate objects. For instance, by rubbing a virus-contaminated paper tissue, a fact that can have relevant implications—e.g. aerosolised fomites for respiratory virus transmission—in other animal models and for transmission between humans. Results in that study showed that dried influenza virus remains viable in the environment, on materials like paper tissues and on the bodies of living animals. And long enough to be aerosolised on non-respiratory dust particles that can transmit infection through the air to new mammalian hosts. Similar elegant results involving infected caged animals that were connected to separately caged uninfected animals via an air duct have shown transmission of SARS-CoV-2 that can be adequately explained only by aerosols (Kutter et al., 2021).

Figure 3 – Influenza virus-naive guinea pigs are infected by aerosolised fomites

A) Transmission experiment schematic, showing a virus-naive recipient guinea pig placed downwind of, but physically separated from, a virus-immune, virus-contaminated donor guinea pig. B) Nasal wash virus titers, in plaque-forming units (pfu) ml⁻¹, from 12 immunes, contaminated donor guinea pigs, each represented by a different color. C) Nasal wash virus titers from 12 recipient guinea pigs. Each color represents an individual recipient. Dotted line indicates the limit of detection (LOD).

Reproduced from Asadi et al. ‘Influenza A virus is transmissible via aerosolised fomites’, Nat. Commun., 2020. DOI: 10.1038/s41467-020-17888-w PMID: 32811826 PMCID: PMC7435178 under a Creative Commons CC BY-ND license.
Asadi et al. (2020) showed how the animal models harboured viable virus on their bodies for up to 4 days post-contamination, which was subsequently transmitted through the air to infect 3 of 12 virus-susceptible partner animals housed in separate cages (25% transmission rate, 95% credible interval 8–52%). This transmission rate is lower than previously observed under similar environmental conditions, with the same influenza virus isolate after intranasal inoculation into donor animals. These results suggest that influenza virus transmission via aerosolised fomites may be less efficient than transmission by respiratory droplets or droplet nuclei. This pointed to the need of further replicate similar studies in a wider set of conditions and scenarios. Again, whereas these conclusions cannot be directly extrapolated for SARS-CoV-2 and specific research would be desirable given the differences between the two types of viruses, new results by Kutter et al., 2021 appear to give further credit to similarities with SARS-CoV-2 dynamics.

Despite the former, considering the fact that the viability of SARS-CoV-2 on many types of surfaces has been reported (e.g., on metals for 48 h, plastic for 72 h, cardboard for 24 h, and copper for 4 h; NAAQS; van Doremalen et al., 2020), it is likely that the virus on inanimate surfaces can be potentially lodged on the PM2.5 and redistributed or transported back into the air. Air particle measurements have suggested that SARS-CoV-2 can be carried by PM2.5 in the air when healthcare workers remove their personal protective equipment (PPE, Chan et al., 2020; Ong et al., 2020). Furthermore, it is also suggested that suspended tiny dust in the air could couple with microorganisms of diameter < 5 μm during aerosolisation. Since the diameter of the SARS-CoV-2 is two orders of magnitude smaller—the airborne transport is still unclear and, therefore, worth exploring.

At a mechanistic level, PM concentration has been shown to be linked with the increased infection rates in many of the virus-related outbreaks in the past two decades caused by RNA viruses. For instance, Severe Acute Respiratory Syndrome (SARS) in 2003 (Cui et al., 2003), Swine flu H1N1 (Influenza) pandemic in 2009 (Morales et al., 2017), H5N2 Influenza outbreak in United States (Zhao et al., 2019) and the measles outbreak in 2019 (Peng et al., 2020).

Virus deposition in the case of influenza, possibly via direct nose and mouth contact, may be more efficient than the transfer of dried virus from the bodies of contaminated persons or its retention on the surfaces. Respiratory mucus may also have a preservative effect on non-porous surfaces, such that deposited virus retains its infectivity longer. These hypotheses remain open for future research and for SARS-CoV-2. However, there are already results that serve as a clear proof of principle that influenza virus can transmit through the air when carried on micron-sized, non-respiratory particulate matter from the environment.

Indeed, influenza virus transport on dust has been infrequently hypothesised (Chapin, 1916; Andrewes, C. H. & Glover, 1941; Khare, P. & Marr, 2015) and experimentally explored (Edward, 1941) in the past, and other respiratory pathogens are known or suspected to initiate human infection in this manner (Jonsson et al. 2010, Sarute, N. & Ross, 2017). However, current opinion about influenza virus transmission, both in humans (Weber and Silianakis, 2008; Tellier 2019; Killingley & Nguyen-Van-Tam, 2013; Jones, R. M. & Brosseau, 2015; Tellier et al. 2019) and in animal models (Richard, M. & Fouchier, 2016; Bouvier, 2015), appears to presume that airborne infectious virus derives solely from exhaled, coughed, or sneezed respiratory particles, or occasionally from aerosol-generating medical procedures (Brankston et al., 2007; Tellier et al., 2019).

Recent research provides direct experimental evidence that the airborne particles mediating mammalian influenza virus transmission need not be directly emitted into the air from the respiratory tract of an infectious host. Rather, aerosolised fomites from a virus-contaminated environment can also spread influenza viruses through the air. The former, if also true for SARS-CoV-2 might imply updating regulations for occupational health and will deserve further investigation.
It is also suggested that for influenza, the stability of the hemagglutinin (HA) protein in the environment is one critical factor in influenza virus transmissibility by airborne routes. Given the overall complexity of influenza virus transmission, it is unlikely that the presence of aerosolised fomites or their environmental stability entirely explains why some influenza viruses transmit through the air efficiently while others do not. More likely, airborne transmission efficiency for a standard virus, depends variably on multiple factors. Among these, the infectiousness of the virus donor, the susceptibility of the virus recipient, and the stability of the virus in the environment between them.

During the early stages of the Covid-19 pandemic in China, air sampling in various hospital locations found the highest airborne genome counts of SARS-CoV-2 in rooms where health care workers doffed their PPE equipment, hinting that virus was possibly being aerosolised from contaminated clothing as it was removed (Liu et al., 2020). However, other research suggests that fomite transmission would unlikely be a major route of transmission as attempts to culture SARS-CoV-2 from surfaces were largely unsuccessful (Goldman, 2020; Mondelli et al., 2020). It must be noted that lack of viral cultivation might not always reflect absence of the virus, given the large technical problems in such methodologies, as formerly reported. On the other hand, airborne transmission of SARS-CoV-2, although plausible (Zuo et al., 2020), was not officially endorsed by the World Health Organization (WHO) as a general transmission route (WHO IPC Recommendations, accessed 29/03/2020 and 14/12/2020).

There is, however, growing evidence that SARS-CoV-2 can be transmitted by aerosols (droplets ≤50 μm or even defined as under 100 μm, despite there are differences in terminology depending on disciplines, Lednicky et al., 2020; Y. Liu et al., 2020; Tang et al., 2020). Insumuch, the relative importance of airborne aerosol transmission in relation to contact transmission (infection through direct contact with an infectious person or contaminated surface) or droplet transmission (infection through virus-containing respiratory droplets over 100 μm within shorter distances of 1-2 meters) and other modes of SARS-CoV-2 transmission, is still controversial at the level of policy and public health agencies. Voices that demand further investigation (Klompas et al., 2020) have emerged, despite the aerosol's scientific community seems in May 2021 very much aligned in this airborne route of transmission. Instead, positive correlations between PM2.5 and other respiratory viruses such as the influenza virus have been reported (Su et al., 2019), emphasizing the possibility of particulate matter as a transport carrier also for SARS-CoV-2.

Nor et al. (2021) report a four weeks study during 48-h measurement intervals in four separate hospital wards in Malaysia, and proved the involvement of fine indoor air particulates with a diameter of ≤2.5 μm (PM2.5) as the SARS-CoV-2 virus’s transport agent. Instead, other studies stated that the presence of SARS-CoV-2 on the ICU surfaces could not be determined, if a strict cleaning protocol was supported with sodium hypochlorite, a high air change rate, and a negative pressure, therefore preventing environmental contamination in the intensive care units, ICU (Escudero et al., 2020). Lane et al. 2021 also investigated whether virus-containing aerosols were present in nursing stations and patient room hallways and found no detectable levels (i.e. a threshold of over 8 viral copies/m³ of air). In another study, air samples collected at a measuring station in Leipzig as well as and purified pollen were analysed for SARS-CoV-2 typical signals or for virus-induced cytopathic effects. The study intended to test if the virus could bind to bioaerosols and if so, whether these complexes were infectious. The results showed that neither air samples nor purified pollen were infectious or could act as carrier for virus particles (Dunker et al., 2021).

For other diseases, aerosols have been seen to remain in the air for an extended period of time and be carried over greater distances (i.e. > 6 m, such as in reported for outbreaks of tuberculosis, measles, and chickenpox, Dbouka & Drikakisb, 2020; Ather and Edemekong, 2020). Transmission of SARS-CoV-2 in a range of particulate matter (PM) from submicrometer to supermicrometer ranges have been reported (Liu et al., 2020; Guo et al., 2020). As PM2.5 in indoor environments is mainly
derived from common outdoor sources such as motor-vehicles, biomass burning, and industrial emissions, both environments appear closely related.

In essence, the longer lifetime of smaller particles may pose a significant viral exposure to healthcare personnel, especially in indoor environments, more so given that they can easily propagate by tiny turbulent eddies in the air (Wang et al., 2006; Gemenetzis et al., 2006; Quian et al., 2012; Liu et al., 2018; Chatoutsidou et al., 2015). However, despite numerous studies that have demonstrated the transmission route of SARS-CoV-2 via respiratory droplets, direct evidence on aerosols-borne transmission remains more limited (Liu et al., 2020; Peng et al., 2020; Morawska & Cao, 2020).

Virus size for known viruses can range from 20 nm to as large as 500 nm, with SARS-CoV-2 being approximately twice the size of influenza A. By using electron microscopy, different researchers have had varying results, but the diameter of this spherical virus has been found to range between 50 nm to 140 nm. Size is important mainly for two reasons in relation to aerosols: namely because it determines which characteristics face masks must comply with to be protective, and second as size also conditions its airborne dispersal range and persistence. However, as viruses may travel embedded in larger particles, filtration of sizes larger than 140 nm may be efficient for small viruses as well.

Also, the dynamic behaviour of a particle may not correlate exactly with its size, since depending on the containing matrix and aerosol’s structure, a small particle may behave as a larger particle in its dynamic properties. Respiratory droplets are typically 5-10 micrometers (µm) in length, while aerosols smaller than 5 µm and controlled experiments from ill (and infectious) patients indicate a variable amount of viruses (differences of the order of several thousands) contained depending on the size of aerosols. No study instead has reported a significant correlation between the virus concentration and PM’s diameter. Whilst N95 masks from different producers may have slightly different specifications, the protective capabilities offered by N95 masks are largely attributed to the masks’ obligation to remove at least 95% of all particles with an average diameter of 300 nm or less.

Recent longitudinal studies have begun to investigate the associations of PM2.5 and influenza. For example, a study in Beijing, China, reported the association between the delayed impact of short-term exposure of PM2.5 and monthly influenza cases (Liang et al. 2014). A follow up study found correlations between PM2.5 exposure and daily influenza risk by age group in Beijing, China, suggesting a 1-day optimal lag effect (Feng et al., 2016). A more recent study showed consistently increased odds of healthcare encounters for influenza for elevated PM2.5 exposure estimates averaged across several lag periods, 0–28 days (Horne et al., 2018). Building on models of airborne disease transmission in order to derive an indoor safety guideline that would impose an upper bound on the ‘cumulative exposure time, Bazant and Bush, 2021 investigated by means of a theoretical model an upper bound on the product of the number of occupants and their time spent in a room. They showed how specifically the Six-Foot Rule is a guideline that offers little protection from pathogen-bearing aerosols sufficiently small to be continuously mixed through an indoor space.

For SARS-CoV-2, the viral load of infectious individuals is very variable by orders of magnitude and it was demonstrated both experimentally and by model simulations, that most environments and contacts are under conditions of low virus abundance (virus-limited). In these conditions, surgical masks are, in principle, effective at preventing virus spread. Instead, more advanced masks and other protective equipment are required in potentially virus-rich indoor environments including medical centres and hospitals (Cheng et al., 2021). It is therefore clear also experimentally that reducing background aerosols (i.e. ventilation, distancing) reduces infection risk.

Aerosols generated by infected people act merging together with background aerosols, what implies that as well as removing aerosols by ventilation, their generation should also be minimized.
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(Ashworth 2021). A common means of aerosol generation –much overlooked but of great relevance in many societies- is the toilet flush, which increases background aerosol content not only in the same room but over larger distances, thus acting as a transport system for viral particles. It has been reported in Edinburgh’s hospitals (Ashworth, 2021) that toilets are not provided with lids and therefore nosocomial transmission can take place. Simple and inexpensive evidence-based measures such as lids could largely reduce indoor aerosols as could also ionizers in public spaces. Reducing background aerosols could, in turn, reduce infectivity.

3.2. Effects of AP on disease susceptibility and the well-being of individuals. Can Covid-19 effects be exacerbated by AP and is there an enhanced effect in people with co-morbidities?

Studies have pointed out that AP may be a contributing factor to the Covid-19 pandemic. However, the specific links between AP and infection by the SARS-CoV-2 yet remain unclear. Epidemiological investigations have related various air pollutants to Covid-19 morbidity and mortality at the population level, however, those studies often suffer from several limitations. AP may be linked to an increase in Covid-19 severity and lethality through its impact on chronic diseases, such as cardiopulmonary diseases and diabetes, but controlling for previous co-morbidities is a difficult task when length of experimental time is, as here, much limited. Experimental studies have, in general, shown that exposure to AP leads to a decreased immune response, thus facilitating viral penetration and replication. Viruses may also persist in air through complex interactions with particles and gases depending on: 1) chemical composition; 2) electric charges of particles; and 3) meteorological conditions such as humidity, ultraviolet (UV) radiation and temperature. In addition, in principle, by reducing UV radiation, air pollutants may promote viral persistence in air and reduce vitamin D synthesis.

In the specific case of AQ, research on Covid-19 and other respiratory illnesses can be divided into: (1) studies that are concerned with the transmission of the pathogen, primarily related to aerosol dynamics, and (2) studies related to the effects of certain pollutants on the immune response function, influencing the severity of disease symptoms and probability of death. And as a last category, that related to (3) previous co-morbidities. There is substantial evidence for (2) and likely also for (3), although drawn from a number of other respiratory diseases to which Covid-19 and its causing virus, resembles.

In addition, concerns exist that long-term conditions, resulting from Covid-19 infections can be worsened by previous and current AP exposure, increasing hospital admissions for respiratory and cardiovascular ailments/diseases (Brunekreef et al., 2021). This may have a direct impact on Covid-19 symptom severity, since the body’s ability to respond to the infection is further compromised, and it also means that individuals with a history of exposure to AP are more likely to have comorbidities that make them more susceptible to severe health impacts when faced with a viral infection (Ciencewicki and Jaspers, 2007; Kim et al., 2018). This includes cardiovascular diseases and other vasculitis, respiratory diseases, diabetes, and hypertension (Yang et al., 2020).

Most support for the alleged relationships between APs and Covid-19 may therefore come from age-related studies. Age is one of the most important prognostic factors associated to Covid-19 lethality (Pierce et al., 2021; Lara et al., 2020). The rationale is that eldest people, after long time living in highly polluted areas, could acquire higher levels of predisposition to display an increase of their hyper-inflammatory biomarkers. This cascade of events has been shown to leads to pulmonary fibrosis or other organ damage due to interaction with pollution and with further reactive oxygen species (e.g. the latter activating the NLRP3 inflammasome). Also, dementia or Alzheimer disease, developed mainly in the eldest population, is described to relate with an overexpression of the angiotensin-converting enzyme-2 (ACE-2) via reactive oxygen species production and the
subsequent NLRP3 inflammasome activation. As mentioned, SARS-COV-2 infection has also been linked to inflammation via ACE-2 receptors.

Recent population studies suggest a role for the NLRP3 inflammasome activation in lung inflammation and fibrosis in SARS-CoV and SARS-CoV-2 infections (Lara et al., 2020). AP is also documented to show increased amounts of radioactivity depending on particular conditions, and some studies relate these characteristics and the presence of SARS-CoV-2 in bioaerosols to an activation of the cytokine cascade (Ratajczak et al., 2020).

At a mechanistic level the diagram below (Fig. 4) could—at least partly—illustrate the connections between AP, meteorological factors and both the virus transmission and propagation of the disease at the population level.

Figure 4 – Air pollutants/virus interaction according to atmospheric conditions

Relative humidity plays a role in the desiccation or hydration of viral droplet and, thus, influences the size of the droplet and the persistence of respiratory viruses in the air. Solar ultraviolet (UV) radiation has in vitro antiviral activity and leads to an increase in vitamin D synthesis. Atmospheric air pollutants may lead to decreased UV penetration leading to reduced vitamin D synthesis and temperature influences the size of the viral droplets. In addition, low temperatures decrease the functioning of airways ciliated cells, while high temperatures may have antiviral activity. Droplet nuclei refers to viral droplets \( \leq 50 \mu m \) (also called viral airborne or viral aerosols). In addition to the common effect of air pollutants, which lead to a decrease in immune respiratory defense, particulate matter (PM) may be involved in respiratory virus transport. (AMP: antimicrobial proteins and peptides; ELF: epithelial lining fluid; RASS: renin-angiotensin-aldosterone system; AT1R: angiotensin 2 receptor type 1.

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On (3) above, AP may increase Covid-19 morbidity and mortality through its action on associated co-morbidities. Experimental studies conducted for other respiratory viruses support the hypothesis that AP exposure may facilitate the occurrence of Covid-19 infection through a decrease in immune response. In vitro, animal and human studies have reported that exposure to air pollutants leads to increased mucosal permeability and oxidative stress, decreased antioxidants and surfactant antimicrobial proteins, as well as impaired macrophage phagocytosis. In addition, SARS-CoV-2 entry in host cells through ACE 2 requires the cleavage of the viral spike protein by proteases, and such protease activity may be increased by AP, as is documented for several other respiratory viruses.

According to their composition, PM and viruses can interact and modify viral activity as shown by in vitro studies. In addition, PM is known to carry microorganisms such as viruses, and there is controversy whether SARS-CoV-2 RNA has been identified in PM in open-air aerosols. It is clear, though, that it is present in aerosols in closed spaces (e.g. hospital wards, metro stations and other crowded spaces). It is therefore absolutely clear that this topic deserves urgent investigation, as it is of paramount importance for issuing appropriate regulations for occupational health and for associated policy actions. Although there is a need for more specific studies exploring interactions between air pollutants and SARS-CoV-2 in the ambient air and their impact on human health, this review highlights that both short and long-term exposures to AP may be important aggravating factors for SARS-CoV-2 transmission and Covid-19 severity and lethality through multiple mechanisms, some of them yet unclear. Future studies should also examine the role in Covid-19 epidemiology of both outdoor and indoor AP, and the physical and chemical composition of aerosols. The fact that both biology and atmospheric chemistry are separately implicated suggests that a more holistic approach to disease management and mitigation is necessary both in addressing the current Covid-19 pandemic and other future viral epidemics.

Chronic exposure to PM2.5 and NO2 are described by Frontera et al. 2020 to correlate with alveolar angiotensin-converting enzyme-2 (ACE-2) receptor overexpression, that could ultimately lead to more severe Covid-19 infection. Mechanisms proposed are two-fold: (1) Chronic exposure to PM2.5 causing alveolar ACE-2 receptor overexpression, which might lead to an increase in viral load in patients exposed to pollutants.

This in turn would deplete ACE-2 receptors and impair host defenses, or/and (2) High atmospheric NO2 may provide a second hit causing a severe form of SARS-CoV-2 in ACE-2 depleted lungs resulting in a worse outcome (Macías-Verde et al., 2021). Dalan et al. (2020) found out that SARS-CoV-2 uses the same pathway as SARS-CoV, infecting humans through the angiotensin-converting enzyme-2 (ACE-2) receptor (Conti et al., 2020). Neuron and glial cells are also a potential target of Covid-19 due to the overexpression of ACE-2 receptors in dementia or Alzheimer’s Disease patients [39]. Ratajczak & Kucia (2020) reports, as well, SARS-CoV-2 infection and overactivation of the NLRP3 inflammasome as a trigger of the cytokine storm and a risk factor for damage of hematopoietic stem cells. For instance, the relationship between PM and SARSCoV-2 entry factors has been investigated in mice and new evidence provided regarding the underlying mechanism and susceptibility factors related to the increase in Covid-19 prevalence following PM exposure (Zhu et al., 2021).

With respect to AQ, there is strong evidence for influenza and other respiratory viruses that poor AQ contributes to an increase in lower respiratory infection mortality (Troeger et al., 2018). Long-term studies of AP have presented convincing evidence of effects of fine particles (PM2.5) on all-cause mortality, morbidity and mortality from cardiovascular and respiratory diseases as well as with diabetes and lung cancer. In addition, nitrogen dioxide (NO2) and ozone (O3) are associated with respiratory disease and mortality, for which there also exists strong evidence from short-term studies, demonstrating effects on mortality and hospital admissions from very low exposure levels.

Chronic diseases such as asthma, COPD, lung cancer, heart disease and diabetes can predispose to and worsen the outcomes of respiratory infections such as Covid-19 according to recent studies (Brunekreef et al., 2021). Exposure to polluted air can lead to oxidative stress and damage to the
respiratory system, which reduces resistance to infection (Ciencewicki and Jaspers, 2007). This applies to both acute and chronic exposure. NO2 levels, for example, have been found to correlate with respiratory infection hospitalisations on a timescale of days (Fusco et al., 2001) and with the prevalence of respiratory infections between different cities (Jaakkola et al., 1991). The influence of NO2 on infection rates for other respiratory diseases than Covid-19 has been supported in laboratory studies (Rose et al., 1988).

Similarly, elevated particulate matter (PM) levels in outdoor air have been found to correlate with respiratory infection rates and severity for both acute (Chen et al., 2017; Dominici et al., 2006; Lin, 2005; Schwartz et al., 1991; Wordley et al., 1997) and chronic (Dockery et al., 1989; Pope III et al., 2004) PM exposures. Similar evidence exists for carbon monoxide (CO) and sulphur dioxide (SO2) exposures, while studies of ozone have yielded mixed results (Ali et al., 2018; Domingo and Rovira, 2020; Wolcott et al., 1982). A seven-year study documented a positive relationship between ozone and paediatric influenza incidence. This study further demonstrated a significant interaction between particulate matter and temperature, whereas findings for ozone were found to be temperature independent (Xu et al., 2013). Other modelling analyses showed that ozone was negatively associated with influenza risk (Ali et al., 2018; Sù et al., 2019).

Specific to coronaviruses, AP was found to increase the case fatality rate for SARS in China (Cui et al., 2003). Wind speed has been shown to interact with AQ factors (Cox et al., 1975; Kurita et al., 1985), i.e. low wind speed can favour the stagnation of particulate matter mixed with viral agents (Coccia, 2021, 2020). Formerly, a negative association was found between wind speed and the secondary attack rate of SARS, indicating that high wind speed potentially contributes to the dilution and removal of droplets, decreasing the suspension time of SARS in the air (Cai et al., 2007). Other studies suggested that increased wind speed might support the diffusion of virus particles, increasing the likelihood of transmission between individuals over longer distances (Peci et al., 2019). These conflicting findings emphasise the need for further studies to investigate the role of wind speed in modulating virus transmission.

In relation to the role of PM2.5, PM10 and NO2, in in particular Covid-19 spread and lethality, evidence is yet inconclusive. Studies often used different research methods or did not generally include potential confounding factors (Copat et al., 2020). Investigating cardiovascular comorbidities affected by pollution during the Covid-19 pandemics Versaci et al., 2021, for instance, appraised the impact of Covid-19, weather, and environment features on the occurrence of ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) in a large Italian region and metropolitan area. However, changes in STEMI and NSTEMI could not be explained successfully and more investigation is needed. Multi-stage and multiply adjusted models highlighted reductions in STEMI to be significantly associated with Covid-19 data (p<0.001), whereas changes in NSTEMI were significantly associated with both NO2 and Covid-19 data (both p<0.001). The latter might point to the combined effect of lockdowns and reduction of pollutants on the health of individuals. Therefore, evaluating the validity of this relationship demands yet further and more rigorous assessment.

Alongside, Middya and Roy (2021) analysing data for India at a high-resolution spatial level obtain strong positive relationships between Covid-19 deaths hotspots in western India and both PM2.5 and population density. The former approach added to generally underestimated incidences and mortality data in most countries highlighted in some studies and the need to more accurately evaluate the contribution of both PM2.5 and NO2 as potential facilitators of Covid-19 spread and lethality (Zoran et al., 2020). As a consequence, more studies including longer time periods and designs that can overcome representability constraints and data inaccuracies are needed to strengthen scientific evidences and support firm conclusions.
3.3. Is there higher risk of Covid-19 in more polluted cities?

As summarized in the briefing by ENVI report (2020) Europeans are not all affected by AP in the same way, what raises questions about potential differences in Covid-19 incidences. Whereas Eastern Europe is more impacted by high levels of PM2.5 due to its higher emission rates, instead NO2 concentrations are the highest in the most densely populated areas in western Europe and are linked to local sources such as traffic, domestic and industrial emissions. And as in the case of ozone, it is formed under the effect of light and sunlight and therefore appears linked to the warmest and sunniest regions, resulting in a division that shows a north-south difference. Alongside, segments of population most sensitive to the health effects of AP are children, pregnant women, the elderly and people with pre-existing health problems. Therefore, studies should be conducted that analyse Covid-19 rates and incidences differences to check whether same patterns apply. Potential linkages with places with poorer AQ standards, where also the more vulnerable live should also be conducted.

A few studies have shown a possible link between AP and Covid-19 pulmonary severity also relating it to increased fatality. Early on April 2020, Ogen (2020) reported high concentrations of tropospheric NO2 over two regions in Europe (Northern Italy and Madrid metropolitan area), as detected by the Sentinel-5P satellite. The NO2 buildup close to the surface was hypothesised to be associated to high incidence of respiratory problems and inflammation. This chronic exposure to NO2 is consequently argued to be an important contributor to the high Covid-19 fatality rates observed in these regions. Frontera et al. (2020) found that regions of the world with high concentration of air pollutants, especially PM2.5 and NO2, have higher infection rates from SARS-CoV-2 and result in a higher mortality, despite the mechanistic link was, unfortunately, not established. Chronic exposures to these same air pollutants are correlated with alveolar angiotensin-converting enzyme-2 (ACE-2) receptor overexpression, in principle leading to more severe Covid-19 infection.

A study taking as a focus the city of Lodi in Lombardy, where the first outbreak occurred in Italy in the first pandemic wave, found that SARS-CoV-2 cases and mortality increased in a non-linear way, when the distance from Lodi reduced below 92 km and 140 km, respectively. These relationships were intriguingly amplified by ozone (O3) pollution (Tripepi et al., 2020). Similarly, a study analysing the impact of four ambient air pollutants on the Covid-19 mortality rate in the United States of America, established that high ground-level ozone and nitrogen dioxide concentrations contribute to a greater Covid-19 mortality rate (Liu and Li, 2020). However, as authors themselves state, this study was subject to multiple limitations that could result in inaccuracies, as many other confounder variables could not be properly accounted for and the sample size was also very small. Along similar lines, Zoran et al. (2020) found that air relative humidity in Milan was -albeit moderately- significantly inversely correlated with all confirmed Covid-19 cases (i.e. Total Covid-19 deaths, and Covid-19 daily new and total numbers).

There are reports of multiple gastrointestinal symptoms in patients with Covid-19 linked to poor AQ and high levels of particulate matter (Crawford et al., 2021). Moreover, in addition to industrial and urban pollution, health disparities in the United States (U.S.) are seen among minorities and immigrants who account for the majority of seasonal farm workers frequently exposed to PM in agricultural dusts (Lighthall 2001; Schenker et al., 1998). Strikingly, many farm workers live below the poverty level with limited access to healthcare services thus increasing their risk of developing respiratory disorders from exposure to airborne pollutants (Elliott and von Essen, 2016; Lineker & Smedley, 2002). Most AP is man-made and derived from fossil fuels including toxins from car exhaust and industrial waste (Winkler et al., 2018).

Additionally, agricultural enterprises including concentrated animal feeding operations include a variety of dusts, vapors and fumes that can promote and exacerbate respiratory diseases including
chronic obstructive pulmonary disease (COPD), hypersensitivity pneumonitis (Charavaryamath & Singh, 2006; Nordgren & Bailey, 2016) and organic dust toxic syndrome (Von Essen SG, Auvermann, 2005; Seifert et al., 2003). More specifically, farmers who are in daily contact with livestock (e.g. pigs) are exposed to dust composed of microorganisms originating from animal dander and fecal matter (White et al., 2019). While the inhalation of dust and other airborne pollutants are major factors in the development of cardiovascular and respiratory complications, recent studies have also shown that urban airborne particulate matter can have adverse effects on the gastrointestinal (GI) tract (e.g. barrier function and microbial composition) and immune system.

An additional vulnerability appears to be the association between increased deaths from Covid-19 in areas with high levels of AP, more specifically, elevated exposure to the toxic component nitrogen dioxide (NO2). Ogen et al. (2020) assessed long-term exposure to NO2 in European countries and found a strong correlation between high levels of NO2 (>100 μmol/m2) and Covid-19 fatalities (Ogen, 2020), despite causation could not be established. Nitrogen dioxide can also react with other chemicals and produce secondary pollutants such as ozone and PM (US EPA 2019). A recent USA nationwide cross-sectional study revealed that an increase of just 1 ug/m3 of PM corresponded to an 8 % increase in Covid-19 deaths (Wu et al., 2020). This study, adjusted for multiple county-level confounders, covered more than 3000 US counties and examined whether the Covid-19-related mortality per capita varied by estimated county level PM2.5 concentrations across the 2000–2016 period.

After adjusting for population density, average body mass index, levels of poverty, smoking rates, average temperature, humidity, and the number of tests performed in each state, the study concluded that a 1 μg·m3 increase in long-term PM2.5 concentrations were associated with an 8 % increase in Covid-19 mortality, which is a factor of 10 higher than all-cause mortality rates in the same counties reported in a previous analysis. By taking into account the time of virus introduction in each county, this study also took into account the dynamic of the disease. Although this study adjusted for potential confounders, it is based on the assumption that previous PM2.5 concentrations were still representative of those during 2016–2020. Another limitation comes from the fact that many of the county-level adjustment factors resulted from the Behavioral Risk Factor Survey that excluded institutionalised residents, whereas they represent a large part of Covid-19 deaths.

While the mechanisms by which AP modifies severity of Covid-19 responses have yet to be determined, very little is known about the host factors that determine mild or even asymptomatic responses compared with life-threatening or fatal outcomes. As with many inflammatory diseases, it is the combination of specific host and environmental factors in certain individuals that provokes more severe disease outcomes. What does appear to be emerging from evidence generated thus far is that environmental air pollutants have a positive correlation with overall Covid-19 severity.

Among the studies addressing short-term effects of AP, Setti et al. 2020 were the first to observe an association between the number of Italian provinces with daily averaged PM10 concentrations exceeding the European limit values of 50 μg·m−3 and the subsequent number of Covid-19. Significant associations were found between mean concentrations of PM2.5 during the month of February 2020 and the total number of Italian Covid-19 cases on 31 March 2020. However, a similar study focusing on the Lombardy and Piedmont regions in Northern Italy from 10 February to 27 March 2020 reported a null association between the number of Covid-19 cases and PM10 concentrations measured several days before the COVID emergency explosion (Bontempi et al., 2020).

A study exploring Covid-19 cases in Italy, France, Germany and Spain reported a positive association between PM2.5 and PM10 concentrations between February and April 2020 and the number of SARS-CoV-2 infected cases, while a negative association was found for O3 (Bourdrel et al., 2021). In China, city-specific effects of PM10 and PM2.5 on daily confirmed Covid-19 cases were examined in
more than 70 cities (Jiang et al., 2020). Short-term lagged (7 and 14 days) increases in PM2.5 were associated with daily Covid-19 confirmed cases, and the magnitude of effect was greater for PM2.5 than for PM10. Another study in China looked at short-term levels of six different pollutants (PM2.5, PM10, SO2, CO, NO2 and O3) in 120 cities to determine their association with daily Covid-19 confirmed cases (Yao et al., 2021). The study reported an approximate 2% increase in daily Covid-19 cases for every 2-week lagged 10 μg·m⁻³ increase in PM2.5 and PM10. However, this very limited increase casts doubt on the overall impact in this particular study, and larger studies need urgently be developed (Bourdrel et al., 2021).

Regarding the role of long-term exposure to AP, an Italian study reported that mean levels of NO2, O3, PM2.5 and PM10 during the past 4 years, as well as the number of days exceeding the limit values established by the European Commission during the past 3 years, were both correlated with the number of Covid-19 cases in Italy (Fattorini et al., 2020). A UK study using individual data from the UK Biobank of 1450 participants, including 669 Covid-19 confirmed cases, that adjusted the models for confounding variables, reported significant positive associations of PM2.5 and PM10 with SARS-CoV-2 infectivity. In addition, to explore the link between AP and the spread of Covid-19, several studies have analysed the effect of AP on the prognosis of Covid-19.

Although these studies answer a different question and may also have their own weaknesses, exploring the prognosis of Covid-19 is less influenced by the dynamics of infection and thus leads to less internal validity threats such as unmeasured confounding factors. In terms of Covid-19 mortality, NO2 was found to be related to Covid-19 in a study covering Italy, Spain, Germany and France that revealed 83% of Covid-19 fatalities occurred in the regions with the highest NO2 levels (Pansini and Fornacca, 2020), despite a mechanistic link was not shown. In an Italian study, Covid-19 mortality on 31 March 2020 was twice as high in the regions with the highest levels of PM2.5 compared to that in the regions with the lowest levels of PM2.5. Interpretations of these short- and long-term effects should be made with caution and always in the context of their respective epidemiologic designs.

Furthermore, it has been described that members of racial and ethnic minority groups are at a greater risk of contracting Covid-19 due to social inequalities and health disparities. This increased vulnerability is also seen among seasonal agricultural workers in Covid-19 high-risk rural counties in the US (NCFH, 2020). Moreover, while the specific influences of aerosolised agricultural dust on Covid-19 are unknown, it is not unreasonable to suggest that given its causal role in many respiratory conditions, agricultural dust may represent a potential additional risk factor for Covid-19 infection, or more severe outcomes, in agricultural workers. This may be particularly relevant to the high levels of Covid-19 in Imperial County, California. This rural and agriculture-intense inland county has a number of disadvantages as it battles the pandemic including limited access to healthcare, high levels of poverty, obesity, and asthma hospitalisations (Tulimiero et al., 2020), as well as poor AQ with higher levels of particulate matter exposure than the state or national averages (Jones & Fleck, 2020; Man et al., 2017; NIEHS, 2020).

Recently, another large study conducted at the county level in the USA showed a significant relationship between long-term exposure to NO2 and Covid-19 mortality (Wuet al., 2020). This study used both single and multi-pollutant models and controlled for spatial trends and a comprehensive set of potential confounders including state-level test positive rates, county-level healthcare capacity, phase-of-epidemic, population mobility, socio-demographics, socioeconomic status, behaviour risk factors, and meteorological factors. Furthermore, the previously mentioned UK study, adjusted for population density, found that the levels of SO2 and NO2 recorded between 2018 and 2019, were positively linked to Covid-19 cases and Covid-19 mortality, while O3 was negatively correlated.

Although population density is important because it can promote both viral spread and AP, it fails to explain why some highly populated regions have larger numbers of Covid-19 cases and fatalities,
pointing to socioeconomic and racial inequalities, including disparities related to environmental exposure. Recent data from the USA indicated that the number of Covid-19 cases and fatalities experienced by Black citizens were higher (up to 75%) than in the rest of the population, although they constitute only a small proportion (32% at maximum) of the overall population. Outside conventional epidemiology, comprehensive econometric methods were applied to study the effect of PM2.5 and Covid-19 cases, hospitalisations and deaths in all 355 municipalities in the Netherlands (Cole et al., 2020). The authors attempted a number of sensitivity analyses to account for unmeasured confounding (or omitted variable bias as commonly known in econometrics), measurement error in the exposure and the outcome and spatial spill-over.

They found that a 1 μg·m−3 increase in long-term PM2.5 is associated with nine additional cases, three additional hospital admissions, and two additional deaths. Interestingly, this study found that the relationships between AP and Covid-19 are also observed in rural zones, which suggests that AP plays a direct role in impacting Covid-19, independent of an urban setting with all its characteristics, such as density or crowding. In those rural zones, PM2.5 mainly arises from agricultural sources and especially from intensive livestock farming that leads to NH3 release. By interacting with other gaseous pollutants such as NOx, atmospheric NH3 leads to PM2.5 formations. In Europe, agriculture is one of the main sources of PM2.5 (Lelieveld et al., 2015).

Finally, an additional and interesting avenue of research that can help provide evidence is the in vitro, animal and human studies. Bourdrel et al., 2021 review the different studies to date from different perspectives. For instance, for diseases such as influenza and measles, they state that several studies have demonstrated that increases in air pollutant concentrations were associated with an increased occurrence of respiratory viral diseases among children and adults, in particular when the viral infection was concomitant to a short-term increase in exposure to AP. Increases in PM2.5 concentrations have been associated with increased rates of viral infection, namely influenza, respiratory syncytial virus (RSV) and measles. In these studies, concentrations of PM2.5 were correlated with the number of new cases of respiratory viral infections with a lag time of a few days (Su et al., 2019; Chen et al., 2017).

It is still unclear, however, how long this virus remains infectious in ambient air and whether the low viral load contained within the aerosol is sufficient to induce infection. Atmospheric interactions between gases and viruses are also complex and depend on meteorological contributing factors such as UV radiation and relative humidity. By reducing UV radiations (which have antiviral activity) air pollutants may promote viral persistence in ambient air and also reduce vitamin D synthesis, and thus may play a role in the immune response against viral infections.

3.4. Can meteorological factors facilitate aerosol-mediated transmission of SARS-CoV-2?

A thorough understanding of the role of meteorological factors on both Covid-19 incidence and SARS-CoV-2 transmission is not the central objective of this part of the review. An exhaustive compendium of the evidences to date is presented in the 1st Report of the WMO Covid-19 Task Team on Meteorological and AQ (MAQ) factors affecting the Covid-19 pandemic (WMO, 2021). Although there is as yet no consensus on the subject, it seems likely that a decrease in humidity leads to dehydration of macro droplets into smaller droplets that are able to remain in suspension in the ambient air, while an increase in humidity may lead to increased water content of viral droplets, and thus increased weight, enabling them to fall to the ground faster (Bourdrel et al., 2021). And in the case of temperature, whereas colder conditions lead to an increase in other respiratory viral transmissions such as influenza, there are yet contradictory results on the link between Covid-19 and temperature (Moriyama et al., 2020).
While several studies found that temperature was negatively associated with Covid-19 mortality and transmission, others did not find any evidence of an association (Liu et al., 2020; McCarter and Byrne, 2020; Tobias, 2021). Massive amounts of preprints and fast-tracked publications bearing low-quality criteria have added more confusion to the field (Chen et al., 2021). Some recent studies have also tried to investigate the link to meteorological factors by studying the potential role of seasonality in the disease dynamics. The explicit addition of climate was evaluated as significant, in a process-based model tailored to simulate the potential role of both, seasonality (Lopez and Rodó, 2020; Liu et al., 2021) and temperature or absolute humidity (Rodó et al. (2021) on the spatial and temporal evolution of the Covid-19 pandemic.

Complementary approaches to prediction of Covid-19 cases using deep learning techniques integrating weather information for India suggest that there might be skill at medium range (1–7 days lead) in some of the states in India (Bhimala et al., 2021). In particular, long short-term memory (LSTM) models using either specific humidity and temperature were skillful at these lead times, depending on the geographical location of states,

The base assumption of the linkage with meteorological factors is that, dry (relative humidity <20%) and cold air affects both immunity and viral spread owing to the fact that dry air may facilitate airborne viral transport, and that cold conditions, in addition to low humidity, may impair the functioning of airways ciliated cells (Moriyama et al., 2020).

Depending on the geographical location and local conditions, in a cold season, the dense cold air may cause a temperature inversion, which reduces air mixing and thus, exacerbates existing particulate pollution. The persistence of air pollutants can also be influenced by the lack of wind, preventing dispersion. Finally, atmospheric conditions that promote PM formation and stagnation may also promote SARS-CoV-2 persistence in the air (Fronza et al., 2020). In contrast, sunny days with hot temperatures and solar UV radiation may increase the oxidative potential of the atmosphere, leading to higher O3 concentrations and may also lead to a reduced viability of SARS-CoV-2 in the air. However, although an increasing body of data appears to report the detection of SARS-CoV-2 RNA in air, this does not correlate to the presence of infectious viruses nor it does inform on the risk for airborne transmission of SARS-CoV-2. Hence there is a marked knowledge gap that requires urgent attention (da Silva et al., 2021).

As described above, the expectation that the transmission of SARS-CoV-2 and/or the severity of Covid-19 symptoms may be sensitive to MAQ factors stems from laboratory studies that have shown the ability of many viruses to survive in the air or on surfaces is sensitive to AQ factors (Marr et al., 2019; Tang, 2009). Many studies on Covid-19 have focused on the first line of reasoning, and have sought to quantify the potential association between variations in AQ factors and Covid-19 using epidemiological records (Briz-Redón and Serrano-Aroca, 2020, p.; McClymont and Hu, 2021; Mecenas et al., 2020; Shakil et al., 2020; Smit et al., 2020). These studies have applied Covid-19 case data in a variety of ways, including analysis of raw case numbers through time, cumulative case numbers, case growth rates, and estimates of the basic reproduction number (the mean number of new infections caused by an infected individual in a completely susceptible population and in the absence of interventions) or effective reproduction number (reproductive number accounting for acquired immunity and interventions) derived from case data.

The results of early epidemiological studies on the meteorological influence on Covid-19 rates yielded inconclusive and sometimes controversial results. A number of these studies reported potential associations between one or a combination of several meteorological variables and metrics of Covid-19 spread, growth-rate, or prevalence (Briz-Redón and Serrano-Aroca, 2020; Carleton et al., 2021; McClymont and Hu, 2021; Mecenas et al., 2020; Pan et al., 2021; Shakil et al., 2020; Smit et al., 2020; To et al., 2021). However, there is no consensus across studies on the relative importance of various meteorological variables (e.g., UV radiation, temperature, humidity) and at
this stage no firm or generalizable conclusions can be drawn (Briz-Redón and Serrano-Aroca, 2020; Mecenas et al., 2020; Shakil et al., 2020; Smit et al., 2020).

In this regard, even claimed evidence of decreasing growth rates in Covid-19 spatial distribution due to increasing UV radiation is not devoid of controversy (Carleton et al., 2021). Indeed, relative to an average Covid-19 incidence growth rate of 13.2 %, a 1 % decrease in this growth over the subsequent 2.5 weeks has been attributed to a one standard deviation increase in UV. Such mild changes, obtained from a large database covering 173 countries, with econometrics methods such as temporal distributed lag regression models, despite claiming to control for confounding variables, call for more research once the temporal extent of the database increases, and inconsistencies in the extent of data reporting have a more limited negative effect on analyses (Carleton et al., 2021). Inconsistent results to date, however, do not necessarily imply AQ factors will not affect SARS-CoV-2 transmission or Covid-19 severity.

Additional challenges to clarify these relationships have included non-independence of certain meteorological variables, exclusion of other social and behavioural modulating factors when testing for associations, residual confounders that are not properly controlled for, data heterogeneities across countries, high proportion of asymptomatic cases, and the difficulty of ascertaining intercomparability for data on Covid-19 cases, also at subnational levels. It has been suggested that during the pandemic phase of Covid-19 non-MAQ factors such as low levels of immunity in the population and vulnerability to infection and disease and impacts of non-pharmaceutical interventions (NPIs) likely predominate in determining epidemiological patterns (Baker et al., 2020; Jüni et al., 2020; Meyer et al., 2020), while seasonality, and effects of MAQ, may emerge during the post-pandemic phase (Kissler et al., 2020).

However, other modeling work has suggested that seasonality does have a potential influence even early in epidemics (López and Rodó, 2020) and may have contributed significantly to sustaining of new pandemic waves of Covid-19 (e.g. in the case of Japan, as highlighted in Rodó et al., 2021). For this reason, it is important to emphasise the uncertainty in our current understanding of the potential impact of AQ factors on Covid-19, while continuing to investigate potential for AQ information to support public health policy and the Covid-19 response.

Peer reviewed laboratory studies of SARS-CoV-2 sensitivity to meteorological and AQ variables are still rare, given the time required to perform and publish such work. Results of available studies do include some evidence of meteorological sensitivity. This includes findings that the survival of SARS-CoV-2 in aerosols as well as on surfaces appears to decline in the presence of increased UV-A and UV-B radiation (Ratnesar-Shumate et al., 2020; Schuit et al., 2020b). Results for humidity are less clear, with some indication that there is a slight increase in virus survival at lower relative humidity (20 %) (Biryukov et al., 2020; Dabisch et al., 2020) and other experiments showing greater survival at both medium (40-60 %) and high (68-88 %) relative humidity, depending on different suspension matrices (Smither et al., 2020). Results of these types of laboratory studies are critical for understanding the mechanistic basis of the relevance of aerosols to Covid-19 transmission, but at the same time, these studies are fundamentally different from epidemiological studies in that they focus on the specific issue of virus survival under controlled conditions rather than on meteorological and AQ influences on disease risk at the population scale. Their transferability to real-life settings is not always straightforward.

It has so far been hypothesised that cold and dry conditions are particularly suitable for aerosol transmission of other viruses in mid-latitude winter settings, attributing higher importance to aerosol transmission in temperate climates (Huang et al., 2020; Lowen et al., 2008; Tamerius et al., 2011). Other sensitivities might be observed in warm and humid climates, where small respiratory droplets absorb water, increase in size and then settle more readily on surfaces, placing a greater focus on contact transmission over airborne transmission in tropical climates (Lowen et al., 2008; Tamerius et al., 2011). For temperature and humidity, a broader suite of mechanisms has been
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proposed. The first mechanism relates directly to virus stability and transmission. Laboratory studies of several enveloped viruses such as influenza and other human coronaviruses have indicated a sensitivity to relative or absolute humidity and temperature (Chan et al., 2011; Harper, 1961; Ijaz et al., 1985; Schaffer et al., 1976), which is assumed to be due to environmental effects on viral surface proteins and lipid membrane (Tang, 2009).

Lower temperature was found to enhance the structural organisation of lipids of the influenza virus envelope and improve stability (Polozov et al., 2008). Laboratory results of environmental sensitivities vary by virus, but point to the fact that low humidity environments favour the rapid evaporation of water from exhaled aerosols, forming droplet nuclei (supposedly of <5µm in diameter) that might allow for prolonged viability and transmissibility of influenza virus (Lowen et al., 2007; Tellier, 2006; Weinstein et al., 2003). This raises the possibility that the seasonality of these viruses may be related to higher survival rates in cooler and drier environments. Laboratory studies of viral transmission in animals, which have focused on influenza, also show that low relative humidity (20-35 %) and cool temperatures (5°C) favour enhanced transmission in experiments that span a wide range of humidity and temperature conditions (Lowen et al., 2008, 2007).

It is now well-established that SARS-CoV-2 transmission commonly occurs in closed spaces (ECDC, 2020). As is often noted, people tend to spend more time congregating in poorly ventilated environments when it is cold/hot and/or precipitating outside, and this behavioural change might also help explain seasonal patterns in the risk of respiratory viral infections like those producing Covid-19 (Audi et al., 2020). In hot climates, people tend to escape the heat, spending increased time in air-conditioned indoor spaces. The importance of these behavioural factors relative to direct environmental influence on virus survival or host response is an active area of research, and no firm conclusions can be drawn for Covid-19 at this time. However, as evidence builds for the importance of aerosolised transmission of Covid-19 (Doremalen et al., 2020; Lednicky et al., 2020; Yuan Liu et al., 2020), the role of weather in pushing people towards closed indoor environments requires attention. Extremely warm weather might also have a negative impact on efforts to reduce transmission rates (ECDC, 2020; Lu et al., 2020).

The hypothesis that ventilation and airflow might influence SARS-CoV-2 transmission in indoor environments builds on studies that have shown ventilation to be a predictor of transmission rates for other viruses, including influenza and SARS (Knibbs et al., 2011; Li et al., 2007). For SARS-CoV-2, quantitative empirical evidence of these relationships is beginning to emerge, though the relationships are complex and are beyond the scope of this report. The expectation that airflow and ventilation might influence SARS-CoV-2 transmission, combined with this emerging evidence, is strong enough that health authorities have issued recommendations. For example, the European Centre for Disease Prevention and Control (ECDC) recommends that direct airflow should be diverted away from individuals.

Also, the minimum number of indoor-outdoor air exchanges per hour, depending on the applicable building regulations, should be ensured given that an increase in the number of air exchanges per hour can reduce the likelihood of indoor transmission (ECDC, 2020). From a meteorological perspective, it is known that outdoor meteorological conditions have a significant influence on indoor air exchange rates, and that outdoor temperature is a particularly strong predictor in most situations (Wallace et al., 2002). Given this association and the general understanding that air exchange is a factor in indoor transmission, the potential for meteorology to influence indoor SARS-CoV-2 transmission via its impact on air exchange rates warrants further investigation.

Sewage and human excreta have long been recognized as potential routes for transmitting human pathogens. SARS-CoV-2 has been detected in human feces and urine, where it could remain viable for days and still show infectivity (WHO, 2020; Xiao et al., 2020; Giacobbo et al., 2021). Urban flooding, a common threat caused by heavy rainfalls, is frequently reported in urban communities
along with sewage overflows. Han and He (2021) report sewage-associated transmission linked to hot-spots of Covid-19 cases, and highlighted the roles of sewage overflow and sewage-contaminated aerosols in two publicised events of community outbreaks.

A few studies point to the fact that exceptionally high temperatures, combined with health inequities exacerbated by the Covid-19 outbreak, may have increased vulnerability to heat in 2020 (Pascal et al., 2021). In summary, the interaction between meteorology and AQ should also be considered as it can potentially be very relevant throughout the pandemic waves (Chen et al., 2020; Le et al., 2020; P. Wang et al., 2020; Wang and Zhang, 2020). In addition to its direct impact on virus stability, meteorology may also influence virus transmission through affecting AQ (Yansui Liu et al., 2020), e.g., ozone is formed by photochemical reactions between sunlight and precursor pollutants, which is favoured in warm conditions (Guarnieri and Balmes, 2014). A few promising studies (yet in a pre-print stage) show clear indication of climate sensitivities linked to Covid-19 spatial and temporal heterogeneity, despite these studies are not yet considered in the current report.

A last point to highlight despite the well-known – albeit limited and short-lasting – decrease in AP detected nearly in every country and also worldwide as a consequence of the massive movement restrictions applied during lockdown regulations, is that the Covid-19 pandemic has also resulted in harmful side effects that demand quick mitigation actions. Namely, the unrestrained use of disposable plastic bags, lunch boxes and masks within the nationwide quarantine (e.g. in China) led to hundreds of millions of plastic wastes every day. The potential environmental pollution caused by the use of disposable plastic products worldwide during the pandemic is of much social concern and should be contained and redressed (Liu et al., 2021).

3.5. Outbreaks in meat-processing factories: A real link with indoor air conditions?
Covid-19 infection clusters have been reported already in the first wave of the pandemics in Europe related to both the fresh meat and seafood industry in different countries, which caused concerns about potential foodborne transmission of SARS-CoV-2 (Hu et al., 2020). Frequent outbreaks of Covid-19 infections were also reported among workers in slaughtered meat processing plants in different countries, such as Canada, Brazil, Germany, and Ireland. In Auckland, New Zealand, four new Covid-19 infected cases were reported in August 2020 following a period of no new infections for more than 100 days in the country, one of whom was a worker engaged in handling frozen food. In Qingdao, China, two dockers handling imported frozen seafood tested positive which resulted in a small-scale Covid-19 outbreak, despite the origin could not be unequivocally traced to the seafood. Although it is hard for SARS-CoV-2 to replicate after leaving the host, evidence exists that the virus can survive even on frozen surfaces for prolonged periods of transit and export (Munnink et al., 2021; Pang et al., 2020; Kampf et al., 2020). It remains to be confirmed, though, whether causes are the handling of contaminated food, or the facilitated airborne transmission in conditions that resemble those (cold and dry) in natural open spaces in winter in temperate areas, in which the virus can be more easily aerosolised and persist longer (Fig. 5).
Transmission of SARS in concentrated livestock rearing operations and meat-processing factories have been raised as part of a more general public concern over airborne biological and chemical emissions from such operations, as well as more specific health scares related to them. A seminal study in this regard was the epidemiological study of Wing and Wolf (2000). They noted increased incidences of headaches, runny nose, sore throat, excessive coughing, diarrhoea and burning eyes among those living near industrial livestock operations in North Carolina in the USA, compared with a control group of those not living within 2 miles of such operations. Although this epidemiological study was merely correlative, it stimulated much research on the airborne transmission of microbial pathogens from livestock operations – a potential route for disease transmission.

Analysing the data from one large-scale study, it appears there is no strong correlation between the number of animals in a concentrated animal feeding operation (CAFO) and the microbial biomass it produces (Hong et al. 2012). Therefore, any potential abnormal occurrence of Covid-19 outbreaks in these premises should be in principle thought to be motivated by both the close proximity among workers in an environment with optimal conditions for both virus survival and aerosols propagation.

Most of the current knowledge on the risk of environmental transmission of SARS-CoV-2 through the food chain is based on previous studies of other CoVs, such as SARS-CoV-1 and MERS-CoV (Kampf et al., 2020), but not yet on SARS-CoV-2. Enveloped viruses are typically adsorbed on surfaces via electrostatic, van der Waals, and hydrophobic interactions (Joonaki et al., 2020), which is highly dependent on the properties of different surfaces. To investigate the surface behaviour of SARS-CoV-2 under real scenarios (Biryukov et al., 2020; Chia et al., 2020) the precise characterisation of the surface properties and the associated microenvironment such as humidity, pH, and biofluid is needed. In addition, more attention should be paid to the adsorption and desorption characteristics of SARS-CoV-2 at both cellular and tissue surfaces as food product, to evaluate the viability of SARS-CoV-2. Based on this understanding of the underlying adsorption and survival mechanisms, new packaging and shipment surface materials could be designed to reduce or prevent the viability of SARS-CoV-2.
To date, the number of studies or news appearances reporting such clusters of cases (e.g. outbreaks) is limited, and possibly concentrated to the first months of the pandemics. At that time, a certain alarm was created as many local outbreaks were reported. In this regard, not only healthcare workers, but also workers in food/meat-processing factories wearing surgical masks had become infected without being involved in aerosol generating procedures (Nguyen et al., 2020; Klompas et al., 2021; Goldberg et al., 2021). Regarding potential mitigation actions to reduce the risk of infection in this labour premises, disinfection is still considered as an essential tool in the prevention of foodborne transmission of SARS-CoV-2. Ultraviolet light is currently used for the disinfection of any pathogen as it is with SARS-CoV-2 on the surface of imported packages. At a personal level the use of N95 face masks and eye-protective equipment should be encouraged. However, given the frequent and extensive infection processes that would currently be required combined with the health concerns regarding the use of the disinfection products, alternative ideas are still needed for the development of effective disinfection methods with low side effects.

A similar situation has been explored in the case of seafood markets, such as for the presumed original source in Wuhan (Zhang et al., 2021). Zhang et al. (2021) conducted a quantitative microbial risk assessment (QMRA) to evaluate the aerosol transmission risk by using the South China Seafood Market as an example (Fig. 6). The key processes were integrated into a high-resolution simulated modelling framework including aerosol movement simulations, covering viral shedding, dispersion, deposition in air, biologic decay, lung deposition, and the infection risk based on a dose–response model.

Figure 6 – Quantitative microbial risk assessment (QMRA) for SARS-CoV-2 aerosol transmission in the sea-food market in Wuhan

Such studies should be encouraged in those factories, markets and other facilities to be identified in a catalogue of high-risk aerosols’ transmission environments. Results simulating different infective caseloads (in terms of infected people present) might be useful and help deploy specific and highly-effective mitigation strategies (ventilation, operating rules for functioning, policy practices, etc...). These sorts of simulations should be incorporated into mandatory regulations for occupational health safety in high-risk premises. With the current information available, however, large uncertainties in these approaches remain mainly due to the limited information available on the credible dose–response relation and the viral shedding which need further studies. As a main conclusion, the simulated risk of having one infected person in the market exhaling SARS-CoV-2 viruses rapidly decreased outside the market due to the dilution by ambient air. It became below 10−6 at 5 m away from the exit. Multiple (>1) infected individuals were, however, not simulated.

The abundance of SARS-CoV-2 in the different environments should therefore be accurately determined based on a standardised method, including standards of sampling, pre-treatment, storage, and quantitative/qualitative analysis, and applied for the comparison of different processes, especially for the global food supply chain (Pang et al., 2020). The integrity and viability of SARS-CoV-2 on packaged, stored and transported materials need to be fully evaluated, and the relationship between abundance, viability, and infectivity of SARS-CoV-2 clearly established (Ong et al., 2020; Prather et al., 2020).

Along similar grounds and given the more recent weight given to aerosol transmission of SARS-CoV-2, special attention is deserved all workers having an enhanced exposition to aerosols. In particular, health care workers and oral health-care workers may carry the greatest risk. (Jungo et al., 2021). An online survey in this regard was conducted within a population of French dental professionals between April 1 and April 29, 2020. Univariable and multivariable logistic regression analyses were performed to explore risk indicators associated with laboratory-confirmed Covid-19 and Covid-19-related clinical phenotypes (i.e. phenotypes present in 15% or more of SARS-CoV-2-positive cases). 4172 dentists and 1868 dental assistants responded to the survey, representing approximately 10% of French oral health-care workers. The prevalence of laboratory-confirmed Covid-19 was 1.9% for dentists and 0.8% for dental assistants. Higher prevalence was found for Covid-19-related clinical phenotypes both in dentists (15.0%) and dental assistants (11.8%). Also Covid-19 incidence has also been recorded in dialysis centre during a nosocomial outbreak, underscoring the need to improve regulations for occupational health and for compromised patients in critical health care facilities (Io et al., 2021).
4. Discussion and conclusions

4.1. Air pollution effects on SARS-CoV-2 and/or Covid-19

While a number of studies have found associations between air pollution (AP) and Covid-19 rates, concerns among the scientific community have arisen about serious methodological caveats and inconsistencies in some of these studies (Carlson et al., 2020). As for other respiratory infections, early studies indicated that there is a positive relationship between prevailing air quality (AQ) conditions, especially fine particulate matter and Covid-19 mortality rates. The same has been stated with regard to Covid-19 incidence (Bourdrel et al., 2021). However, disentangling any independent effects of AP from effects of other causes related to Covid-19 outbreaks has been challenging, potentially resulting in perhaps, an overestimation or an underestimation of the effects of AP on Covid-19 occurrence and severity.

While direct epidemiological evidence of AQ influence on Covid-19 is only beginning to emerge, there is more mature evidence from other respiratory viruses. For instance, aerosols can enhance the stability of some viruses, including Middle East respiratory syndrome coronavirus (MERS-CoV; van Doremalen et al., 2021). Also, in the case of influenza, airborne transmission was found to occur by two modes, either by sprays of virus-laden respiratory droplets or by the eventual inhalation of droplet nuclei: microscopic aerosol particles consisting of the residual solid cores of evaporated respiratory droplets (Asadi et al., 2020). At a mechanistic level, particulate matter (PM) concentration has been shown to be linked with increased infection rates in many of the virus-related outbreaks in the past two decades caused by ribonucleic acid (RNA) viruses (Mishra et al., 2020). Examples include the severe acute respiratory syndrome (SARS) in 2003, H1N1 swine influenza pandemic in 2009, H5N2 influenza outbreak in the United States and the measles outbreak in 2019.

For other diseases, recent studies show consistently increased odds of healthcare encounters related to seasonal influenza with elevated PM2.5 exposure estimates averaged across several lag periods, 0-28 days (Landguth et al., 2020). Such results question the six-foot rule (which is defined as the safe distance to maintain against other people’s exhaled aerosols) as a guideline that offers little protection from pathogen-bearing small aerosols, for these may be continuously mixed through an indoor space. In the specific case of AQ, research on Covid-19 and other respiratory illnesses can be divided into:

1. studies that are concerned with the transmission of the pathogen, primarily related to aerosol dynamics;
2. studies related to the effects of certain pollutants on the immune response function, influencing the severity of disease symptoms and probability of death; and
3. studies analysing the impact of Covid-19 on people with previous co-morbidities.

Evidence on point 1 is relatively limited at the time of finalising this study, which considers published studies. However, a small but important amount of substantial evidence in a few studies points to the airborne route as dominant. Instead, there is substantial evidence for (2), and likely also for (3), although drawn from a number of other respiratory diseases resembling Covid-19 and its causing virus.

Most support for the alleged relationships between air pollution and Covid-19 may therefore come from age-related studies. Age is one of the most important prognostic factors associated to Covid-19 lethality (El Hasbani et al., 2020; Pearce et al., 2021). The rationale is that elderly people, living in highly polluted areas for a long time, could acquire higher levels of predisposition to displaying an increase of their hyper-inflammatory biomarkers. This cascade of events has been shown to lead to pulmonary fibrosis or other types of organ damage due to interaction with pollution and with further reactive oxygen species (e.g. the latter activating the NLRP3 inflammatory, Stout-Delgado et al., 2016). Also, dementia or Alzheimer’s disease, developed mainly in the oldest section of the
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Population, is described to relate with an overexpression of the angiotensin-converting enzyme-2 (ACE-2) via reactive oxygen species production and the subsequent activation of the NLRRP3 inflammasome (Kehoe et al., 2016). As mentioned, SARS-CoV-2 infection has also been linked to inflammation via ACE-2 receptors.

Experimental studies conducted for other respiratory viruses support the hypothesis that AP exposure may facilitate the occurrence of Covid-19 infection through a decrease in immune response. In vitro, animal and human studies have reported that exposure to air pollutants leads to increased mucosal permeability and oxidative stress, decreased antioxidants and surfactant antimicrobial proteins, as well as impaired macrophage phagocytosis (Bourdrel et al., 2021). In addition, SARS-CoV-2 entry in host cells through ACE-2 requires the cleavage of the viral spike protein by proteases, and such protease activity may be increased by AP, as is documented for several other respiratory viruses (Zhu et al., 2021).

In addition, concerns exist that long-term conditions, resulting from Covid-19 infections can be worsened by previous and current AP exposure, increasing hospital admissions for respiratory and cardiovascular diseases. This may have a direct impact on Covid-19 symptom severity, since the body’s ability to respond to the infection is further compromised. This also means that individuals with a history of exposure to AP are more likely to have comorbidities making them more susceptible to severe health impacts when faced with a viral infection (Roychoudhury et al., 2020). This includes cardiovascular diseases, vasculitis, respiratory diseases, diabetes and hypertension. Air pollution may increase Covid-19 morbidity and mortality through its action on associated co-morbidities. Experimental studies conducted for other respiratory viruses support the hypothesis that AP exposure may facilitate the occurrence of Covid-19 infection through a decrease in immune response. In vitro, animal and human studies have reported that exposure to air pollutants leads to increased mucosal permeability and oxidative stress, decreased antioxidants and surfactant antimicrobial proteins, as well as impaired macrophage phagocytosis (Bourdrel et al., 2021). In addition, SARS-CoV-2 entry in host cells through ACE-2 requires the cleavage of the viral spike protein by proteases, and such protease activity may be increased by AP, as is documented for several other respiratory viruses. On point 3 mentioned above, AP may increase Covid-19 morbidity and mortality through its action on associated co-morbidities.

To date, however, there is substantially less evidence for Covid-19 disease regarding impacts of AQ on SARS-CoV-2 virus transmission arising from field studies and epidemiological data. In relation to the role of PM2.5, PM10 and NO2, in particular for Covid-19 spread and lethality, evidence is as yet inconclusive. Studies often used different research methods or did not generally include potential confounding factors.

4.2. Role of airborne transmission in the Covid-19 pandemics

Aerosol transmission has been identified to occur in other coronaviruses and other respiratory viruses, which offers reason to believe that it could be important for SARS-CoV-2 as well (WMO, 2021). Insomuch as particulate matter might serve as a transport medium for virus agents enhancing aerosol stability or virus survival on aerosols, it is reasonable to expect that it might similarly enhance SARS-CoV-2 transmission potential. This is consistent with recently emerged strong evidence showing SARS-CoV-2 virus as predominantly transmitted through aerosols, therefore urging a change in public health measures (as they still fail to treat the virus as predominantly airborne). Silent (asymptomatic or pre-symptomatic) transmission of SARS-CoV-2 from people who are not coughing or sneezing accounts for at least 40 percent of all transmissions. In fact, long-range transmission of the virus between people in adjacent rooms in hotels or hospitals, who were never in each other’s presence, has been documented (Greenhalgh et al., 2021).
For other diseases, aerosols have been observed to remain in the air for an extended period of time and be carried over greater distances (i.e. > 6 metres, such as in reported outbreaks of tuberculosis, measles, and chickenpox, Klompas et al., 2020). Transmission of SARS-CoV-2 in a range of PM from submicrometer to supermicrometer ranges has already been reported. In fact, virus size for already known viruses can range from 20 nanometres (nm) to as large as 500 nm, with SARS-CoV-2 being approximately twice the size of influenza A. However, as viruses may travel embedded in larger particles, filtration of sizes larger than 140 nm may be efficient for small viruses as well (Chua et al., 2020). Also, the dynamic behaviour of a particle may not correlate exactly with its size, since depending on the containing matrix and aerosol’s structure, a small particle may behave as a larger particle in its dynamic properties. Respiratory droplets are typically 5-10 micrometers (µm) in length, while aerosols are smaller than 5 µm. On the one hand, controlled experiments from ill (and infectious) patients indicate a variable amount of viruses (with differences of the order of several thousands) contained, depending on the size of aerosols (Milton et al., 2013). On the other hand, no study has reported a significant correlation between the virus concentration and PM diameter.

Airborne control measures (as for when an infected person exhales, speaks, shouts, sings, or sneezes), include ventilation, air filtration, reducing crowding and the amount of time people spend indoors, wearing masks whenever indoors (even if not within 6 feet or 2 metres of others). Special attention should be paid to mask quality and fit, and higher-grade personal protective equipment (PPE) for healthcare and other staff when working in contact with potentially infectious people.

Aerosol sizes and protection measures are still a matter of great controversy. Possibly one of the reasons is the confusion emanating from different understandings of the terminology introduced on the concept of aerosols during the last century. This created poorly defined divisions between ‘droplet’, ‘airborne’, and ‘droplet nuclei’ transmission, leading to misunderstandings over the physical behaviour of these particles (Tang et al., 2021). In essence, all are aerosols, as they can be inhaled directly from the air. Ventilation is therefore of the utmost importance, as the tiniest suspended particles can remain airborne for hours, therefore constituting an important route of transmission. Under these conditions, air replacement or air cleaning mechanisms become much more important. As reported in some studies, asymptomatic or pre-symptomatic transmission of SARS-CoV-2 from people who are not coughing or sneezing is likely to account for at least a third, and perhaps up to 59%, of all transmission globally (Greenhalgh et al., 2021). It is thus a key way in which SARS-CoV-2 has spread around the world, supportive of a predominantly airborne mode of transmission.

The enhancing role of PM in virus-to-person interaction has also been highlighted. The complexities associated to the potential binding of virus particulates to PM have been hypothesised on the basis of former studies with similar viruses, although it is clear that more research is needed in this direction. Although other studies have failed to capture viable SARS-CoV-2 in air samples, this is to be expected. Sampling of an airborne virus is technically challenging for several reasons, including the limited effectiveness of some sampling methods for collecting fine particles (Greenhalgh et al., 2021). In fact, measles and tuberculosis, two primarily airborne diseases, have never been cultivated from room air. A crucial implication of this airborne spread is that the quality of the mask matters for effective protection against inhaled aerosols. Masks usually impede large droplets from landing on covered areas of the face, and most are at least partially effective against inhalation of aerosols provided there is high filtration efficiency and a good fit.

4.3. Polluted cities and the occurrence of Covid-19

Europeans are not all affected by AP in the same way, which raises questions about potential differences in Covid-19 incidences. Whereas Eastern Europe is more impacted by high levels of PM2.5 due to its higher emission rates, nitrogen dioxide (NO2) concentrations are highest in the most densely populated areas in western Europe and are linked to local sources such as traffic,
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domestic and industrial emissions. A few studies have shown a possible link between AP and Covid-19 pulmonary severity, which is related to increased fatality (Li et al., 2021; WMO, 2021). Proposed factors are high concentrations of tropospheric NO2, as detected by the sentinel-5P satellite. The NO2 build-up close to the surface was hypothesised to be associated to a high incidence of respiratory problems and inflammation. This chronic exposure to NO2 is consequently argued to be an important contributor to the high Covid-19 fatality rates observed in these regions. There are reports of multiple gastrointestinal symptoms in patients with Covid-19 linked to poor AQ and high levels of particulate matter (Lai et al., 2021). Moreover, in addition to industrial and urban pollution, health disparities are seen among minorities and immigrants who account for the majority of seasonal farm workers frequently exposed to PM in agricultural dust.

An additional vulnerability factor appears to be the association between increased deaths from Covid-19 in areas with high levels of AP, more specifically, elevated exposure to the toxic component NO2. While the mechanisms by which AP modifies severity of Covid-19 responses have yet to be determined, very little is known about the host factors that determine mild or even asymptomatic responses compared with life-threatening or fatal outcomes. As with many inflammatory diseases, it is the combination of specific host and environmental factors in certain individuals that provokes more severe disease outcomes. What does appear to be emerging from evidence generated thus far is that environmental air pollutants have a positive correlation with overall Covid-19 severity. A study exploring Covid-19 cases in Italy, France, Germany and Spain reported a positive association between PM2.5 and PM10 concentrations between February and April 2020 and the number of SARS-CoV-2 infected cases, while a negative association was found for ozone (O3; Bourdrel et al., 2021). In China, city-specific effects of PM10 and PM2.5 on daily confirmed Covid-19 cases were examined in more than 70 cities. Short-term lagged (7 and 14 days) increases in PM2.5 were associated with daily Covid-19 confirmed cases, and the magnitude of effect was greater for PM2.5 than for PM10.

It is still unclear, however, how long this virus remains infectious in ambient air and whether the low viral load contained within the aerosol is sufficient to induce infection. Atmospheric interactions between gases and viruses are also complex and depend on meteorological contributing factors such as ultraviolet (UV) radiation and relative humidity. By reducing UV radiation (which has antiviral activity), air pollutants may promote viral persistence in ambient air and also reduce vitamin D synthesis, and thus may play a role in the immune response against viral infections.

In summary, studies should be conducted that analyse differences in Covid-19 rates and incidences to check whether same patterns apply and the mechanistic link is justified. Potential linkages with places presenting poorer AQ standards, where more vulnerable people are likely to live, should also be conducted urgently.

4.4. Climate as facilitator, or not, of Covid-19 pandemics

Although there is as yet no consensus on the subject, it seems likely that a decrease in humidity leads to dehydration of macro droplets into smaller droplets that are able to remain in suspension in the ambient air (Bourdrel et al., 2021). An increase in humidity may lead to increased water content of viral droplets, and thus increased weight, enabling them to fall to the ground faster. In the case of temperature, whereas colder conditions lead to an increase in the transmission of other respiratory viruses (such as influenza), the results are thus far contradictory on the link between Covid-19 and temperature. Some recent studies have also tried to investigate the link to meteorological factors by studying the potential role of seasonality in disease dynamics (López and Rodó, 2020). The explicit addition of climate was evaluated as significant in a process-based model tailored to simulate the potential role of both, seasonality and temperature, albeit more studies are similarly needed (Rodó et al., 2021).
The base mechanistic assumption of the linkage with meteorological factors is – similar to influenza and other milder respiratory viruses – that, dry (relative humidity <20%) and cold air affects both immunity and viral spread. A reason might be the fact that dry air may facilitate airborne viral transport, and that cold conditions, in addition to low humidity, may impair the functioning of airway ciliated cells.

Additional challenges to clarify these relationships include the non-independence of certain meteorological variables, exclusion of other social and behavioural modulating factors when testing for associations, residual confounders that are not properly controlled for, data quality and heterogeneities across countries, high proportion of asymptomatic cases, and the difficulty of ascertaining intercomparability for data on Covid-19 cases at subnational and city levels.

Peer reviewed laboratory studies of SARS-CoV-2 sensitivity to meteorological and AQ variables are still rare, given the time required to perform and publish such work. Results of available studies do include some evidence of meteorological sensitivity. This includes findings regarding the survival of SARS-CoV-2 in aerosols as well as on surfaces, which appears to decline in the presence of increased UV-A and UV-B radiation (Storm et al., 2020). Results for humidity are less clear, with some indication that there is a slight increase in virus survival at lower relative humidity (20%). Results of laboratory studies attempting to uncover relationships under controlled conditions are critical for understanding the mechanistic basis of the relevance of aerosols to Covid-19 transmission. At the same time, though, these studies differ from epidemiological studies in which the focus is on disease risk at the population scale. Their transferability to real-life settings is, however, not always straightforward.

It has so far been hypothesised that cold and dry conditions are particularly suitable for aerosol transmission of other viruses in mid-latitude winter settings, attributing higher importance to aerosol transmission in temperate climates. Other sensitivities might be observed in warm and humid climates that, similar to influenza, are largely unresolved. It is now well established that SARS-CoV-2 transmission commonly occurs in closed spaces. As is often noted, people tend to spend more time congregating in poorly ventilated environments when it is cold/hot and/or precipitating outside (ECDC, 2020), and this behavioural change might also help explain seasonal patterns in the risk of respiratory viral infections like those producing Covid-19. In hot climates, people tend to escape the heat, spending increased time in air-conditioned indoor spaces. The importance of these behavioural factors relative to direct environmental influences on virus survival or host response is an active area of research, and no firm conclusions can be drawn for Covid-19 at this time (WMO, 2021). A few studies point to the fact that exceptionally high temperatures, combined with health inequities exacerbated by the Covid-19 outbreak, may have increased vulnerability to heat in 2020.

4.5. Covid-19 surges in meat factories as indicators of potential foodborne transmission of SARS-CoV-2

Covid-19 infection clusters were already reported in the first wave of the pandemic in Europe, related to both the fresh meat and seafood industry in different countries, which caused concern about potential foodborne transmission of SARS-CoV-2 (Pittito et al., 2021). Although it is hard for SARS-CoV-2 to replicate after leaving the host, evidence exists that the virus can survive even on frozen surfaces for prolonged periods of transit and export. It remains to be confirmed, however, whether causes are the handling of contaminated food, or the facilitated airborne transmission in conditions that resemble those (cold and dry) in natural open spaces in winter in temperate areas, in which the virus can be more easily aerosolised and persist for longer.

Most of the current knowledge on the risk of environmental transmission of SARS-CoV-2 through the food chain is based on previous studies of other CoVs, such as SARS-CoV-1 and MERS-CoV, but
not as yet on SARS-CoV-2 (Dhama et al., 2020). Enveloped viruses are typically adsorbed on surfaces via electrostatic, van der Waals, and hydrophobic interactions, which is highly dependent on the properties of different surfaces. To investigate the surface behaviour of SARS-CoV-2 under real scenarios, the precise characterisation of the surface properties and the associated microenvironment, such as humidity, pH, and biofluid, is needed. In addition, more attention should be paid to the adsorption and desorption characteristics of SARS-CoV-2 at both cellular and tissue surfaces of food product, to evaluate the viability of SARS-CoV-2. Based on this understanding of the underlying adsorption and survival mechanisms, new packaging and shipment surface materials could be designed to reduce or prevent the viability of SARS-CoV-2. To date, the number of studies or news appearances reporting such clusters of cases (e.g. outbreaks) is limited, and possibly concentrated to the first months of the pandemics.

The affected population in specific workplaces, not only healthcare workers, but also workers in food/meat-processing factories wearing surgical masks, had become infected without being involved in aerosol generating procedures. Regarding potential mitigation actions to reduce the risk of infection in these workplaces, disinfection is still considered an essential tool in the prevention of foodborne transmission of SARS-CoV-2. Ultraviolet light is currently used for the disinfection of any pathogen, as it is with SARS-CoV-2, on the surface of imported packages. At a personal level, the use of N95 face masks and eye-protective equipment should be encouraged. However, given the frequent and extensive infection processes that would currently be required, combined with the health concerns regarding the use of the disinfection products, alternative ideas are still needed for the development of effective disinfection methods with low side effects. The integrity and viability of SARS-CoV-2 on packaged, stored and transported materials needs to be fully evaluated, and the relationship between abundance, viability, and infectivity of SARS-CoV-2 clearly established.
5. Policy options

**Policy option 1. Increase the recognition of the airborne transmission of SARS-CoV-2**

There is consistent and increasing evidence that SARS-CoV-2 spreads by airborne transmission. Although other routes can contribute, the airborne route is likely to be the dominant mode. The public health community and health agencies could act accordingly, referring to this mode as the principal mode of transmission in their recommendations and statements, and work to issue corresponding occupational guidelines.

**Policy option 2. Coordinate the development of early-warning systems for Covid-19**

Early-warning systems could be developed by research groups and companies and quality-controlled comparison exercises stimulated and funded by international agencies and governing bodies. Results of such an initiative could be based on open data and results made publicly accessible. Process-based modelling studies at this time begin to anticipate that Covid-19 transmission may become seasonal over time, suggesting that extrinsic climatic and environmental factors (also AP and AQ) may be relevant for disease prediction.

Therefore, articulated networks of expert groups and institutions could be supported for the optimal forecasting of Covid-19 (and other potential viruses) in the future. In summary, the interaction between meteorology and AQ should also be considered, as it can potentially be very relevant throughout pandemic waves. In addition to its direct impact on virus stability, meteorology may also influence virus transmission through its indirect effects on AQ.

**Policy option 3. Upgrade the monitoring network for aerosols in Europe**

An improved network of aerosol and AP monitoring stations in Europe could be encouraged. A new generation of AQ stations could supply a more updated portfolio of a wider variety of atmospheric chemicals (in addition to those few that are at present mandatory under European Union regulation). These physical, chemical, as well as biological determinations of the aerosols we breathe could, whenever possible, be provided on a near-real-time basis for a broader range of AQ composition. The current EU regulatory legislation is very limited in this regard.

**Policy option 4. Investigate the links between AQ and Covid-19**

Research quantifying links between AQ factors and Covid-19 is needed urgently. It is critical that analytical and modelling studies are properly designed to: accurately account for confounding factors; consider both direct and indirect extrinsic environmental effects; integrate limitations in the Covid-19 data record; make use of mathematical or statistical techniques to explicitly integrate data errors in models; report uncertainty ranges; evaluate predictive capacity properly (for out-of-fit data); and apply appropriate statistical or process-based modelling techniques.

**Policy option 5. Higher investment in epidemiological and laboratory research**

In vitro, in vivo, as well as epidemiological and modelling studies at the population level are also strongly needed, in particular to explore more precisely the particle-virus interaction in air and in person-to-person transmission, as well as to precisely quantify any potential sensitivity and dose-response function of the virus. No studies exist as yet on the specific effects that the chemical nature of aerosols may exert in facilitating, or not, SARS-CoV-2 transmission, or in conditioning human susceptibility (e.g. in enhancing inflammatory responses, promoting the cytokine cascade etc.).

These studies should be supported. Effects exerted by the aerosols' chemistry that may explain geographical/spatial propagation in Covid-19 cases within and between populations are thus far contradictory, and deserve more investigation. Research on aerosol size and chemical composition with regard to the viability and infectivity of SARS-CoV-2 are also needed urgently. In parallel, better
precision equipment and methodologies to monitor the presence of viruses – and other pathogens – could be developed. The availability of this methodology and the installation of the necessary equipment in critical sites, ideally offering rapid detection of viruses in aerosols, would have a great impact for the timely reduction of transmission and the control of pandemics.
6. Appendix I. Data quality and methodological considerations

Open and free access to the best quality data is required for effective extraction of relevant information at these critical stages in the pandemic progression worldwide. Good governance and sustainable funding are required to establish truly interdisciplinary studies and equitable cooperation, enabling systemic change at international, national, regional and local levels. This proposition is not new but brings multiple challenges, including establishing principles of cooperation, for example in terms of clarity of parameter definitions, format standards for data interoperability, statistical methods, data resolution, data aggregation methods, frequency, updates, standardised protocols (for reporting, for example), meta-data requirements, code sharing, privacy considerations where applicable, etc... In some cases, open collaboration can run into conflict with national data policies (WMO, 2021).

This is a persistent challenge that calls for diplomacy and appropriate enabling environments to encourage open findability, accessibility, interoperability, and reusability (FAIR) data exchange. Indeed, the EU AQ Report 2020 (addressing policy makers): 'The overall impact of AP on heart and chronic lung disease is more than large enough to motivate aggressive reduction policies. Such policies that protect the population from the effects of AP are likely to protect as well against Covid-19 deaths possibly attributable to AP.

Data quality, usability, and interoperability pose significant challenges for studies of AQ influence on Covid-19 risks. These challenges apply to at least three types of data: the Covid-19 related outcome variables, meteorological and air quality datasets, and data on other potential influences on Covid-19 risk, including space- and time-varying influence of social and behavioural measures (e.g. non-pharmacological interventions, NPIs) and other behavioural factors (WMO, 2021).

With respect to the outcome variable, Covid-19 analysis has, in general, struggled with inconsistent and predominantly unreliable and not fully comparable data on Covid-19 case numbers, These challenges have stemmed from uneven policies on and access to Covid-19 testing, reporting delays, limited health system resources, and the lack of existing standards and mechanisms to create and maintain databases for pandemic monitoring and response (Gardner et al., 2020). Given these limitations, potential biases in the health data used in the analyses will very likely exist.

The use of quality controlled centralised Covid-19 databases such as the Johns Hopkins University Coronavirus Dashboard (Dong et al., 2020), the New York Times Case Inventory (The New York Times, 2020), Our World in Data Covid-19 database (Roser et al., 2020) the COVID Tracking Project (The Atlantic, 2020), the Financial Times excess mortality database (Burn-Murdoch et al., 2020), or others offers some confidence in the raw data used. Nevertheless, even these data aggregators can inherit data artifacts from contributing sources, such that additional quality control is required when the data are applied to large, automated analyses (Badr et al., 2020).

For the meteorological and air quality (MAQ) variables themselves, studies typically made use of in situ station-based data and the Copernicus Atmospheric Data Store for main air pollutants (Copernicus Atmosphere Monitoring Service, 2020). The quality of these data sources should, however, be verified with data producers or directly with the information provided in the respective peer reviewed publications.

To quantify associations between these weather and environmental factors and variations in Covid-19, predictive models should also consider other intrinsic and extrinsic factors that influence the trajectory of the epidemic. and include time-varying non-environmental factors that have evolved over the course of the pandemic, such as mobility, adoption of protective behaviours, and the implementation and enforcement of NPIs. There is no clear consensus regarding the best
sources of information on these diverse epidemiological factors, and in many cases there is simply an absence of reliable data (WMO, 2021). Given these limitations, it is critical that empirical studies of meteorological and environmental influences clearly state a rationale and methodology for the treatment of non-environmental factors, both to ensure that a best effort is made to control for relevant confounders and to indicate relevant limitations, assumptions, and uncertainties. This risk must be acknowledged, communicated, and guarded against. Collaboration across fields, including by climate data providers, epidemiologists, health data scientists, and experts in risk communication, is particularly important in this regard.

Both longitudinal and cross-sectional studies of the environmental influence on Covid-19 risk must, at a minimum, account for behavioural change and public health interventions in response to or with the aim at controlling Covid-19 spread. While an argument can be made that Covid-19 awareness and interventions were low in the very earliest stages of the pandemic, it is evident that already by late spring of 2020 there was generalized change in behaviours and policies that influenced disease transmission and that may interfere with any potential environmental effect, if present, also that exerted by pollution.

It is therefore complex to account for these diverse behavioural changes and interventions when assessing the impact of environmental factors on Covid-19. Measures of personal mobility (Google LLC, 2020), inventories of Covid-19 response policies (Hale et al., 2020), pollutant emissions changes (Guevara et al., 2020), and dates of cessation of in-person schooling or other public activities (Auger et al., 2020) have all been employed as controls alongside pollution variables.

In addition, studies need to adjust for factors that might considerably influence the estimate of the response variable, including Covid-19 testing rates and reporting methodologies/delays. Emerging research is now considering the global and regional deployment of mass-scale Covid-19 vaccinations and their regional differences, including vaccine production capacities, population coverage, at a time when new variants set a new and even more complicated scene.

Research in the topics of relevance for the current Covid-19 pandemic has to face all kinds of unprecedented pressures, essentially governed by fast processing for prompt publication and the high demand for sound results. These external conditions do not favour strict and quality-controlled procedures and the maintenance of good research practices (see Fig. 7 for a proposition of best practices to be kept). For instance, a clear separation should be made among laboratory studies performed under controlled conditions—which are critical for informing mechanistic understanding of environmental sensitivities—and epidemiological studies that attempt to infer potential meteorological or air quality influences.
Other noted limitations throughout the review process often have to do with the lack of full statistical accuracy when reporting on relationships, in particular correlations. For instance, Li et al. (2020) reported a significant correlation between Covid-19 incidence and the AQ index (AQI) in both Wuhan ($R^2 = 0.13$, $p < 0.05$) and XiaoGan ($R^2 = 0.223$, $p < 0.01$), but the percentage of variance accounted for by these associations did not even reach 5% of the variability and the maximum reported values less than 10% (e.g., between NO2 and Covid-19 incidence in Wuhan: $R^2 = 0.329$, $p < 0.01$). A similar result was reported by Mai et al. (2021), highlighting the need for more robust approaches to these controversial associations. These type of results cast serious doubts on the validity and relevance of resulting conclusions, given the problems in the experimental design and statistical approaches.

Approaches with time-series analysis studies also varied greatly, from simple ones (e.g., Li et al., 2020) performing linear correlations to more solid statistical analysis (Landguth et al., 2020). The latter used Bayesian spatial linear statistics with covariance models, employing uniform and uninformative priors for the regression parameters. In very few of those studies the resulting models were cross-validated. For instance, Landguth et al. 2020 evaluated results using a leave-one-out data...
cross validation approach). Fully operational models proving skilful with out-of-fit data intervals are still missing at the time of the completion of this report.

Methodological approaches to investigate the health impacts of AP on epidemics should differ from those used for chronic diseases, but the methods used in these studies have not been appraised critically. Effective communication among researchers, data providers, disseminators of information, and end users is therefore a critical component of successful climate services, particularly in the case of MAQ-informed Covid-19 risk analysis (WMO, 2021). Public health policies and personal behavioural decisions are being made quickly and with imperfect information, and a miscommunicated or ineffectively communicated informed risk analysis has the potential to do substantial harm (Carlson et al., 2020).

For this reason, the research and forecast communities must assume extra responsibility when disseminating results (see suggested procedure in Figure 7 above and in Zaitchik et al., 2020). This includes clear, plain-language summaries of key findings, limitations of the analysis, generalizability, and relationship to other relevant studies. It also includes engaging with media and social media in a measured and balanced manner. In the case of Covid-19, researchers and data providers must engage carefully to pre-empt misinterpretation or over-interpretation of results (Carlson et al., 2020).

Various studies that suffer from important limitations, have also reported a link between AP exposure and Covid-19 morbidity and mortality in humans. For instance, from an epidemiological point of view, several concerns may arise from non-randomized studies that have investigated this relationship. First, the values for the number of confirmed Covid-19 cases, including the number of deaths, are often determined without standardised methodologies and tools, and without reliable testing in many cases during the first months of the Covid-19 pandemic. These may have led to severe underestimations in the total number of Covid-19 ‘outcomes’. Secondly, the studies suffer from AP exposure misclassification.

Available assessments come from either satellites or local monitoring stations without any detail on individual exposures. Aside from the study by Travaglio et al. (2021) with individual level data from the UK Biobank, all epidemiological studies are ecological with aggregated assessments at the population levels (countries, counties and cities); thus, more longitudinal studies with individual level data are also needed (Villeneuve and Goldberg, 2020).

Ambient outdoor pollution concentrations can be a general indicator of AQ, but they are not a reliable substitute for the exposure experienced by a given individual. In this context, using exceedance levels established by public authorities is also limiting, although it can be considered as a proxy of chronic exposure to elevated levels of AP. Another weakness encountered arises from the fact that both AP and infections are auto-correlated both spatially and temporally, which has not always been taken into account so far by many of the existing studies. Therefore, studies lacking a control for spatio-temporal autocorrelations have been shown to bias the estimation of the results.

In this context it has to be underlined that Covid-19 cases mainly arise from clusters of infections or super-spreading events, (i.e. at work, that are not taken into account in epidemiological studies (Villeneuve and Goldberg, 2020). Furthermore, a great proportion of analyses have not properly taken into account the role played by important confounders, i.e. factors related to both AP and Covid-19, such as population density (Villeneuve and Goldberg, 2020). The problem of confounders is extensive to many studies that approach this problem from typical social sciences statistical designs, testing for odds ratios or limited cohort studies, due to the short records available.

Especial care should be held in excessively underscoring those results, for controlling for all confounders might result unrealistic. In fact, viral spread may vary considerably across different areas depending on population density, the time of the virus introduction, and the time of infection control measures, such as physical distancing, mask requirements, test policies or stay-at-home
directives. All these factors influence the dynamics of the disease that can be estimated through the daily number of new cases or through the calculation of the basic reproductive number (R0) and effective reproductive number, both depending on transmissibility, contact rates and duration of contagiousness, as well as on virus mutation time. As AP may also influence both transmissibility and duration of infectiousness, the analysis of the impact of AP on the dynamic of Covid-19 has to take into account confounders such as population density, the time of the virus introduction and the time of introduction of infection control measures (Heederik et al., 2020).

Additional limitations of these observational studies include the fact that most environmental health studies estimate conditional associations between non-randomized environmental exposures and health outcomes by directly regressing observed data without conceptual and design stages (Bind and, Rubin, 2019). This approach, that is well documented does not guarantee valid causal inferences in general, especially in AP studies in which environmental exposures can be correlated with each other and effects are small (Rubin, 2007; Bind 2019). Disentangling independent air pollutant effects has been a challenge for observational studies, but can be achieved if the latter is embedded into a hypothetical multi-pollutant randomized experiment (Bind, 2019).

Moreover, to assess the robustness of epidemiological conclusions, AP studies should systematically consider sensitivity analyses that either: 1) vary the magnitude of the relationships between the unmeasured background covariates and both the exposure assignment mechanism and the outcome; or 2) study deviations from the assumed exposure assignment mechanism or 3) approach potential relationships by inspecting how shapes in the epidemiological dynamics appear consistent at a multiplicity of time and spatial scales. Further investigations taking into account these limitations are needed to better understand the relationship of AP exposure to Covid-19.
7. Appendix II. Air collection methodologies

Although normally overlooked, differences among techniques and methodologies used for SARS-CoV-2 identification and quantification in aerosols may be critical to assess the presence of the virus in aerosols. Previous studies have demonstrated that the efficiency of different samplers for collection and preservation of the infectivity of microorganisms can vary as a function of the specific microorganism. This is an important technical problem compromising results obtained and conclusions drawn. For instance, Ratnesar-Shumate et al., (2021) compared the performance of eight different equipment (low-flow aerosol sampling devices) to both sample SARS-CoV-2 virus particles and obtain viable virus in small particle aerosols.

The influence of sampling duration on recovery of infectious virus was also evaluated. Similar concentrations of infectious SARS-CoV-2 were measured in aerosols for the majority of the samplers tested, with the exception of the midget impingers, which measured significantly lower concentrations of SARS-CoV-2. Additionally, in three of the four impingers tested, additional clean airflow through the device following collection of infectious virus resulted in a decrease of the infectious concentration of virus over time, suggesting that virus was being inactivated and these devices may not be suitable for sampling for long durations (Ratnesar-Shumate et al., 2021).

More research and consensus methodologies are encouraged as discrepancies among studies may simply arise from non-standardised approaches to sample collection and to the proper extraction of genetic material. For instance, when dealing with the aerosol’s isolation of SARS-CoV-2 viruses, several equipment and methodologies have been used that may add uncertainty to the results obtained. In this regard, there is no uniform and publicly validated approach to the sampling of air, RNA extraction from aerosols and ulterior sequencing protocols (or amplification if needed), which makes intercomparison difficult or even impossible.

For instance, Noor et al, 2021 conducted air sampling for 48 h during a 29 days sampling period using two types of instruments; an AQ sensor known as AiRBOXSense (AIRBOXSENSE V3.0, UKM Tech. Sdn Bhd, Malaysia) and a low volume sampler (LVS) (MINIVOL, AirMetrics, USA). Instruments were treated using ultraviolet light for 20 min (UV) (UV-C 253.7 nm), further disinfected with 70% alcohol and calibrated before being translocated to the next wards.

The same instruments were used to avoid variability during sampling but AiRBOXSense was used to continuously measure PM2.5, while the LVS was used to determine the virus loading in PM2.5 trapped on filter paper (WHATMAN glass microfiber filters, Grade GF/F) with a tight specification of 0.6–0.8 μm particle retention and pure borosilicate glass structure, GF/F. A 5 L min⁻¹ of air was drawn into the AiRBOXSense. Instead, the Minivol’s pump draws air at 5 L min⁻¹ through a filter paper. Each filter paper was collected after 48 h of sampling and stored in a sealed container and kept in −80 °C laboratory freezer. The filter papers were extracted for viral load analysis using reverse transcription quantitative real time polymerase chain reaction (RT-qPCR) approach. The former is an example of a methodological pathway to virus determinations that is not necessarily followed by other studies.
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Epidemiological studies of Covid-19 have, in most cases, provided inconclusive results to date regarding the role of air pollution in the transmission of the SARS-CoV-2 virus and the geographical spread of the disease, both regionally and globally.

The present review analysed just under 6 000 articles published up to 31 May 2021, looking at the role of pollution and air quality factors in the transmission of SARS-CoV-2 and in the geographical differences in Covid-19 propagation. A body of evidence shows that chronic and short-term exposure to different fractions of aerosols and types of air pollution exacerbates symptoms, affects co-morbidities and increases mortality rates for respiratory diseases similar to Covid-19, as well as for Covid-19. Although other pathways can contribute, the airborne route is likely to be the dominant mode.

There is consistent and increasing evidence that SARS-CoV-2 spreads by airborne transmission, and it is possible that different variants have different environmental sensitivities. Safer indoor environments are required, not only to protect unvaccinated people and those for whom vaccines fail, but also to deter vaccine-resistant variants or novel airborne threats that may appear at any time.

The public health community, governments and health agencies should act accordingly, referring to this mode as the principal mode of transmission in their recommendations and statements, enhancing associated research and improving monitoring networks.