

# Are there medium to short-term multifaceted effects of the airborne pollutant PM<sub>2.5</sub> determining the emergence of SARS-CoV-2 variants?

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## ABSTRACT

The COVID-19 pandemic has been characterised by successive outbreaks effecting large swathes of the world's populations. These waves of infection have been mainly driven by a number of more transmissible variants which appear to evade the populations' immunity gained from previous outbreaks. There appears to be a link between COVID-19 and a ubiquitous airborne pollutant called particulate matter, PM<sub>2.5</sub>. Particulate matter through a number of mechanisms, including its anthropogenic effect, appears to be associated with the incidence and the mortality related to the COVID-19 pandemic. This paper poses a number of hypotheses on the short to medium-term mechanisms whereby PM<sub>2.5</sub> may be party to the natural selection of SARS-CoV-2 virus, with the consequent emergence of variants.

## Background

Airborne particulate matter has been suggested as a co-factor for SARS-CoV-2 infection [1]. The SARS-CoV-2 pandemic has reappeared in subsequent waves in the form of more transmissible and potentially more virulent variants. It has been suggested that particulate matter PM<sub>2.5</sub> may not only responsible for SARS-CoV-2 transmission, but may also have been involved in this virus' evolution [2,3].

The first study suggesting an association between PM<sub>2.5</sub> and SARS-CoV-2 was noted in the United States, whereby a link between long-term exposure to particulate matter PM<sub>2.5</sub> and COVID-19 related mortality was demonstrated [4]. A recent preprint has confirmed that PM<sub>2.5</sub> was a robust variable in connection with increasing SARS-CoV-2 rates [5]. Morphological evidence also confirmed that genes coding for SARS-CoV-2 were found attached to particulate matter [6].

A recurring set of mutations, mainly E484K, N501Y and K417N suggests SARS-CoV-2 may be undergoing convergent evolution [7]. This convergent evolution may be catalyzed by the presence of a common environmental mutagen such as the ubiquitous pollutant PM<sub>2.5</sub> which has repeatedly been shown to be a robust co-factor in the SAR-CoV-2 Pandemic [3,4,5,6,8].

### Hypothesis 1: Does particulate matter have adverse effects on pulmonary immunity increasing vulnerability to SARS-CoV-2?

Particulate matter adversely affects pulmonary immunity at all levels

of its defences which may occur in both the short and medium to long-term (Chart 1). This is more so with PM<sub>2.5</sub> as its micrometre diameters allow easy passage through the narrowest bronchioles and enter the alveoli. The mucociliary system is impaired by particulate matter disturbing its cleansing function of the respiratory tract. Pulmonary exposure to particulate matter appears to cause mucociliary paresis and promotes goblet cell mucus hypersecretion similar to tobacco smoking [9–11].

The respiratory epithelium is rendered more permeable at the cell junctions and cell membranes due to particulate matter. Respiratory epithelial permeability to viral invasion is further encouraged by allowing particulate matter-induced pro-inflammatory mediators which weaken the baso-lateral aspect of respiratory host cells and reducing the concentration of tight junction proteins [12].

Particulate matter may encourage uncontrolled viral dissemination by disturbing macrophage function. Inefficient clearance by viral phagocytosis may be due to deficient Human leucocyte antigen recognition, inhibition of cytokine production and altered function of toll-like receptor genes expressed on cell membranes [13]. Particulate matter exposure may influence ability of Natural Killer cells to eliminate cells infected by viruses [14]. Exposure to particulate matter PM<sub>2.5</sub> was linked to increased levels of antiangiogenic and proinflammatory cytokines [15].

Particulate matter exposure appears to affect CD4+ and CD8+ T cells leading to the suppression of interleukin IL-2 and interferon 1-γ production [16]. In severe cases of SARS-CoV-2 infection due to resultant

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significant loss of CD4+ and CD8+ T cells early in the infection, there appears to be delayed adaptive immune responses, leading to prolonged viral clearance [17].

### Hypothesis 2: Does PM<sub>2.5</sub> increase the ACE-2 receptor, the point of viral entry advantaging highly transmissible variants?

The occurrence of PM<sub>2.5</sub> spikes a few weeks prior to the emergence of SARS-CoV-2 variants may have primed the effected populations to be more susceptible to COVID-19. The point of entry of the SARS-CoV-2 virus is the Angiotensin II Converting Enzyme Receptor (ACE-2) which is commonly found on type-2 pneumocytes responsible for gaseous exchange and mucus producing goblet cells (Chart 1). Specifically the ACE-2 protein acts as the receptor for the attachment of the SARS-CoV-2 spike protein, consequently increasing the risk for infection as well as severity of the disease in humans.

Preclinical studies utilizing the murine model exposed to particulate matter impacted both the ACE-2 protein and TMPRSS-2 (transmembrane protease serine type 2) [18]. Both the ACE-2 protein and TMPRSS-2 are required for the entry of SARS-CoV-2 into respiratory host cells. Immunohistochemical assessments indicated that exposure to particulate matter increased the expression of ACE-2 protein and TMPRSS-2. Image cytometry demonstrated increased expression of ACE-2 protein and TMPRSS-2 specifically in the type-2 pneumocytes which are potential targets for SARS-CoV-2 [19]. In another murine model endowed with human ACE-2 receptors, the bronchial instillation of particulate matter significantly increased the expression of ACE-2 and TMPRSS-2 in the lungs [19]. Furthermore, particulate matter exacerbated the pulmonary lesions caused by SARS-CoV-2 infection in this mouse model [19].

In humans, during the COVID-19 pandemic in Italy, Borro et al showed that in response to exposure to PM<sub>2.5</sub>, bioinformatic analysis demonstrated increased DNA sequences encoding for the ACE-2 receptor

[20]. The bioinformatic analysis of the ACE-2 gene identified nine recognized nucleic acid sequences for the aryl hydrocarbon receptor. In the same study correlations were noted between PM<sub>2.5</sub> levels and COVID-19 incidence (R = 0.67, p < 0.0001), the mortality rate (R = 0.65, p < 0.0001) and the case fatality rate (R = 0.7, p < 0.0001) [20].

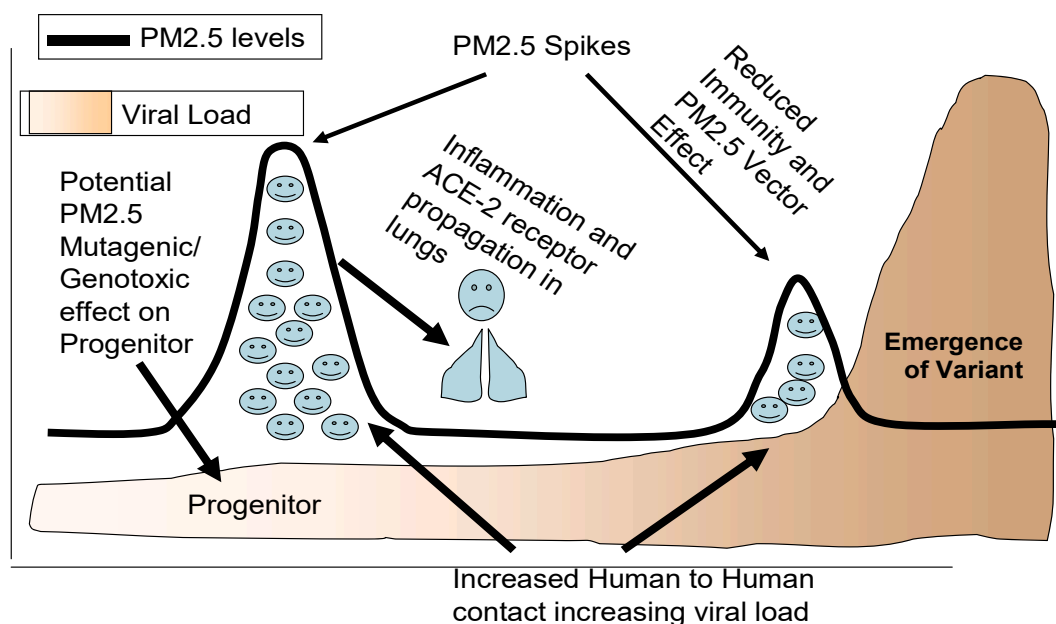
Pollution with both nitrous oxide and PM<sub>2.5</sub> has been shown to increase the concentration of ACE receptors in the lung [21]. Both pollutants induce an inflammatory change in the respiratory epithelium. This may occur with both chronic and acute inflammation. In an effort to cleanse the bronchial tree from pollutants, the number of mucus-producing goblet cells increase, with a consequent increase in these cells' ACE-2 receptors [21].

The above suggest a close link between exposure to particulate matter and the increase in the viral points of cell entry, the ACE-2 receptor. The increase PM<sub>2.5</sub> may have acted differentially according to the time before variant emergence. The spike in PM<sub>2.5</sub> a few weeks before the variant emerged, may have instigated an inflammatory response with a consequent induction in ACE-2 receptors in the respiratory tract. The PM<sub>2.5</sub> spike immediately prior to the emergence of the variant may have indicated heightened human to human contact increasing viral load, which in the presence of readily available points of entry, increased infection rates. In the presence of high infection rates and a higher viral load the possibility of viral mutation became a greater possibility.

### Hypothesis 3: Could PM<sub>2.5</sub> act as a vector for SARS-CoV-2 transmission giving variant an infectious advantage?

The COVID-19 pandemic appears to have spread during March 2020, from Wuhan in China, then to Qom in Iran and soon later to the Lombardy region in Northern Italy. An environmental variable common to all these three cities is the presence of elevated atmospheric levels of particulate matter [8,9]. Atmospheric particulate matter in the

## Short to Medium Term Effects of PM<sub>2.5</sub> Prior to Emergence of SARS-CoV-2 Variants



**Chart 1.** Schematic view of Atmospheric PM<sub>2.5</sub> levels with contemporaneous viral load leading to Emergence of SARS-CoV-2 Variant. First medium-term PM<sub>2.5</sub> spike associated with anthropogenic effect due to increased human activity and contact, leading to lung inflammation, ACE-2 receptor propagation, and potential PM<sub>2.5</sub> viral mutagenic induced variant emergence and genotoxicity to the progenitor expediting the latter's eventual displacement by the emerging variant. Second short-term PM<sub>2.5</sub> spike also related to diminished population immunity and potential PM<sub>2.5</sub> vector effect.

Lombardy region showed that out of 34 RNA extractions for the genes E, N and RdRP coding for SARS-CoV-2, twenty detected one of these genes [6].

High transmissions rates of SARS-CoV-2 infection were evident from outset of the pandemic [8]. At the pandemic's peak, the highest  $R_0$  SARS-CoV-2 achieved was estimated at 5.7 [22], significantly higher than the  $R_0$  1.4–1.67 of the H1N1 2009 Influenza pandemic [23] and 2.2 for SARS-CoV-1 [24]. The substantially elevated  $R_0$  compared to other epidemics suggested that besides human to human transmission, other variables including particulate matter may accelerate SARS-CoV-2 spread [25].

Setti et al. 2020, showed that COVID-19 spread in 110 Italian provinces correlated with atmospheric levels of both  $PM_{2.5}$  and  $PM_{10}$ . It was suggested that SARS-CoV-2 transmission could be further hastened by particulate matter carriage beyond the social distance of two metres up to 10 m [25]. In a similar study,  $PM_{2.5}$  and  $PM_{10}$  atmospheric levels correlated with COVID-19 infection rates in Italy and reaffirmed the hypothesis that particulate matter may also act as a vector for SARS-CoV-2 transmission (Chart 1) [1]. A physicist's model examining droplets behaviour when exhaled by the respiratory system of an infected person further gives credence to a vector effect of  $PM_{2.5}$  [26].

In a teaching hospital in Kuala Lumpur Malaysia, a study showed that the highest SARS-CoV-2 RNA on  $PM_{2.5}$  in the ward correlated with number of patients with COVID-19 and the absence of air purifiers. High levels ( $74 \pm 117.1$  copies  $\mu L^{-1}$ ) of SARS-CoV-2 genes on  $PM_{2.5}$  were noted in the single room ward without an air purifier compared to a general ward with an air purifier ( $10 \pm 7.44$  copies  $\mu L^{-1}$ ) [27].

The link between airborne pollution and infectious disease is not a novel one. Measles has the highest  $R_0$  of all infectious diseases with an  $R_0$  of 18 and has been closely associated with airborne pollution. In China, "dust events" in the Gansu region, have been linked with increased incidence of measles [28]. In the Niger, greater atmospheric pollution during the dry season is associated with measles-related childhood deaths which subside at the onset of the rainy season [29]. In 1935 during the Dust Bowl period, the state of Kansas experienced the most severe measles epidemic in USA history [30]. Following World War II, outbreaks of polio in the USA initiated at the beginning of summers and declined with the arrival of September rains [31].

#### **Hypothesis 4: Does $PM_{2.5}$ have a mutational and genotoxic effect on SARS-CoV-2 progenitor encouraging emergence of variants?**

In January 2020 the genome of SARS-CoV-2 was sequenced indicating that it consisted of a single strand RNA containing approximately 29,000 nucleotide bases. Following the first sequenced RNA strand, a multitude of SARS-CoV-2 genomes have been sampled confirming that over 13,000 mutations had occurred in 2020 [32]. The vast majority of variants do not survive, however if the mutation confers an adaptation advantage, then through natural selection it will survive to outpace the incumbent variant.

Mutational potential on SARS-CoV-2 may occur through selective pressure due to an adaptation to the environmental milieu which may possibly be either mutagenic or genotoxic (Chart 1). The environmental factor may also come into play as a vector which may differentially favour variants increasing their transmission. One such environmental factor may include airborne particulate matter. If this hypothesis is proven, it would be of singular importance as it may suggest that particulate matter may act as both a vector and mutagen for SARS-CoV-2. Moreover particulate matter may furthermore differentially favour variants by not only acting as a mutagen resulting in variant emergence, but actually be genotoxic to the progenitor virus expediting the latter's disappearance.

It has been suggested that particulate matter  $PM_{2.5}$  acting as a vector, was not only responsible for SARS-CoV-2 transmission but may also have been involved in this virus' evolution developing the first variant G614 in China (Muscat Baron, 2021a) [2]. Acting as SARS-CoV-2's

vector, the quantity and quality of  $PM_{2.5}$  may have exerted selective pressure determining the emergence of the first highly transmissible variant G614 in China [2].

Another mechanism of variant emergence may hypothetically involve reversal of the variant to the progenitor which will then go on to produce another variant. This mechanism may have occurred in the case of the B.1.1.7 variant in the U.K. in mid-September 2020. Prior to mid-September, the 20A.EU1 variant was dominant in Spain in mid-August and was transferred to the U.K. possibly by tourists returning from their holidays in Spain. The B.1.1.7 variant and the 20A.EU1 variant appear to evolve from the same 20A progenitor clade [33]. Under the influence of an environmental factor, possibly the  $PM_{2.5}$  acting as a vector, the 20A.EU1 variant, may have reversed its mutation to the progenitor which later went on to produce the B.1.1.7 variant.

A recurring set of mutations, namely E484K, N501Y, and K417N may suggest that SARS-CoV-2 is undergoing convergent evolution [7]. This convergent evolution of SARS-CoV-2 may be due to the presence of a common mutagenic catalyst and vector in the form of the omnipresent pollutant  $PM_{2.5}$  which has repeatedly been shown to be a consistent cofactor in the SARS-CoV-2 Pandemic [34–36].

Contrasting effects by  $PM_{2.5}$  on viral infectivity have been shown possibly due to mutations in viruses and bacteriophages. Viral transmission may be considered a phenotypic reflection of genomic mutation. During the 1968 influenza pandemic and its aftermath, mutations were noted in the influenza virus hemagglutinin serotype H3 molecule and appear to have provided an advantage to the resultant variant to evade antibodies and consequently cause disease in previously immune individuals [37].

RNA viruses unlike DNA viruses lack the proofreading function of polymerase enzymes. This may be due to the hypothesized evolutionary precedence of RNA, which appears to have emerged well before the inception of DNA [38]. As opposed to DNA, RNA may act both as a genetic carrier and as an enzyme. RNA viruses have mutation rates resulting in  $10^{-3}$  to  $10^{-4}$  errors per incorporated nucleotide, which is significantly higher than DNA viruses' error rate calculated at  $10^{-8}$  to  $10^{-11}$  errors per incorporated nucleotide [39]. SARS-CoV-2 variants' increased transmissible behaviour may therefore be dictated by these relatively frequent (compared to DNA viruses) RNA viral mutations [40].

Viral mutagenicity due to particulate matter  $PM_{2.5}$  has been suggested with an experimental study on bacteriophage transmissibility in the presence of this pollutant [41]. A study suggested differential effects on the transmissibility of two bacteriophages  $\Phi 6$  and  $\Phi X174$  in the presence of  $PM_{2.5}$ . Whereas the aerosol admixture of  $PM_{2.5}$  with  $\Phi 6$  reduced this bacteriophage's transmissibility, a diametrically opposite effect was noted on the bacteriophage  $\Phi X174$ , demonstrating superior infectivity compared to controls [41].

#### **$PM_{2.5}$ and the emergence of SARS-CoV-2 variants- an ecological fallacy or a surrogate for increasing viral burden**

There is literature that has not confirmed the role of particulate matter in the seeding and spread of COVID-19. A study done by Ong et al. 2020, demonstrated that SARS-CoV-2 could not be detected in all of the air samples assessed. A caveat to this study indicated that the short sampling time of  $\frac{1}{4}$  h–4 h might not be representative of the total air volume in the ward and the presence of SARS-CoV-2 might have possibly been diluted during air exchanges in the ward [42].

Another study in Northern Italy by Collovigorelli et al. put the association between particulate matter and COVID-19 in doubt [43]. Collovigorelli et al. excluded a significant correlation between atmospheric particulate matter and the incidence of COVID-19 [43]. This latter study suggested that there may be other factors, including meteorological factors, that may have synergised with particulate matter to spread COVID-19. If one were to look closely at the provinces in Northern Italy as regards seeding and doubling time of COVID-19, the

highest rates are to be found in land-locked provinces especially in Lodi, Bergamo, and Aosta. The impact of the vicinity to the sea as a factor determining COVID-19 rates has been alluded to [8,9]. By virtue of the absence of particulate matter sources from the sea, the level of this pollutant is likely to be lower and diluted in coastal provinces. Moreover the increased sodium chloride content in particulate matter derived from marine sources may have had a role in deterring the adhesion of the hydrophobic regions in the SARS-CoV-2 spike protein to particulate matter [9].

The association between particulate matter and COVID-19 has its support. The increase in pulmonary ACE-2 receptors and its effect on respiratory immunity after exposure to particulate matter has been scientifically confirmed [18,21]. The presence of SARS-CoV-2 genes on particulate matter provides circumstantial evidence of the potential vector effect of this airborne pollutant [25].

It is also biologically plausible that particulate matter's mutagenic and genotoxic effect may also affect SARS-CoV-2 both outside and inside the host, leading to the emergence of variants and the displacement of the progenitor virus. Lastly the appearance of similar mutations in the different variants, increasing their transmissibility, in widely disparate and distant regions, lends its itself to suggest that convergent evolution of SARS-CoV-2 is occurring in the presence of an ubiquitous environmental factor.

#### Actions that may be undertaken

1. Particulate Matter Sensors need to be installed in areas where social distancing cannot be employed effectively e.g. underground travel.
2. Effective indoor ventilation and measures to implement efficient social distancing need to be employed.
3. A determined global effort has to be undertaken to reduce reliance on fossil fuels and other sources of particulate matter.
4. On a global scale the sudden spikes of atmospheric Particulate Matter may be used as a surrogate for the emergence of SARS-CoV-2 variants.
5. Continued genomic surveillance of SARS-CoV-2 needs to be maintained for both epidemiological reasons and most importantly to tailor vaccines to emerging new variants so as address the potential risk of vaccine escape.

#### Conclusion

There appears to be a link between atmospheric PM<sub>2.5</sub> and the emergence of SARS-CoV-2 variants. There may be both short to medium term spikes in PM<sub>2.5</sub> before variant emergence due to this pollutant's multifaceted effects. These effects include: a). Anthropogenic activity increasing the viral burden, b). PM<sub>2.5</sub>-induced propagation of the ACE-2 receptor (the viral point of host cell entry), c). Potential PM<sub>2.5</sub>-induced viral mutagenesis resulting in variant emergence and genotoxicity to the progenitor, d). PM<sub>2.5</sub> toxicity diminishing host pulmonary immunity and e). Possible PM<sub>2.5</sub> vector effect, increased the prospect of the emergence SARS-CoV-2 variant. If this link is confirmed then significant changes in PM<sub>2.5</sub> levels may not only contribute to viral transmission, but also to the evolution of SARS-CoV-2. A preprint demonstrating two distinct groups of medium and short-term peaks in PM<sub>2.5</sub> prior to the emergence of SARS-CoV-2 variants was published while this article was in press [44].

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#### Declaration of Competing Interest

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

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