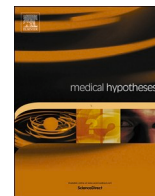




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Could changes in the airborne pollutant particulate matter acting as a viral vector have exerted selective pressure to cause COVID-19 evolution?

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ABSTRACT

Air pollution with particulate matter has been implicated in the incidence and the mortality due to COVID-19 infection. The levels of particulate matter have been shown to have decreased after regional and national lockdowns in a number of countries. COVID-19 possesses an elevated reproduction number (R_0) due to its high transmission rate. COVID-19 genes have been found adherent to particulate matter which has been suggested as a vector for this virus' transmission. Following lockdown in China, the original viral Clade D steadily decreased mirroring the decline in particulate matter. Two months after the COVID-19 index case was reported in Wuhan early December 2019, a persistent mutation was noted at the D614 gene position of the viral spike protein establishing the Clade G variant. Clade G started to appear early in February and steadily attained predominance after lockdown in late February. It may be postulated that the changes in the source of airborne particulate matter, possibly derived from tobacco smoking (66% of Chinese males are smokers), may have contributed to the appearance of Clade G. Once the pandemic spread beyond China, in all countries affected except for Iceland, a consistent pattern arose whereby the initial viral Clade D outbreak was rapidly displaced by Clade G. It is hypothesized that changes in the source of COVID-19's vector in the form of particulate matter may have contributed to natural selection favouring Clade G. The "open orientation" of Clade G spike protein's three peptides as opposed to the "closed orientation" of the Clade D may have allowed easier adherence of the viral mutant to cells and as a corollary also to particulate matter. There may also have been differences between both viral Clades in the spike protein's hydrophobic properties. Experimental research on the hypothesis that particulate matter may potentially act as a COVID-19 vector needs to be undertaken. Besides the potential vector effect, the deleterious effects of particulate matter on respiratory immunity and cardiovascular health are well known and consequently airborne pollution in all its forms should be addressed on a global scale.

Background

A resurgence of COVID-19 has occurred and continues to impact populations adversely on a global scale [1]. The application of social distancing to the extent of instituting regional and national lockdown momentarily arrested the pandemic only for it to resurface as a 2nd wave in most countries [2]. Long-term exposure to particulate matter PM_{2.5} has been shown to increase COVID-19 related mortality. An increase of 1 $\mu\text{g}/\text{m}^3$ in long-term PM_{2.5} exposure correlated with an 8% increase in the COVID-19 related mortality [3]. Concomitant with lockdown a significant reduction in pollution including particulate matter (PM) was noted globally in particular China [4]. In mainland China, where the first index case was noted, the daily combustion of coal (a prime cause for PM_{2.5}) decreased from 80,000 tonnes to approximately 50,000 tonnes per day following lockdown earlier this year [5].

Contemporaneous with the elevated PM_{2.5} levels in China, the COVID-19 index case was noted in early December 2019. Genomic studies were carried out confirming the single RNA strand composed of 29,903 genes. The first variant called "Wuhan 1" (Clade D) appears to have dominated the COVID-19 Clade landscape in China until another Clade (Clade G), was detected in February [6]. The difference between both clades involved a mutation at the 614th position of the spike protein amino-acid chain, whereby aspartic acid was consistently replaced by glycine. Early in March the pandemic spread globally and a similar pattern appeared, whereby Clade D was initially detected in most cities only to be later replaced by Clade G [6].

Hypothesis

1. Could particulate matter act as a vector for COVID-19?

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2. Could changes in atmospheric particulate matter and its sources following lockdown have a bearing on the predominance of COVID-19 Clade G displacing Clade D (Wuhan 1)?

Support for hypothesis

Hypothesis 1. Could particulate matter act as a vector for COVID-19?

In early March this year the pandemic spread from Wuhan initially to Qoms in Iran and soon after to Bergamo in Italy. From the outset all three cities showed a high reproduction number (R_0) indicating an elevated transmission rate [7]. At its height the R_0 of influenza is 1.1 while that of COVID-19 was 3.28 [8]. This may suggest that besides human to human transmission there may be another variable accelerating COVID-19 transmission.

A common characteristic that stood out between Wuhan, Qoms and Bergamo, besides recent arrivals from China, was the elevated levels of air pollution including particulate matter [7]. A study in a large number of Chinese cities showed a 2% increase in new cases of COVID-19 with every $10 \mu\text{g}/\text{m}^3$ increase in atmospheric PM2.5 [9]. Research from Milan in Italy by Setti et al. (2020) indicated that compared to control air samples of particulate matter, 34 RNA extractions for the COVID-19 E, N and RdRP genes, detected 20 positive results for one of these genes [10].

Setti et al. (2020) suggested a correlation between the atmospheric levels of particulate matter and the COVID-19 transmission in 110 Italian provinces. The same authors intimated that COVID-19 transmission could be further augmented by particulate matter beyond the social distance of 2 m up to 10 m [11]. Another study by Comunian et al. confirmed the elevated levels of both PM2.5 and PM10 coincided with infection rates in Italy and reaffirmed the hypothesis that besides the adverse effects of particulate matter on pulmonary antimicrobial defences, PM could also act as a vector for COVID-19 [12]. Besides acting as a vector for COVID-19, particulate matter has shown to be associated with the angiotensin-converting enzyme 2 receptor which acts as the point of viral entry into the cell. Angiotensin-converting enzyme 2 receptors are sited mainly on respiratory epithelial goblet cells which are especially abundant in smokers [13].

Viral infection and air pollution

COVID-19 is not the only viral infection which is has been associated with air pollution. Exposure to particulate matter has been shown to adversely affect respiratory immunity increasing the risk for microbial invasion [14,15]. Inhaled particulate matter has the proclivity for causing oxidative stress at the pulmonary epithelial level by creating free radicals [16,17].

During the 2003 SARS (severe acute respiratory syndrome) epidemic, the air pollution index was shown to correlate with death rates. The mortality from SARS (severe acute respiratory syndrome) in Chinese provinces with high air pollution index had double the death rates compared to provinces with low air pollution index (RR = 2.18, 95% CI: 1.31–3.65) [18]. In 1997 elevated particulate matter, PM10 and PM2.5 were implicated in the transmission of the Avian flu [19].

Geographical dissemination of COVID-19 and impact of particulate matter

During the initial stages of the pandemic (1st wave), a number of cities were left relatively unscathed by COVID-19. A characteristic common to these cities was their geographical location whereby a number of them were either islands or sited close to the sea, having high levels ambient salinity [7,20]. Coronavirus spike protein has an N-terminal peptide which possesses hydrophobic sites [21,22]. Ambient salinity through salt's hygroscopic properties may have increased the atmospheric humidity making the environment adverse to the hydrophobic N-terminal peptide of the Coronavirus. Particulate matter also possesses a water element which is determined by the PM's sodium

chloride and ammoniac salts' component [23,24].

Lockdown in these coastal cities was more effective and easier to implement. The marine physical barrier prevented mass movements of individuals decreasing the risk of infection transmission. The concentration of particulate matter in these coastal cities was found to be significantly lower than cities which sustained high incidences of COVID-19 infection. The lower concentrations of particulate matter in coastal areas may also be due to the dilution effect due to the paucity of carbon sources of particulate matter from the sea and the presence of meteorological factors such as the wind and sea spray [7].

Although coastal cities appeared relatively unscathed during the 1st wave, this was not the case during the 2nd wave. Both cities distant from the sea and close to the coast were affected by the pandemic. This coincided when Clade G became well established having displaced Clade D completely [6]. It would be interesting to explore whether the D614G mutation affected the hydrophobic properties of the N-terminal peptide of the Coronavirus spike protein.

The single most notable indoor location with the highest exposure to particulate matter is underground travel [25]. To compound matters this is associated with high commuter congestion. A preprint demonstrated that in the presence of high concentrations of particulate matter, COVID-19 mortality was found to be significantly higher even after correcting for the effect of underground train ridership [26]. This may have been case for the extraordinary elevated case-fatality ratios noted particularly in the East Coast of the USA where there exists a dense underground network connecting the states of New York, Connecticut, Massachusetts and Rhode Island [27].

Hypothesis 2. Could changes in particulate matter and its sources following lockdown have a bearing on the predominance of COVID-19 Clade G at the expense of Clade D (Wuhan 1)?

Following lockdown in China there was a steady decline in atmospheric particulate matter due to reduction in industry and combustion of coal [5,28]. Concomitantly the original viral Clade D steadily decreased, mirroring the decline in particulate matter. From early December till mid-February the viral Clade D dominated the pandemic until a consistent mutation at the D614 gene for the viral spike protein was noted [6]. The mutation delineated as Clade G slowly dominated the genomic scene after lockdown in mid-February. It may be inferred that the changes in atmospheric particulate matter may have contributed to the eventual dominance of the mutant Clade G.

After the pandemic spread beyond China, a common pattern was noted whereby Clade D was initially detected in most countries only to be later displaced by the mutant Clade G. Clade G was found to have greater in vitro infective potential in cells and was noted to replicate 1.22 times more than Clade D [6]. This pattern of Clade displacement was noted practically in all countries except in Iceland. In Iceland pollution levels are perennially low and no lockdown variation in atmospheric particulate matter concentrations occurred as in other countries [29].

Particulate matter constituents and the adherence and hydrophobic properties of COVID-19 spike protein

There are several species of particulate matter as determined by their composition. The species' composition is affected by the environment the particulate matter originated from. Particulate matter has a water component delineated as particle bound water. Particle bound water is differentially determined by particulate matter's main hygroscopic components of sea salt, ammonium nitrate and ammoniated sulphate [23]. The ratio of sodium chloride, ammonium nitrate and ammoniated sulphate depends on the origin of the particulate matter e.g. particulate matter close to the coast has a higher proportion of sodium chloride. Moreover these components may also have a bearing on pulmonary pathology since ammonium nitrate and ammoniated sulphate are

certainly more toxic than sodium chloride. Sodium chloride in the respiratory tract is useful in pulmonary defences as it makes bronchial mucus less viscous and encourages ciliary movement [30].

As mentioned earlier the presence of water in particulate matter may be relevant to the different geographical distribution between the 1st and 2nd waves of COVID-19. Coronavirus' spike protein has an N-terminal peptide which is highly hydrophobic and PM's particle based water content may deter viral adherence as may be suggested by the apparent resistance to the 1st wave in coastal cities [7,24]. This may not be the case with Clade G which dominated the 2nd wave. Clade G possesses a different orientation of its spike protein three peptides and possibly may influence its hydrophilic behaviour.

Other components of particulate matter may also have a bearing on COVID-19 adherence to PM. Particulate matter in subways has a significant haematite element as opposed to the particulate matter which is rich in carbon. In the absence of carbon's adsorbance properties, viral release in the respiratory system may be more possible from air inhaled in subways [26].

Tobacco smoking and COVID-19 adherence to PM

Surface morphology and composition of particulate matter depends on its constituents. These constituents may have changed after lockdown due to the change in its sources. Of singular interest in the case of the COVID-19 pandemic is the role played by tobacco smoking [31,32]. Tobacco smoking is the single most evident activity whereby humans are exposed to very high concentrations of particulate matter in a short space of time. Moreover the deleterious effects of passive smoking due to inadvertent exposure to particulate matter are well documented. A preprint has suggested that USA states with lower bans on smoking and a higher percentage smoking population had a 23% higher incidence of COVID-19 infection rates than states with more restrictive legislation on smoking and lower percentage smoking populations [32].

As mentioned earlier particulate matter levels decreased after lockdown in China following which Clade G started to appear. With 50% of Chinese males indulging in tobacco smoking, in the presence of reduced atmospheric particulate matter, Clade G may have found a more favourable vector in the form of particulate matter derived from tobacco smoking. Particulate matter derived from tobacco smoking increases in volume 1.5 times due to the added water content attained while travelling in the bronchial tree [33]. If Clade G is more hydrophilic than Clade D, then particulate matter derived from tobacco smoking would be an ideal vector. Possibly the asymptomatic COVID-19 positive smoker may potentially act as a superspreader to both smokers and nonsmokers. Moreover the necessary removal of face protection during smoking obviously encourages further transmission [34].

COVID-19 adherence to cells depends on spike protein's tripeptide orientation. The three peptides in spike protein adhere to cell if at least two of them are positioned in an "open orientation" [35]. The Clade G variant has been found consistently in an open orientation as opposed to Clade D spike protein peptides [36]. This peptide orientation may also affect COVID-19 adherence to particulate matter derived from tobacco smoking and the viral hydrophilic properties.

What needs to be done?

1. Experimental work needs to be done to confirm or refute the vector effect of particulate matter for COVID-19.
2. For health reasons including reducing the impact of COVID-19 "Particulate Matter Sensors" need to be installed in areas where social distancing cannot be employed effectively and in areas prone to high pollution e.g. underground travel and inner cities [33].
3. Effective indoor ventilation and measures to implement efficient social distancing need to be employed.
4. A determined global effort has to be undertaken to reduce reliance on fossil fuels and other sources of particulate matter. Particulate matter

and COVID-19 besides its deleterious effect of the body's immune system may act in concert to increase the case-fatality ratio [37].

5. On a global scale the persistent elevation of atmospheric particulate matter may be used as a surrogate for the recrudescence of future outbreaks and pandemics.
6. Legislation has to be endorsed so that the public is protected from 2nd hand smoking.
7. In the current and future pandemics widespread face protection has to be vigorously encouraged.
8. Similar to the successful displacement of Clade D by Clade G, experimental work needs to be directed to possibly replicate this evolutionary step towards a more benign variant.

Conclusion

This paper supports the hypotheses that particulate matter is strongly implicated in the pathogenesis of COVID-19 infection and its transmission. Moreover the atmospheric changes in particulate matter may have encouraged COVID-19 evolution to the more ubiquitous and possibly more contagious Clade G. In view of the huge health burden and the havoc to economies COVID-19 has caused, it is imperative that measures on a global scale are undertaken in a multimodal manner to arrest the onslaught of the pandemic.

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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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