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Game of transmissions (GoT) of SARS-CoV-2: Second wave of COVID-19 is here in India
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Abstract
Corona virus disease (COVID-19) pandemic had taken the humankind by surprise, yet the world laid out a historical battle against all the odds. Laboratory findings have never been so rapidly made available to common public and authorities. Experimental data on COVID-19 from across the globe was directly made accessible worldwide. The second wave of the pandemic in India caused unprecedented havoc and it can be stated that all the knowledge of the game of transmission of COVID-19 acquired and shared was not played with right precision and preparations. Rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the second phase made us rethink if the choice of information given to the common people pertaining to the selective transmission restriction pathways with pressing concern on lethality were inadequate. Most of the governmental and non-governmental organizations (NGOs) including the World Health Organization (WHO) recommended droplet-based and airborne transmission restrictions as the major steps to control rapid spread of the virus. While, no caution was advised for other plausible pathways like sewage, wastewater-based and non-ventilated indoor air-based transmissions, which are still unknown or not well investigated, and are equally dangerous. The main focus of this article is to analyse the past development about SARS-CoV-2 transmission pathway related recommendation(s) provided by WHO and track the trajectory to alert all the concerning stakeholders and policymakers to rethink and to collect adequate scientific data before they recommend or neglect any specific or all the possible transmission pathways to control the spread of infectious agents further.

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Introduction
COVID-19 had detrimental effect on billions of individuals globally. Restraining the virus from further spreading requires a better understanding of SARS-CoV-2 transmission. Thorough understanding of the transmission capabilities of the virus, after a year and half since the onset of the pandemic, has once again become crucial to assess its true potential [1]. Although globally followed isolation among the population do have a potential of restricting the spread of the disease, its effectivity lies in the detection of asymptomatic infected individuals [2]. Therefore, isolation should also be followed by rapid contact tracing and clinical testing. There are several documented modes of SARS-CoV-2 virus transmission including fomites, aerosols, droplets, etc. Here, we are trying to explore other plausible routes of transmission that can lead to further spreading of the virus. Further, referring to very popular proverbs viz., “Prevention and protection is better than cure” and “It is definitely better to be safe than to be sorry”, until extensive research data nullifies or ascertains pathways of transmission, we believe that all the probable routes/modes should be considered and relevant guidelines should be formulated which can be updated upon availability of newer data. In order to get a better understanding of the various transmission channels and the probable dynamics SARS-CoV-2 has been compared with its counterpart viruses [3].

This current pandemic clearly showed us that one directional thinking and approach can become our deficiency in identifying, understanding, and analyzing/estimating all the risks, routes and impact related to SARS-CoV-2 transmission which, created and aided the already devastating pandemic state of affairs.
Neglecting any/many specific modes of transmission of such pernicious diseases can lead to dreadful denouement worldwide. Thus, the main aim of this article is to sensitize the public, all the stakeholders and policy makers universally to recognize all potential mode for transmission of highly contagious and deadly diseases through rigorous investigations beforehand and formulation of simple strict regulations for public health safety.

Modes of transmission (confirmed)
There are currently three confirmed modes of transmission of SARS-CoV-2 that are known and verified: a) direct contact with infected individuals and surfaces (fomites) b) large size respiratory droplets, and c) small (airborne) aerosols [4]. The airborne transmission of the virus is still getting studied rigorously with new research techniques and results uncovering various new aspects about it. As per traditional understanding, it involves the inhalation of infectious aerosols or droplets smaller than 5 μm coming from a distance of more than 1–2 m from the infected individual [5]. A few studies have detected SARS-CoV-2 RNA in air using polymerase chain reaction (PCR) testing [6]. The RNA concentration ranged from 2.9 copies/L (patient room) [7], 2.6 copies/L (isolation room) [8], 0.02 copies/L (washroom), to 0.03 copies/L (personal protection equipment (PPE) removal room [9]. The other modes of transmission such as particles from wastewater discharge point, wastewater sprinklers, direct exposure during wastewater sampling/handling, public washrooms, etc., need to be investigated in a comprehensive manner, as are being done for air-borne transmission, to get the complete picture about how the virus is spreading in different environments. This, in turn, will enable us to come up with more effective prevention measures and effective guidelines.

Modes of transmission (theories)
Figure 1 shows that the extent of deadliness and contaminating efficacy of COVID-19 virus is much lesser than other life-threatening diseases. However, the transmission capacity of SARS-CoV-2 seems higher than causal microbes of those diseases. Thus, there must be other possible transmission route of SARS-CoV-2 virus. Some of the routes of transmission may include fecal-oral and bio-aerosols (pollution to human) transmissions [10,11] [Anand et al., 2022] Even though, these pathways are not well investigated and are at a speculative juncture now, they cannot be ignored/totally discarded, solely based on the lack of concrete evidence [12] for safety. Accumulating and analyzing evidence from the current pandemic and previous outbreaks, it can be postulated that wastewater and other aquatic environments can be a potential transmission media/route for the virus [9]. However, collecting data and gathering knowledge is a time taking process and therefore, even if the chances are remote, the possibility of such transmission pathways should not be ignored as
it can put precious life at risk. Further, more resistant and infectious mutations of SARS-CoV-2 may appear when mediated by contact with wastewater [13]. SARS-CoV-2 and other infections may be able to survive in wastewater plumbing systems (faecal aerosol transmission), according to new findings [14].

While hand cleanliness is important in avoiding faecal-oral (through contact with respiratory mucosa) transmission, boosting bathroom ventilation and running faucets occasionally to keep U-trap water seals from drying out, especially in high-rise buildings, may also assist. However as per WHO directives, there are no significant evidence of COVID-19 spreading through contaminated water as the virus is more quickly inactivated in the presence of high temperature, oxidants, and other disinfectants [15]. A study by Wölfel et al., [16] also adds to the growing body of data suggesting infectious SARS-CoV-2 transmission in faeces is uncommon, if it happens at all, and that fecal-oral transmission is unlikely to be a key mode of virus transmission. Patients with COVID-19 often face diarrhoea, vomiting, nausea, and stomach discomfort, which can occasionally forego respiratory symptoms. SARS-CoV-2 virus RNA has been identified in stool samples of COVID-19 patients in a number of investigations, sometimes at extremely high levels. While this indicates that the virus may infect cells in the gastrointestinal system, it should not be mistaken with the residence of the viable or infectious virus in faeces or the possibility of fecal-oral transmission. This notion will have to wait for larger-scale experiments to be confirmed.

As per air transmission route is studied, it transformed into a more complicated phenomena with the availability of more research data and development of the aerosol transmission theory, there could be possibility of virus stability in air for a longer distance and longer duration depending upon the host-particle size and meteorological conditions. A study set up to validate the transmission of SARS-CoV-2 using ferret model concluded that the viral particles transmission occurred over more than 1 m through air [17]. This ‘through-air’ transport of virus-laden particles can be attributed to the dominance of air currents on smaller droplets compared to the gravitational force. Ambient particle (aerosols) size ranges from a few nanometers (nm) to several micrometers (μm) with the highest residence time (about a week) of the accumulation mode particles (0.1–1 μm). Further, smaller particles (< 1 μm) are relatively much more in number/concentration compared with bigger particles (> 2 μm). Also, accumulation mode particles also have larger surface area, suggesting that these particles can be a good host for supporting viruses. Any virus that once attaches to a particle surface can travel over long distances along with the particle (up to thousands of km, in principle). Ambient meteorological conditions such as wind speed and direction, relative humidity, temperature, etc. also play an important role in particle’s transport. These droplets can travel through 10s of meters depending on the above-mentioned parameters [3,18]. Further, particles with less than 10 μm (aerodynamic diameter) are inhalable, and even finer particles (< 1 μm) have deeper reach in the lungs (lower respiratory tract) [19]. The aerodynamic analysis of SARS-CoV-2 and SARS-CoV-1 illustrates that both can spread through air [20]. Similar characteristics were shown by Influenza and Norwalk virus following air transmission route to infect ferrets and children [21,22].

The next most conjectured transmission route of the virus is through water and wastewater [13,23]. Contamination via sewage and wastewater is a potential transmission route that needs to be analyzed and studied meticulously. Recent reports indicated that the Coronavirus can survive for days in wastewater and even longer in drinking water [24,25]. It can contaminate the drinking water supply through leakage in the pipeline or in low disinfectants conditions. The aerosol generated from those contaminated water resources can infect human [24,26]. The presence of SARS-CoV-2 RNA in fecal matter of COVID-19 positive patients for long duration indicates the possibility of presence of viable viral particles in wastewater/greywater [19,27–29]. Wastewater data from more than 11 countries reported to contain SARS-CoV-2 RNA. Thus, water related activities like swimming, fishing, canoeing/rowing, and shower can generate aerosols that contains live viral particles and infect new hosts [30]. Apart from this, the spread of infection might also occur through aerosols being generated during the investigation of these aqueous matrices [13], boarding flights, physical gatherings, and meetings, exposure to body fluids, visiting dentist clinics and hospitals, intrapartum, etc. This highlights the necessity for a risk assessment and management framework specialized to SARS-CoV-2 transmission via wastewater, as well as new environmental surveillance techniques and proper disinfection as part of the broader COVID-19 pandemic containment strategy [31].

A study on the viability of SARS-CoV-2 virus in river water and wastewater (filtered and un-filtered sample) at two different temperatures of 4 and 24 °C, generated concern about the infectious nature of the virus, as it was viable longer in filtered sample and low temperature [23]. Pathogens that are detected and known to have certain amount of health risk(s), transmissible through wastewater are Adeno, Astro, Hepatitis, Rota, Noro, and few Enteroviruses [25,26,32–35]. Various studies have documented the presence of SARS-CoV-2 in wastewater [13,23–25]. In countries with higher infection rates, consideration of this additional transmission channel might just become a significant event as a certain (infectious) portion of the virus might be still viable [36].
Countries with overburdened Wastewater Treatment Plants (WWTPs) and low sanitation strategies should follow precautionary measures until data on infectivity is obtained from a large number of sample analyses globally [36].

According to the WHO, the existing drinking water disinfection technique could efficiently inactivate most of the bacterial and viral populations found in water, particularly SARS-CoV-2 (more sensitive to disinfectant like free chlorine). Only one research has established that SARS-CoV-2 infectivity in water for humans is nil, based on the lack of cytopathic effect (CPE) in infectivity assays. As a result, more research should be done to see how long SARS-CoV-2 may survive in water and wastewater under various operational settings (such as temperature and water matrix) and if COVID-19-contaminated water can transmit to humans. Although paper-based devices for detecting SARS-CoV-2 residues in water have been suggested, procedures and adequate devices need be developed shortly [37].

Transmission in public and private spaces
The airborne transmission can be a very serious issue in the case of poorly ventilated indoor environments. This form of infection can result in clusters of cases from a small area in a short period of time [38,39]. A recent study showed infectious rate of 16.3% from an index patient to a healthy individual in the same household [40]. Age and spousal relationship were the key factors in SARS-CoV-2 transmission inside the household [41]. Another study indicates the transmission of virus from index patients in one apartment to healthy individuals in other apartments through airflow in pipes [40]. Closed indoor areas (e.g. rooms/elevators/shops/restaurants/air conditioned premises) with improper ventilation and contaminated drainage systems might accelerate the transmission [3].

India’s second wave (possible reasons)
The impactful second COVID-19 wave has infected millions and claimed lives of thousands alone in the month of April, 2021. Our study has cumulated all other studies till now suggesting possible reasons for this massive outbreak: I) Studies on already antibody-prevalent individuals showed that only 7 out of 100 people have antibodies-prevalence at present. This indicates that the existence of antibodies ranges only between 3 and 6 months in majority of population [42]. II) The new variant B.1.617 (Delta) on grounds of B.1.1.7 (Alpha or UK-variant) and B.1.351 (Beta, South African variant) was detected as VOCs (Variant of Concern). Details genetic analysis of these VOCs indicted a dual mutation in spike proteins and RNA polymerase genes that makes these variant more transmissible than the wild-types. B.1.617 infects and colonizes the lower respiratory tract, making the disease more persistent and severe. This emerging mutated delta variant manifesting higher pathogenicity and transmissibility [42,43], was present in most of the samples tested in Maharashtra, India [44]. III) Besides the contagious double mutant variant, the other reasons were the population’s negligent behavior (in wearing protective N-95 masks in public places, inattentiveness towards following strict COVID protocols), certain relaxations from lockdown for smooth functioning of day to day lives [45], population size and density/distribution and lack of proper awareness especially in rural regions. IV) The fourth reason which, is suggested earlier in the article, is the airborne transmission of the mutated variant(s), applicable over a larger area and longer duration. V) With the grand successful vaccination campaign in the country, keenness to keep following the COVID protocols faded and the awareness about the fact that not all variants (also future mutations) might be sensitive to the vaccines was rare.

It is well established that on inhalation, coarse particles (>1 μm) are trapped in the nasal and trachea region whereas, finer particles (1 nm–1 μm) can reach deeper into the lungs (alveolar region) [46]. Virus residing fine aerosols could reach directly to the deeper parts of human lungs and affect the lungs (might be a possible reason for many cases of negative RT-PCR test report but corona positive in the second wave). The virus riding very small particles (<100 nm) can penetrate through the epithelial cells to the blood stream, and in principle can reach any part of the body. This might be amongst possible causes of many happy hypoxia cases in the second wave. Poorly ventilated indoor places such as schools, cinema halls, auditoriums, shopping malls, food plazas, etc. with asymptomatically infected individuals and higher abundance of fine aerosols can be a big source of the uncontrolled spread [47].

Figure 2 indicates WHO’s directive with the timeline on COVID-19 transmission of VoCs and the various direct and indirect routes. It took about five months to develop the timeline of transmission pathways (Figure 2), and more extensive ground research is needed to extend/branch the timeline further. Proper communication and monitoring of all these pathways at the very beginning of the pandemic would have resulted in more effective systems in controlling the COVID-19 transmission and related fatalities. Thus, it is proposed that all the related stakeholders and the controlling bodies should not neglect any of the possible disease transmission pathways unless until it has been proven to be non-transmissible scientifically with valid and sufficient data. Rapid mutation of SARS-CoV genes makes it difficult to understand the exact mode(s) of transmissions due to lack of related data.

Recently, Omicron and Delta variants showed much more infectivity and transmission ability than all of the
previous variants even though their clinical symptoms manifested were different. There are not enough data on how mutation(s) in certain genes makes some variants (e.g., Omicron) much more infectious while other variants (e.g., Delta) much lethal than the parent virus or other strains. Data on population (demography) susceptibility and geological location effect on the occurrence, spread and persistence of the disease are also not established fundamentally. Also, the virus shedding in vaccinated populations and their variations with types of vaccines used are not established profoundly. Thus, a dedicated and efficient surveillance system for all types of transmission mode should be developed to generate enough data sets for quick identification of the right modes for transmission for any such disease(s). Based on these data, standard procedures must be ascertained such as suggestion to continue to wear only surgical (use and throw) followed by N-95 masks, precaution rules to be aware of and careful handling/dealing with water and wastewater, continuation of wearing of PPE gowns and gears for flight travels, maintaining COVID rules in public places, etc., could be sectioned into established guidelines and precautionary/preventive measures for public health safety.

**Conclusion**

The current study provides a collective analysis from various studies around the world on COVID-19 disease and its transmission. The second pandemic wave has proven to be fatal globally and the far-reaching consequences of this were particularly evident in India. During these times, when studies on majorly two of the transmission routes of SARS-CoV-2 are confirmed, the possibility of transmission through other routes should
not be ignored, until discarded with scientific proof. As the negative reported studies on these probable routes are from a definite number of datasets, the infectious nature of virus can still prevail via these lesser studied routes. Hence, there is an urgent need for risk assessment and management framework customized for SARS-CoV-2 transmission via different pathways. In the present manuscript, an effort has been made to accumulate the collective knowledge of these studies along with our own theory and help researchers and policy-holders to be more precautionary about the possible COVID-19 transmissions.

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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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