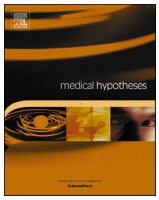
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 158 (2022) 110718

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Are there medium to short-term multifaceted effects of the airborne pollutant $PM_{2.5}$ determining the emergence of SARS-CoV-2 variants?

Yves Muscat Baron

Mater Dei Hospital, University of Malta Medical School, Malta

ARTICLE INFO

Keywords:
$PM_{2.5}$
SARS-CoV-2
COVID-19
Mutations
Variant emergence

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, PM2.5. 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 PM2.5 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 $PM_{2.5}$ 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 $PM_{2.5}$ and SARS-CoV-2 was noted in the United States, whereby a link between long-term exposure to particulate matter $PM_{2.5}$ and COVID-19 related mortality was demonstrated [4]. A recent preprint has confirmed that $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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

E-mail address: yves.muscat.baron@gov.mt.

https://doi.org/10.1016/j.mehy.2021.110718
Received 5 July 2021; Accepted 17 October 2021
Available online 20 October 2021

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 $PM_{2.5}$ increase the ACE-2 receptor, the point of viral entry advantaging highly transmissible variants?

The occurrence of $PM_{2.5}$ 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 $PM_{2.5,}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ may have acted differentially according to the time before variant emergence. The spike in $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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

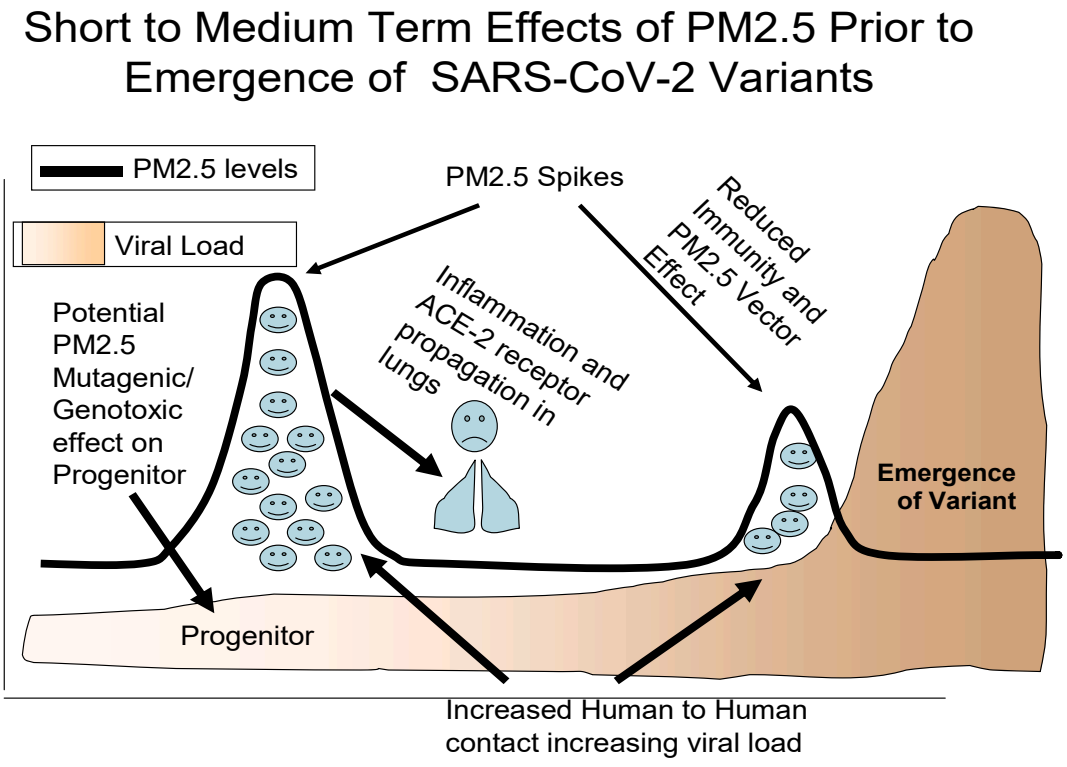


Chart 1. Schematic view of Atmospheric $PM_{2.5}$ levels with contemporaneous viral load leading to Emergence of SARS-CoV-2 Variant. First medium-term $PM_{2.5}$ spike associated with anthropogenic effect due to increased human activity and contact, leading to lung inflammation, ACE-2 receptor propagation, and potential $PM_{2.5}$ viral mutagenic induced variant emergence and genotoxicity to the progenitor expediting the latter's eventual displacement by the emerging variant. Second short-term $PM_{2.5}$ spike also related to diminished population immunity and potential PM2.5 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 PM10. 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 ± 117.1 copies μL^{-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 ± 7.44 copies μL^{-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 the 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 co-factor in the SAR-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 Φ6 and ΦX174 in the presence of $PM_{2.5}$. Whereas the aerosol admixture of $PM_{2.5}$ with Φ6 reduced this bacteriophage's transmissibility, a diametrically opposite effect was noted on the bacteriophage ΦX174, 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 ¼ 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 Collovignarelli et al. put the association between particulate matter and COVID-19 in doubt [43]. Collovignarelli 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 to 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 $PM_{2.5}$ and the emergence of SARS-CoV-2 variants. There may be both short to medium term spikes in $PM_{2.5}$ before variant emergence due to this pollutant's multifaceted effects. These effects include: a). Anthropogenic activity increasing the viral burden, b). $PM_{2.5}$-induced propagation of the ACE-2 receptor (the viral point of host cell entry), c). Potential $PM_{2.5}$-induced viral mutagenesis resulting in variant emergence and genotoxicity to the progenitor, d). $PM_{2.5}$ toxicity diminishing host pulmonary immunity and e). Possible $PM_{2.5}$ vector effect, increased the prospect of the emergence SARS-CoV-2 variant. If this link is confirmed then significant changes in $PM_{2.5}$ levels may not only contribute to viral transmission, but also to the evolution of SARS-CoV-2. A preprint demonstrating two dinstinct groups of medium and short-term peaks in $PM_{2.5}$ prior to the emergence of SARS-CoV-2 variants was published while this article was in press [44].

Funding

There has been no funding for this publication.

Consent statement/Ethical approval

Not required.

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.

References

[1] Comunian S, Dongo D, Milani C, Palestini P. Air pollution and covid-19: the role of particulate matter in the spread and increase of covid-19's morbidity and mortality. Int J Environ Res Public Health. 2020;17(12):4487. https://doi.org/10.3390/ijerph17124487.
[2] Muscat Baron Y. Could changes in the airborne pollutant particulate matter acting as a viral vector have exerted selective pressure to cause COVID-19 evolution? [published online ahead of print, 2020 Nov 21]. Med Hypotheses. 2020;110401. doi:10.1016/j.mehy.2020.110401.
[3] Muscat Baron Y. Atmospheric PM2.5 before and after Lockdown in relation to COVID-19 Evolution and daily Viral Counts: Could Viral Natural Selection have occurred due to changes in the Airborne Pollutant PM2.5 acting as a Vector for SARS-CoV-2? MedRxiv. 2021. doi: https://doi.org/10.1101/2021.01.10.21249548.
[4] Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: A nationwide cross-sectional study. Sci Adv 2020. https://doi.org/10.1126/sciadv.abd4049.
[5] Milicevic O , Salom I , Tumbas M et al. PM2.5 as a major predictor of COVID-19 basic reproduction number in the USA. 2021. http://.arxiv.
[6] Setti L, Passarini F, De Gennaro G et al, 2020a. SARS-Cov-2RNA found on particulate matter of Bergamo in Northern Italy: First evidence. Environ Res, 2020; 188:109754, ISSN 0013-9351, https://doi.org/10.1016/j.envres.2020.109754.
[7] Gupta RK. Will SARS-CoV-2 variants of concern affect the promise of vaccines? Nat Rev Immunol 2021. https://doi.org/10.1038/s41577-021-00556-5.
[8] Muscat Baron Y. Covid-19 Pandemic in relation to PM2.5, and ambient salinity – an environmental wake-up call. MedRxiv. 2020. https://doi.org/10.1101/2020.05.03. 20087056.
[9] Muscat Baron Y. 2020c. Covid-19 and PM2.5 sodium chloride content. research square DOI:2020: MedRXiv https://doi.org 10.21203/rs.3.rs-31884/v1.
[10] Xu X, Zhang J, Yang X, et al. The role and potential pathogenic mechanism of particulate matter in childhood asthma: a review and perspective. J Immunol Res 2020;2020:8254909.
[11] Muscat Baron Y. Incidence and case-fatality ratio of COVID-19 infection in relation to tobacco smoking, population density and age demographics in the USA: could particulate matter derived from tobacco smoking act as a vector for COVID-19 transmission? J Clin Cases Rep 2020;4(S6):16–24.
[12] Liu J, Chen X, Dou M, et al. Particulate matter disrupts airway epithelial barrier via oxidative stress to promote Pseudomonas aeruginosa infection. J Thorac Dis 2019; 11:2617–27.
[13] Fujimoto I, Pan J, Takizawa T, et al. Virus clearance through apoptosis-dependent phagocytosis of influenza A virus-infected cells by macrophages. J Virol 2000;74: 3399–403.
[14] Müller L, Chehrazi CVE, Henderson MW, et al. Diesel exhaust particles modify natural killer cell function and cytokine release. Part Fibre Toxicol 2013;10:16.
[15] Pope 3rd CA, Bhatnagar A, McCracken JP, et al. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res 2016;119:1204–14.
[16] Pierdominici M, Maselli A, Cecchetti S, et al. Diesel exhaust particle exposure in vitro impacts T lymphocyte phenotype and function. Part Fibre Toxicol 2014;11.
[17] Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. Immunol Res 2014;59:118–28.
[18] Sagawa T, Tsujikawa T, Honda A, et al. Exposure to particulate matter upregulates ACE2 and COVID-19 Environmental Dependence 21 TMPRSS2 expression in the murine lung. Environ Res 2021;195:110722. https://doi.org/10.1016/j.envres.2021.110722.
[19] Zhu Y, Xie J, Huang, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. Sci Total Environ, 2020; 727, Article 138704.
[20] Borro M, Di Girolamo P, Gentile G, De Luca O, Preissner R, Marcolongo A, et al. Evidence-based considerations exploring relations between SARS-CoV-2 pandemic and air pollution: involvement of $PM_{2.5}$-mediated up-regulation of the viral receptor ACE-2. Int J Environ Res Public Health 2020;17(15):5573.
[21] Paital B, Agrawal PK. Air pollution by NO(2) and PM(2.5) explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. Environ Chem Lett 2020:1–18. https://doi.org/10.1007/s10311-020-01091.
[22] Sanche S, Lin Y, Xu C, Romero-Severson E, Hengartner N, Ke R. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis 2020;26(7):1470–7.
[23] Coburn BJ, Wagner BG, Blower S. Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1). BMC Med 2009;7:30.
[24] Liu Y, Gayle A, Wilder-Smith A, JR.. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 2020. https://doi.org/10.1093/jtm/taaa021.
[25] Setti L, Passarini F, De Gennaro G et al. Airborne transmission route of COVID-19: Why 2 meters/6 feet of inter-personal distance could not be enough. Int J Environ

Res Public Health. 2020;17(8): 2932. Published online 2020 Apr 23. doi: 10.3390/ijerph17082932.
[26] Carelli P. A physicist's approach to COVID-19 transmission via expiratory droplets. Med Hypotheses 2020;144:109997. https://doi.org/10.1016/j. mehy.2020.109997.
[27] Nor NSM, Yip CW, Ibrahim N, et al. Particulate matter ($PM_{2.5}$) as a potential SARS-CoV-2 carrier. Sci Rep 2021;11:2508. https://doi.org/10.1038/s41598-021-81935-9.
[28] Ma Y, Zhou J, Yang S, et al. Assessment for the impact of dust events on measles incidence in Western China. Atmos Environ 2017;157:1–9. https://doi.org/10.1016/j.atmosenv.2017.03.010.
[29] Ferrari MJ, Grais RF, Bharti N, et al. The dynamics of measles in sub-Saharan Africa. Nature 2008;451:67984. https://doi.org/10.1038/nature06509. pmid: http://www.ncbi.nlm.nih.gov/pubmed/18256664.
[30] Brown EG, Gottlieb S, Laybourn RL. Dust Storms and their possible effect on health: with special reference to the dust Storms in Kansas in 1935. Public Health Rep 1935;50:1369–83. https://doi.org/10.2307/4581653.
[31] Oshinisky D. Remembering the Dreaded Summers of Polio Elsevier 2014.
[32] Callaway E. The coronavirus is mutating - does it matter? Nature 2020;585(7824): 174–7. https://doi.org/10.1038/d41586-020-02544-6. PMID: 32901123.
[33] Lauring AS, Hodcroft EB. Genetic variants of SARS-CoV-2—What do they mean? JAMA 2021;325(6):529–31. https://doi.org/10.1001/jama.2020.27124.
[34] Zoran MA, Savastru RS, Savastru DM, Tautan MN. Assessing the relationship between surface levels of PM2.5 and PM10 particulate matter impact on COVID-19 in Milan, Italy. Sci Total Environ 2020;10(738):139825.
[35] Copat C, Cristaldi A, Fiore M, Grasso A, Zuccarello P, Signorelli SS, et al. The role of air pollution (PM and NO2) in COVID-19 spread and lethality: A systematic review. Environ Res 2020;191:110129. https://doi.org/10.1016/j.envres.2020.110129.
[36] Sharma AK, Balyan P. Air pollution and COVID-19: Is the connect worth its weight? Indian J Public Health. 2020;64(Supplement):S132–4. https://doi.org/10.4103/ijph.IJPH_466_20.
[37] Bean WJ, Schell M, Katz J, et al. Evolution of the H3 influenza virus hemagglutinin from human and nonhuman hosts. J Virol 1992;66(2):1129–38.
[38] Becker S, et al. Wet-dry cycles enable the parallel origin of canonical and non-canonical nucleosides by continuous synthesis. Nat Commun 2018. https://doi.org/10.1038/s41467-017-02639-1.
[39] Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. The RNA World and the Origins of Life. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26876/.
[40] Fleischmann WR Jr. Viral genetics. In: Baron S, editor. Medical microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 43. Available from: https://www.ncbi.nlm.nih.gov/books/NBK8439/.
[41] Groulx N, Urch B, Duchaine C, et al. The Pollution Particulate Concentrator (PoPCon): A platform to investigate the effects of particulate air pollutants on viral infectivity. Sci Total Environ 2018;628–629:1101–7.
[42] Ong SW, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 2020;16:1610–2.
[43] Collivignarelli MC, Abbà A, Caccamo FM, et al. Can particulate matter be identified as the primary cause of the rapid spread of CoViD-19 in some areas of Northern Italy? Environ Sci Pollut Res 2021. https://doi.org/10.1007/s11356-021-12735-x.
[44] Muscat Baron Yves. Airborne PM2.5 and the Emergence of 10 SARS-CoV-2 Variants: The Multifaceted Influence of an Airborne Pollutant on Viral Natural Selection determining SARS-CoV-2 Evolution - An Environmental Wake-up Call or an Ecological Fallacy. medRxiv 2021. https://doi.org/10.1101/2021.06.27.21259602. Submitted for publication.