ejpmr, 2021,8(4), 673-680

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

COVID-19 INFECTION, PROGRESSION AND SEVERITY: A CHALLENGE IN THE WINTER SEASON AND PREVENTIVE APPROACH

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Article Received on 20/02/2021 **Article Revised on 10/03/2021** **Article Accepted on 30/03/2021**

ABSTRACT

Coronavirus disease-2019 (COVID-19) is an infectious respiratory disease caused by Severe Acute Respiratory System Coronavirus 2 (SARS-Cov-2). Warm and wet climate reduce the spread of COVID-19 while opposite weather condition prolongs the survival and transmission of viral agents. Particulate matter particularly PM2.5 enhances viral transmission via aerosol. This systemic review was undertaken to describe the association between meteorological condition and air pollutant in winter season and COVID-19 infection. Winter season is associated with dry and cold weather, short sun light and more PM in ambient air. In dry climate exhaled droplets from COVID-19 infected person evaporate to micro droplets and suspended in the air for longer duration. Thus in cold climate a condition with stagnant air and poor ventilation suspended viral particle concentration will increase and enhance the risk of infection. Dry air inhalation leads to decrease the capability of cilia to expel viral aerosols. The concentration of both PM10 and PM2.5 are significantly higher in winter than summer. PM forms condensation nuclei for viral attachment. Besides these fine particles in polluted air induce citrullination of innate antiviral peptide LL-37. Such citrullination blocks the antiviral capacity of LL-37 and exacerbates COVID-19. The lack of sunlight in winter droplets vitamin-D level. Vitamin-D decreases concentration of pro-inflammatory cytokine, IL-6, in lipopolysaccharide-induced inflammation and enhances formation of antiviral peptide LL-37. Thus vit-D deficiency is associated with increased risk of viral infection. The winter season with low humidity, low temperature and more PM in ambient air promotes sustained transmission of SARS-CoV-2. The lack of sunlight in winter droplets vitamin-D level and makes them more susceptible to COVID-19. Thus maintenance of relative humidity within 40% to 60% is important in indoor spaces to restrict transmission. Improving ventilation of public spaces dilute and clear out potentially infectious aerosols. Vit-D supplementation is recommended for people who are at higher risk of vit-D deficiency in COVID-19 pandemic situation.

KEYWARDS: COVID-19, winter, Vitamin-D, Particulate matter.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an infectious respiratory disease which was reported first in Wuhan, China, in December'2019. This disease is caused by capsulated RNA virus named Severe Acute Respiratory System Coronavirus 2 (SARS-Cov-2). The COVID-19 outbreak and spread of SARS-CoV-2 at an alarming rate is a global threat on public health. Various mitigation measures have been implemented to fight the COVID-19 pandemic. During the rapid increase in COVID-19 infection and death in spite of adaptation of recommended precautions, questions are voiced about routes of transmission of this disease.

There are several plausible pathways for viral transmission of which droplet and aerosol transmission paths become prominent.[1,2] The respiratory droplets from infected person during coughing, sneezing, singing and talking can land onto conjunctiva or mouth or noses of nearby person (direct transmission) or on fomites (indirect deposition). Direct physical touch between an infected person and susceptible host and indirect contact with viral contaminated fomites can cause viral transmission.[3,4] Airborne transmission of SARS-Cov-2 via aerosols is now considered as a potential route for the spreading of the disease.[5-7]

Outbreak of respiratory virus infections is seasonal nature with peak level in low temperature winter season.[8] Winter climate favors the transmission of influenza virus[9] and human coronaviruses.[10,11] The coronavirus can retain its infectivity up to 2 weeks in low temperature and low humidity environment.[12] Increased AQI (Decrease air quality) and PM2.5 those occur in winter enhanced the incident of COVID-19.[13]

Meteorological factors play a role in coronavirus outbreak.[14] High temperature and high humidity reduce the transmission of influenza[15] and SARS coronavirus.[16] Various studies reported the association

between humidity and temperature in COVID-19 transmission.[17-19] The present systemic review was undertaken to analyze impact of winter season particularly its meteoroidal parameters and air pollutants on viability and transmission of SARS-COV-2. This information would be useful to develop awareness among health workers and general public to prevent spread of COVID-19.

MODES OF TRANSMISSION

There are several plausible pathways for viral transmission of which droplet and aerosol transmission paths become paramount. The respiratory droplets from infected person during coughing, sneezing, singing and talking can land onto conjunctiva or mouth or noses of nearby person (direct transmission) or on fomites (indirect deposition). Direct physical touch between an infected person and susceptible host and indirect contact with viral contaminated fomites can cause viral transmission.[4]

Respiratory jet from coughing, sneezing, talking, singing and expiration of infected person's expel respiratory particles loaded with virus. Respiratory particles are categorized into respiratory droplets and aerosols depending on their size. Respiratory particles having diameter above 5 micron are known as respiratory droplets whereas aerosols are small respiratory particles with diameter $\leq$5 micron.[20] Spread of droplets and aerosols depend on their size, velocity of the respiratory jet, temperature, humidity and speed of surrounding air flow.[21,22] Current evidence suggests that droplets released from cough or sneezes settle gravitationally close to the source (with in 1m) whereas smaller droplets which become fine due to evaporation can travel longer distances.[23]

Chin et al, 2020 reported that resistance of SARS-COV-2 was 5 min at 70^0 C whereas it was long time at 4^0C.[24] Wang et al reported that 1^0C increase of the minimum ambient temperature decrease cumulative number of cases by 0.86%.[25] The prevalence of COVID- 19 decreases with increasing humidity and wind speed.[26] Respiratory droplet transmission can occur when healthy person come in close contact with infected individual. Respiratory droplet loaded with virus can reach the mouth, nose or eye of susceptible person and can result in infection.

The larger respiratory droplets loaded with virus will fall due to gravitational settling and causes contact transmission. The smaller droplets due to evaporation loss mass and become so small that transport by air current and remains in the air for long time and infect healthy individuals directly.[27] Recently, SARS COV-2 was found in aerosols in Wuhan Hospital of China (28). SARS-COV-2 RNA was detected in the air collected from inside the hospital.[28] Morawska and Cao reported that fine particles with viral content might travel in indoor environments and cover a distance up to 10m from source.[1] Airborne transmission via spread of smaller particles from expelled air from COVID-19 patients was reported especially in indoors.[29]

AIR POLLUTION IN WINTER AND ITS IMPACT ON PULMONARY HEALTH

Air pollution varies with seasons. In summer O3 concentration is extremely high from long duration of sunshine and high degree of temperature than winter from shorter duration of sunshine lower degree of temperature.[30] Particulate matter (PM), a complex mixture of solid and liquid particles suspended in the atmosphere, are the most common air pollutants. These include PM10 and PM2.5. The concentration of both PM10 and PM2.5 are significantly higher in winter than summer[31] due to inversion of temperature from smog events, slow air flow and least rainfall. The AQI (Air Quality Index) was low in summer seasons than winter due to maximum dispersion and turbulence of wind.[32] PM10 accumulates in the upper respiratory tract like nasal cavity and larynx however, PM 2.5 accumulates both in upper and lower respiratory tract especially in small air ducts and alveoli. PM can adsorb dust mites, allergen and various other pathogenic agents including microorganisms.[33]

Earlier study reported that acute PM2.5 exposure was associated with infiltration of inflammatory cells in lung tissue and increase number of inflammatory cells in broncho-alveolar lavage fluid.[34] PM2.5 stimulates alveolar macrophages to release inflammatory factors. Such factors stimulate inflammatory cells to release more inflammatory factors. This leading to a vicious cycle that damage lung endothelial cells to enhance further lung injury.[33]

COPD is characterized by chronic airway inflammation, accumulation of inflammatory cells (neutrophil, lymphocytes and activated macrophages) in lung parenchyma and increase inflammatory factors like IL-6, IL-8 and TNF-alfa. Thus inhalation of PM augments severity of COPD. Increase concentration of PM2.5 and PM10 increase the risk of mortality in patients with COPD.[35,36] PM inhalation induces ROS production in cells which causes oxidative damage of lung tissue.[37,38]

It has been reported that pathogens adsorbed on the surface of the dust practical and protect from radiation and toxic gases.[39] A positive correlation was noted between infection rate and fractions of PM2.5 and PM10.[40] Xiao et al. reported an association between increase in PM concentration and mortality rate from COVID-19.[41] The presence of SARS COV-2 on airborne particles was supported by Liu et al.[42] Doremalen et al[43] reported that SARS-COV-2 virus remain stable in airborne particles. In high PM concentration with atmospheric stability virus may create cluster with PM to reduce diffusion coefficient. Thus high atmospheric PM concentration (which occur particularly in winter season) increase residence time and

atmospheric abundance of viruses. A correlation was reported between PM2.5 concentration and severity of COVID-19 disease.[44] An increase of 1ug (mm^3) in PM2.5 is associated with an 8% increase in the COVID-19 death rate.[45] The initial outbreak of COVID-19 in Wuhan, China coincide with winter haze season with high level of PM2.5 in air.[46,47] Winter haze conditions enhanced outdoor virus spreading.[48]

METEROIDAL PARAMETERS OF WINTER SEASON AND SARS-COV-2 TRANSMISSION

The winter is cold and dry. Recent studies suggest that both temperature and RH have significant impact on the number of COVID cases in certain location.[49] Exhaled droplets from COVID-19 infected person begins to evaporate or enlarging depending on relative humidity. In dry climate droplets are evaporated to micro droplets[50] and suspended in the air for longer duration. In a condition with stagnant air and poor ventilation (indoor environment) suspended viral particle concentration will increase and enhance the risk of infection.[51] But in humid climate there is increased viral droplet size with increasing relative humidity (RH). As a result droplets fall faster and decrease chance of airborne transmission.

In cold climate outdoor air is drawn indoor and then heated to a comfortable temperature. This process creates low RH value in indoor. Due to low RH, the droplet will evaporate more rapid rate and produce fine droplets. Smaller particles remain suspended in air for long duration and transported to further distance depending on ventilation condition.[52] When indoor RH value lower than 40% there is increased suspension time of aerosol, viral concentration and long distance transmission of aerosols loaded with virus. The viral airborne particles will further travel, and inhaled by other residents to cause direct infection or settle on the surface to induce indirect infection. The infectivity of many viruses including SARS COV-2 are enhanced in low RH state.[53]

In winter due to less daylight and cold weather more people stay indoors for longer period of time. In addition people are more likely to favour social activities in indoor with increasing chance of close interactions with more people. Transmission risk increases with closer contact of man to man and duration of exposure.[54] Winter viral infections (influenza, common cold etc.) can increase the chance of sneezing and coughing to provide more vectors for COVID-19. It was reported that lower humidity, darker conditions and low temperature in winter favors persistence of viruses on surfaces and increase risk of transmission via contaminated objects and surfaces.[55]

IMPACT OF COLD CLIMATE ON COVID-19 SEVERITY

Mucosal barrier in respiratory tract is an active biological barrier which cross links viruses to mucins, secreted by the barrier. Mucin is glycosylated protein. It traps viral particles and then transported out of airway by muco-ciliary clearance.[56] Glycosylated viruses secrete lectins like trefoil factor to mucus which cross link viruses by binding to glycan on both viruses and mucins.[57] SARS-CoV-2 spike glycoprotein is glycosylated and bind to glucosamino glycans[58] and sialylated glycans[59] of mucin. The mucosal barrier only in well hydrated state maintain its structural integrity and enable constant flow of mucus to remove trapped viruses from airways. Dry air inhalation causes mucociliary dysfunction and respiratory barrier impairment which promotes initial infection and expansion of viruses with in airways of infected person.[60] Dry air inhalation particularly in winter causes dryness and viscous of nasal mucus which leads to decrease the capability of cilia to expel viral aerosols, loss of airway epithelial cell cilia, detachment of epithelial cells and inflammation of trachea.[61]

Cold air temperature increases infection and severity of COVID-19 possibly from following reasons: i). Low temperature provide suitable survival and reproductive conditions for SARS-CoV-2, ii). Low temperature induces vasoconstriction of the respiratory tract which leads to weakening of immune system, iii). Dry cold air induces small rupture in nasal mucosa and thereby creating opportunities for virus invasion. iv). Ciliary beating decline in cold temperature which is associated with decrease the capability to expel viral aerosol from respiratory tract.[62]

The concentration of both PM10 and PM2.5 are significantly higher in winter than summer. PM2.5 concentration is correlated with the incidence of COVID-19.[63] It potentiates transmission ability of COVID-19 in three ways: (i) It disrupts the integrity of human respiratory barrier and allows entry of pathogen into deeper respiratory tissue[64], (ii) It forms condensation nuclei for viral attachment[65], (iii) Fine PM due to its smaller size penetrates the respiratory tract and reach alveoli directly.[66] Besides the above fine particles in polluted air induces citrullination of innate antiviral peptide LL-37. Such citrullination blocks the antiviral capacity of LL-37 and exacerbates COVID-19.[67]

Vitamin-D has crucial role in modulating inflammatory response to viral infection.[68] Vitamin-D decreases concentration of pro-inflammatory cytokine, IL-6, in lipopolysaccharide-induced inflammation.[69] IL-6 is the main culprit in COVID-19 induced ARDS. Vitamin-D also reduces lipopolysaccharide-induced lung injury by blocking the effects on the Ang-2-Tie-2 and renin-angiotensin pathway.[70] Vitamin-D deficiency hampers innate immune defense by impairing maturation, lysosomal enzyme synthesis and hydrogen per oxide production of macrophages.[71] Active form of vit-D stimulates transcription of cathelicidin. Cathelicidin is cleaved to form antiviral peptide LL-37 which destroys wide range of microbes including enveloped viruses.[72] Thus vit-D deficiency is associated with increased risk of

viral infection. Mortality rate for COVID-19 is the highest for people having age more than 80 years and same age group are living with highest level of vitamin-D deficiency. Black Asian Minority ethnics in UK particularly affected by COVID-19[73] and at higher risk of vitamin-D deficiency.[74] COVID-19 induced cytokine storm and consequent ARDS is more potent among vitamin-D deficient people.[75] Thus lack of sunlight in winters deplete vitamin-D level and making them more susceptible to COVID-19.

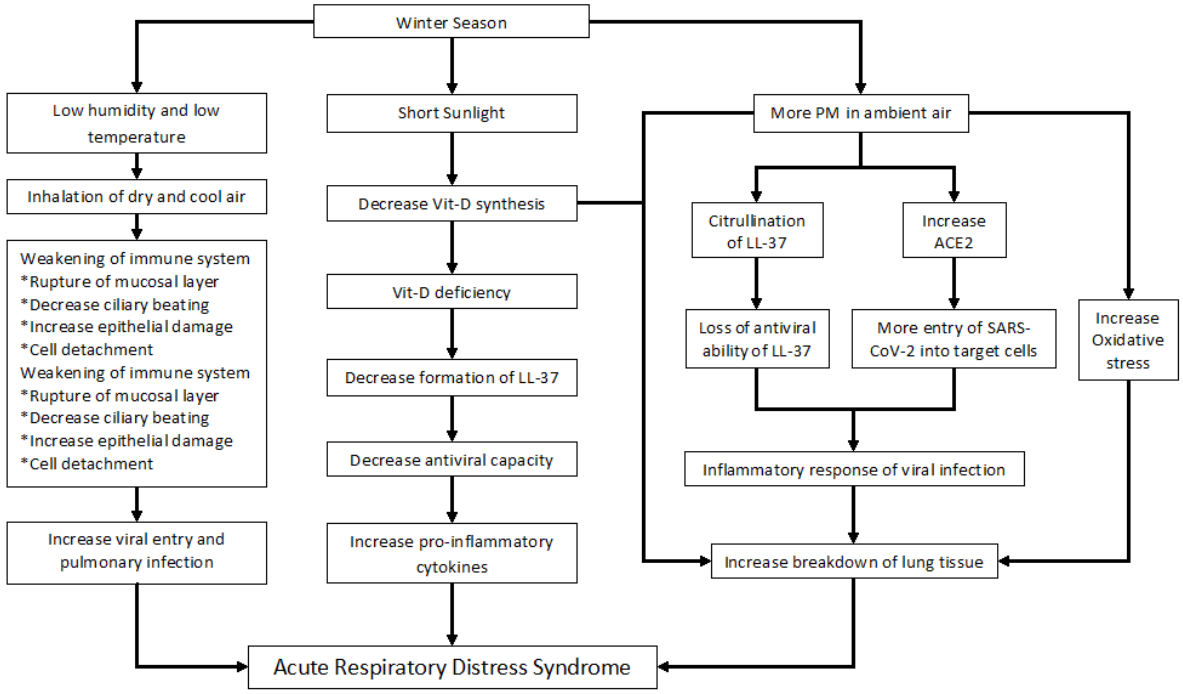

Fig. 1: Impact of winter season on COVID-19 transmission and severity.

PREVENTIVE MEASURES

1. Maintain relative humidity to 40-60% at room temperature.
2. Air ventilation: Poor ventilation and overcrowding increase the density of virus particles in air and surfaces in a room. Concentration of viral particles in the air of an indoor space is inversely proportional to the ventilation rate of the room.[76] Thus improving ventilation in indoor spaces including public transport, hospital, nursing homes shops, offices, schools, restaurants and cruise ships is an important measure to restrict transmission. Following points should be considered for improvement of ventilation:

*Increase natural ventilations like opening of windows during indoor stay.

*Increase existing ventilation rate and its effectiveness using existing system.

* Eliminate any air-recirculation with in ventilation system.

*Enhancement of ventilation capacity with portable air cleaner with mechanical filter system particularly when there is air-stagnation. Mechanical filter system capture airborne micro droplets. Filter must be replace time to time for better results. High –efficiency particulate air filter can remove small particles that may adsorb SARS-COV-2

3. Face mask: Well fitted N95 or similar masks provide effective protection from respiratory droplets and airborne aerosols. Face covering reduces the spread of respiratory droplets from infected individuals during coughing, sneezing, talking and singing. Widely use of face covering suppress community transmission.
4. Sanitization: Proper hand washing is the essential measure to prevent transmission of SARS-CoV-2. Hands should be washed with soap and water for at least 20 second. If soap and water are not available 62-71% alcohol based disinfectant can also be used. Hands must be washed:

- After contact with secretions, excretions and biological liquid.
- After contact with potentially contaminated objects like gloves, masks, clothing, waste etc.
- Immediately after removing gloves and other protective equipment.

5. Reduce close contact: This can be done by applying following recommendations:

- Avoid direct physical contact like shake hands.
- Avoid close contact with people who suffer from acute respiratory infection by keeping at least 1m distance particularly when they cough, sneeze or have fever.
- Avoid direct contact with in 2m and more than 15 min.
- Reduced contact with people in a close environment like class room, public transport and hospital waiting room beyond 15 min and at a distance less than 2m.,

6. Maintain social distancing: Social distancing means reduce interaction between people in a community in which individual may be infectious but have not identified. SARS-Cov-2 are transmitted by respiratory droplets. Such transmission require a certain proximity of people. Thus social distancing of persons will reduce transmission. Social distancing is particularly useful in setting where community transmission is believed to have occurred but where the linkage between the cases is unclear.
7. Avoid touching face: Hands touch many surfaces and can pick up viruses. Once contaminated, hand can transfer the virus to eyes, nose or mouth.
8. Disinfection: In COVID-19 outbreak center extensive surface contamination was detected. SARS-COV-2 were noted not only in medical equipment but also in printers, desktops, key board, door handles and telephones in hospital.[77] Personal objects, such as mobile phones, laptop and mugs those are exposed to respiratory droplets should be disinfected regularly and time to time. Surface disinfectants to remove SARS-COV-2 virus are ethyl alcohol (62-70%), Hydrogen peroxide (0.5%) and sodium hypochlorite (0.1%) with a contact time of 1 minute.[78] Hand soap can also inactivate surface virus but require more time than previous.[79] According to CDC hot water (temperature >65^{0}C) can be used as surface disinfectant.[80] N95 mask can be sterilized and disinfected by thermal method (at least 50^{0}C for 30 minutes). Hydrogen peroxide gas is suitable for disinfecting devices used for viral infected patients, hospital rooms and N95 masks.[81]
9. The people who are at higher risk of vit-D deficiency should consider taking vit-D supplementation to maintain circulating 25 hydroxy cholecalciferol in the optimum level.[82]

CONCLUSION

COVID-19 outbreak, global health emergency is a life threating disease to human being. Both droplets and aerosols generated from expiration of SARS-CoV-2 infected people is the dominant route of transmission of COVID-19. Such transmission is more significant in the built environment. The winter season with low humidity, low temperature and more PM in ambient air promote sustained transmission of SARS-CoV-2. Winter environmental factors (low humidity and low temperature) and more air pollutant (particularly PM) increase respiratory infection. The lack of sunlight in winters deplete vitamin-D level and making them more susceptible to COVID-19. Personal protection including wearing face mask, sanitization, reduce close contact, maintain social distancing and avoid touching face shall be recommended for SARS-CoV-2 protection. In cold winters outdoor temperature is low and indoor environment is heated which leads to reduce relative humidity of air that enters into indoor from outdoor. Low humidity increases airborne transmission. Thus maintenance of relative humidity within 40% to 60% is important in indoor spaces to restrict transmission. Improving ventilation of public spaces dilute and clear out potentially infectious aerosols.

ACKNOWLEDGEMENT

The author would like to acknowledge Mr Sudeep Kumar Das, Assistant Professor in Physics, Durgapur Government College and Dr.Tuhin Ghosh, Assistant Professor of Chemistry for their support in preparation of manuscript.

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