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A chronicle of SARS-CoV-2: Seasonality, environmental fate, transport, inactivation, and antiviral drug resistance

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ABSTRACT

In this review, we present the environmental perspectives of the viruses and antiviral drugs related to SARS-CoV-2. The present review paper discusses occurrence, fate, transport, susceptibility, and inactivation mechanisms of viruses in the environment as well as environmental occurrence and fate of antiviral drugs, and prospects (prevalence and occurrence) of antiviral drug resistance (both antiviral drug resistant viruses and antiviral resistance in the human). During winter, the number of viral disease cases and environmental occurrence of antiviral drug surge due to various biotic and abiotic factors such as transmission pathways, human behaviour, susceptibility, and immunity as well as cold climatic conditions. Adsorption and persistence critically determine the fate and transport of viruses in the environment. Inactivation and disinfection of virus include UV, alcohol, and other chemical-base methods but the susceptibility of virus against these methods varies. Wastewater treatment plants (WWTPs) are major reservoirs of antiviral drugs and their metabolites and transformation products. Ecotoxicity of antiviral drug residues against aquatic organisms have been reported, however more threatening is the development of antiviral resistance, both in humans and in wild animal reservoirs. In particular, emergence of antiviral drug-resistant viruses via exposure of wild animals to high loads of antiviral residues during the current pandemic needs further evaluation.

1. Introduction

With dreadful global lockdown and search for effective medicine against the novel coronavirus (SARS-CoV-2), efforts to understand the perspectives of coronavirus disease 2019 (COVID-19) is still ongoing. Many countries are implementing different plan of actions to deal with the COVID-19 pandemic and understanding their impact on the society (van der Voorn et al., 2020). Also, the prevalence of SARS-CoV-2 in the aquatic environment as a result of this global pandemic is of great concern (Kumar et al., 2020c). In this effort, our team has recently published a review on epidemiology, prognosis, diagnosis, transmission and treatment of COVID-19 (Kumar et al., 2020c).

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SARS-CoV-2 RNA are reported in feces of patients in the US and China (Wang et al., 2020a; Liang et al., 2020). Furthermore, reports have suggested that SARS-CoV-2 are present in patients’ stool as well as in wastewater (Kitajima et al., 2020). This is alarming for possible transmission to humans via contaminated water. At the same time, this has provided an opportunity to carry out wastewater-based epidemiological studies for community-wide estimation of COVID-19 prevalence (Kitajima et al., 2020; Kumar et al., 2020d).

Further, transport and infectivity of SARS-CoV-2 in wastewater/environmental waters are highly dependent on the physical and environmental susceptibility of SARS-CoV-2 as well as inactivation. As per the inactivation mechanism, environmental stressors become critical for the disruptions of proteins and lipids of viral envelope leading to their seasonal variations (Kumar et al., 2020b). Along with host immunity, climatic factors would also influence human respiratory air passage defence. Since such information is barely available related to SARS-CoV-2, there is a dire need to understand similarities and dissimilarities of respiratory coronavirus (positive-stranded RNA viruses with nucleocapsid) with various viruses including enteric viruses (Van Der Hoek et al., 2004). Such information will be of immense help to understand structural, and environmental susceptibility and inactivation mechanisms for SARS-CoV-2.

With surge in COVID-19 patients (>20 million people) as of the second week of August, 2020, large number of antiviral drugs (remdesivir, ivermectin chloroquine and hydroxychloroquine) have been clinically tested. However, there is no data available on the quantum of antiviral drugs being used to treat such extraordinary number of COVID-19 patients. So far, a large number of antiviral drugs have been discovered till date (Fig. 1), but the quest of finding viral cure seems to be never ending due to insufficient effectiveness of such treatments and high viral mutation rates which lead to emergence of resistant strains (Irwin et al., 2016; Race et al., 2020; Sanjuán et al., 2010; Duffy, 2018). Furthermore, studies reported that the administered drugs are not fully metabolised in the human body, thus generating residues and metabolites. The drug residue and metabolite are discharged into the environment through sewage leading to spikes of antiviral drugs in wastewater and ambient waters (Race et al., 2020; Funke et al., 2016; Khetan and Collins, 2007). In addition, studies confirmed incomplete removal of antiviral drugs in wastewater treatment plants (WWTPs) (Nannou et al., 2020; Mlunguza et al., 2020; Ngumba et al., 2020). The unprecedented use of antiviral drug during pandemic events, has led to the development of antiviral-drug resistant viruses within wild animal reservoir and may compromise the treatment of COVID-19 patients (Ahmed et al., 2020; Musharrafieh et al., 2020). Therefore, the occurrence and fate of antiviral drugs in the environment during this unprecedented pandemic need a special attention.

Under the light of above discussions, we hereby present a comprehensive review on physical and environmental susceptibility, seasonal variations, inactivation mechanism, discovery and transport of antiviral drugs, transport and fate of viruses in the Anthroposphere. The review also discusses the role of vital factors like carrier prevalence, treatment efficacy of wastewater burden (virus source), transport among environmental compartments of viruses and their inactivation mechanisms, and the current unprecedented use of antiviral drugs. Special emphasis is given on understanding the transport of both viruses and antiviral drugs, alongside treatments and governing mechanisms of SARS-CoV-2 inactivation. We then finally present the current global status of antiviral drug resistance, and future scenarios of antiviral drug resistance both in pandemic viruses and infected humans. Overall, we intended to prepare an insightful ready reference that can not only help the readers identifying critical variables governing COVID-19, but also raise awareness of some likely aftermaths of the current pandemic.

2. Seasonality of viruses and viral infections

Transmission of viruses and the manifestation of infection depend on transmission pathways, human behaviour, susceptibility and immunity. Environmental factors, such as climatic conditions and behaviour of virus hosts and vectors, also play a formidable role that translates into several distinct seasonal trends of viral infections. Wuhih et al. (1994)
investigated the seasonal pervasiveness of Microsporidiosis and Cryptosporidium parvum in immuno-compromised HIV positive (+ve) patients, and reported a profuse infection in the rainy seasons. However, the reported course of seasonal prevalence of these parasites was not statistically significant. Their prevalence depends on the HIV infection and hence, is mainly related to the fecal-oral route, zoonotic emanation, statistically significant. Their prevalence depends on the HIV infection virus, and human metapneumovirus are identified all along the year and (Anestad, 1982). Antithetically, human bocavirus, rhinovirus, adenovirus, and humidity (Christophers et al., 1998). The reported incidences of variation of respiratory infectious virus and observed that the key factors determining the prevalence of the virus were change in temperature and humidity (Christophers et al., 1998). The reported incidences of influenza and other respiratory epidemics are significantly higher in winter season than summer and spring seasons (Mourtzoukou and Falagas, 2007; Peci et al., 2019). In addition, in line with the various epidemiological research, the majority of the respiratory virus outbreaks in temperate zones exhibit seasonal fluctuations. In particular, human coronavirus (types: HKU1, 229E, OC43, and NL63), influenza virus and respiratory syncytial virus culminate in the winter season and are commonly known as winter viruses (Monto, 2002; Landes et al., 2013; Morikawa et al., 2015; Midgley et al., 2017; Killerby et al., 2018).

Incongruence in the replication of these viruses leads to a non-overlapping prevalence with respect to each other. It has been found that respiratory viruses such as respiratory syncytial and influenza viruses, even being pervasive in winter, do not occur simultaneously (Anestad, 1982). Antithetically, human bocavirus, rhinovirus, adenovirus, and human metapneumovirus are identified all along the year and are called as all-year viruses (Bastien et al., 2006). However, Lee et al. (2012) reported that rhinovirus infection surfaced during fall and spring, but the disease ferocity was highest in winter. On the other hand, the rate of recurrence of several enteroviruses escalates during summer implying the significance of seasonality of viral infections (Haynes et al., 2016; Abedi et al., 2018). Further, the transmission efficiency of viral infections via all possible pathways depends on outdoor and indoor climatic factors. Kudo et al. (2019) illustrated that lower humidity could induce a decrease of Mx1 congenic mice weight, increase in mortality rate, pulmonary viral load, and infection with influenza virus.

Viral epidemics such as SARS (2002–2003), MERS (2012–2015) and the current COVID-19 pandemic emerged in winter before their subsequent worldwide spread (Kuiken et al., 2003; Peiris et al., 2003; Paules et al., 2020), these respiratory viruses (coronaviruses: SARS-CoV, MERS-CoV, and SARS-CoV-2) aggrandizes in the winter season. Seasonality also governs the host propensity by moderating human pulmonary or nasopharyngeal innate defense mechanisms, and thus, regulates respiratory virus effectiveness/viability and dissemination (Moriyama et al., 2020). Therefore, the key determining characteristics of respiratory viral outbreak is pathogenicity which is severely affected by seasonality i.e. sunlight, temperature (winter), absolute humidity (dry season), host susceptibility due to cold weather, and seasonal changes in immunity (Dowell, 2001; Shoji et al., 2011; Sloan et al., 2011; Tamerius et al., 2011; Aziz Baumgartner et al., 2012; Fisman, 2012).

3. Transport of viruses

Adsorption and persistence are the two major elements that affect the fate and transport of viruses in the environment. Survival of viruses is typically evaluated by reduction time: T90, T99, or T99,99, which are the time required for viruses to reduce by 90%, 99%, or 99.99%, respectively, under certain environment. The reduction of various viruses in environmental waters are summarized in Table 1. In general, viruses with high persistence have a high capability of causing infection within the environment. Although literature around transport of SARS-CoV-2 in the surface and subsurface medium is not available, several factors, including soil-specific, virus-specific, and environmental factors might influence the transport of the virus in the environment (Aw and Gin,

| Categories | Types of water | Time | Reduction | Time | Reduction | Time | Reduction |
|------------|---------------|------|-----------|------|-----------|------|-----------|
| Surface Water | T99 | 6.5-8.8 d (Casanova et al., 2009) (HCoV, FCoV), | – | – | 3.8 d (Casanova and Weaver, 2015) | – | 10.8 h (Surface water, L) |
| Groundwater | T99 | 49 d (John and Rose, 2005) (HCoV), | – | – | 53 h (Ye et al., 2016) | – | 540 h (Effluent, D) |

TGEV: Transmissible gastroenteritis virus; MHV: Mouse hepatitis virus; SARS-CoV: Severe acute respiratory syndrome coronavirus; PP: Pseudomonas Phage.
Table 2
Probable inactivation mechanism for enveloped and non-enveloped viruses (Meister et al., 2018; Duizer et al., 2004; He et al., 2004; Darnell et al., 2004; Rabenau et al., 2005; Kingsley et al., 2002; Croughan and Behbehani, 1988; Wilde et al., 2016; Jeong et al., 2010; Shin and Sobsey, 2008; Tree et al., 2003; Kratzel et al., 2020; Kamp et al., 2020; Hu et al., 2020; Glass and O’Brien, 1980; Kapuscinski and Mitchell, 1980; Xing et al., 2019; Andersen, 2019).

| Category         | Virus                      | Morphology | Inactivation Mechanisms | Heat (Temperature Dependent) | Acid/Alcohol | Other                      |
|------------------|----------------------------|------------|-------------------------|------------------------------|--------------|----------------------------|
| **Enveloped**    | **Coronavirus**            | 80–120 nm  | ss RNA                  | 26,000–32,000 bases          |              |                            |
|                   |                            |            |                         | UV-C light/ozone             | Benzalkonium chloride & Laurylamine (RF > 3,8, 60 min) (Kapuscinski and Mitchell, 1980), didecyldimethyl chloride (RF > 3,60 min) (Kapuscinski and Mitchell, 1980), Hypochlorite (0.1–0.5%), 2–4 log₁₀ (Simunek et al., 2016) | Heat Treatment (> 65 °C) (Glass and O’Brien, 1980), Heat Treatment (60 °C, 30 min) (Kapuscinski and Mitchell, 1980), Heat on serum (56 °C, 30 min, 90% inactivation,7–14 min) (Weber and Stillanakis, 2008) | Sterilization (propanol, ethanol) (RF > 4,3, 30 s), (Ethanol, biphenylyl)(Kapuscinski and Mitchell, 1980), Ethanol (80%v/v) (3.8 log₁₀ and 2-propanol (75%v/v) (30 S, > 3.8 log₁₀) (Park et al., 2011) | Catalytic Oxidation (Ag, 5 min & Cu, 20 min) (Hu et al., 2020), Formaldehyde (Glass and O’Brien, 1980) & Glutaraldehyde (Glass and O’Brien, 1980), (Kapuscinski and Mitchell, 1980), Incidin Plus, Wine Vinegar ($\text{Simunek et al., 2016}$), Glutaraldehyde (2%, 2–4 log₁₀) ($\text{Simunek et al., 2016}$), 0.1 mol/LNaOH (Azapdour-Keley and Ward, 2005), Ethylene Oxide surface treatment (Azapdour-Keley and Ward, 2005) | – |
|                  |                            |            |                         |                              |              | Marine bacteria            |
|                   | **Influenzavirus**         | 80–120 nm  | ss RNA                  | 13,500 bases                 |              |                            |
|                   |                            |            |                         | UV-C irradiation²            |              | Ammonium/Alcohol Product   |
|                   |                            |            |                         |                              |              | (> 3.5 log₁₀), 70% isopropyl-alcohol (> 5 log₁₀) (Babich and Stotzky, 1979) | Lysol, Listerine, Alcohol (Vettori et al., 2000) | – |
|                   | **Flavivirus**             | 50 nm      | ss RNA                  | 11,000 bases                 |              |                            |
|                   |                            |            |                         |                              | 500 ppm Cl₂, 50 s (> 4 log₁₀) (Babich and Stotzky, 1979) | Dry Heat Treatment (56–60 °C) (Babich and Stotzky, 1979) | Ammonium/Alcohol Product (> 3.5 log₁₀), 70% isopropyl-alcohol (> 5 log₁₀) (Babich and Stotzky, 1979) | – |
|                   | **Simplexvirus**           | 150–245 nm | ds DNA                  | 152,000 bases                |              |                            |
|                   |                            |            |                         |                              | 50 mM Zinc Gluconate (2 hrs) (100% Reduction) (Xing et al., 2020), Alcide Disinfectant (Vettori et al., 2000) | Temp. of 56 °C in 30 min (Vettori et al., 2000) | Ammonium/Alcohol Product (> 3.5 log₁₀), 70% isopropyl-alcohol (> 5 log₁₀) (Babich and Stotzky, 1979) | – |
|                   | **African Swine fever Virus** | 170–190 nm | ds DNA                  | 189,000 bases                |              |                            |
|                   |                            |            |                         |                              | Nacl and Phosphate Salt (4, 12, 20, 25 °C) (Croughan and Behbehani, 1988) | – | Lysol, Listerine, Alcohol (Vettori et al., 2000) | – |
| **Non-Enveloped** | **Enetrovirus**            | 25–30 nm   | ss RNA                  | 7,200–8,500 bases            |              |                            |
|                   |                            |            |                         | Ozone (Duizer et al., 2004) UV-C irradiation (Rabenau et al., 2005) | Chlorine Dioxide (4 log reduction) (Meister et al., 2018), Monochloroamine (Wilde et al., 2016) 2–4 log₁₀ reduction | Heat (55 °C) (Jeong et al., 2010), Heat (70°C, 30 min) (Shin and Sobsey, 2008) | Methanol & Ethanol (90%) (Tree et al., 2005) | Marine bacteria (Pseudomonas & Vibrio) (He et al., 2004) | Activated Sludge Treatment (Andersen, 2019) |
|                   |                            |            |                         | UV₂₅₄ (Jeong et al., 2010), Sunlight (Jeong et al., 2010) | Y rays (1.0 Mrad) (Shin and Sobsey, 2006), UV (62.50 mW s cm⁻², 4 log₁₀ (Yates and Jury, 1995) | Free Cl (Jeong et al., 2010), ClO₂ (Jeong et al., 2010) | – | Anaerobic digestion under thermophilic condition (Shin and Sobsey, 2008) |
|                   | **HEV/HAV**                | 27–34 nm   | ss RNA                  | 7,200 bases                  |              |                            |
|                   |                            |            |                         |                                | Povidone Iodide (Darnell et al., 2004) | – | Hydrostatic Pressure Processing (continued on next page) | – |
Table 2 (continued)

| Category | Virus | Diameter (Average) | Genome Type | Genome Size | UV Light/ozone | Chloride/iodide/Salts Compounds | Heat (Temperature Dependent) | Acid/Alcohol | Other |
|----------|-------|-------------------|-------------|-------------|----------------|---------------------------------|------------------------------|--------------|-------|
|          |       |                   |             |             | Irradiated with 0.6 J/cm² after dilution with DMEM (Darnell et al., 2004) | Nacl concn. (0.3, 1.3, 3.3, 6.3% [wt/vol])(Kingsley et al., 2002), Monochloroamine (Wilde et al., 2016), free Cl (1 & 5 mg/L)(Schijven and Hassanizadeh, 2000) | 80 °C for 5 min, after dilution with DMEM (Darnell et al., 2004) | Triton, Ethanol, Propanol (Darnell et al., 2009) | (300–450 MPa, 5 min) (Xing et al., 2020) |
| Norovirus | 23–40 nm | +ss RNA | 7,500 bases | UV₂₅₄ (25–100 mJ/cm²) 4 log₁₀ reduction (Kratzel et al., 2020) | 24–85 °C (20 days) (Kingsley et al., 2002) | 4 log reduction (60 °C, 10 min) | Inactivated (85 °C, < 1 min) (Kingsley et al., 2002) | – | – |
| Calicivirus | 27–40 nm | +ss RNA | 7,500–8,500 bases | UV₂₅₄ (25–100 mJ/cm²) 4 log₁₀ reduction (Kratzel et al., 2020), UV-B (0–150 mJ/cm²)(Kampf et al., 2020), UV (62.50 mW s cm⁻², 4 log₁₀)(Yates and Jury, 1995) | Sodium Hypochlorite (300 ppm) (Kampf et al., 2020), Free Cl (30 mg/L, 5 min, 4 log₁₀)(Yates and Jury, 1995) | 3 log reduction at 71.3 °C (Kingsley et al., 2002) | 70% Ethanol (30 min) 3 log₁₀ reduction (Kampf et al., 2020) | – | – |
| Astrovirus | 28–35 nm | +ss RNA | 6,800–7,900 bases | – | – | – | Methanol & Ethanol (90%) (Tree et al., 2003) propan-1-ol, propan-2-ol, butan-2-ol (40%) (10ˢ drop) (Tree et al., 2003) | – | – |
| Rotavirus | 76.5 nm | ds RNA | 37,100 bases | – | – | – | – | – |
| Adenovirus | 90–100 nm | ds DNA | 26,000–48,000 bases | – | Monochloroamine (Wilde et al., 2016) | – | – | – |

DMEM-Dulbecco Modified Eagle Medium; ss-single strand, ds-double strand.
2011) (Supplementary Table 1). Governing features for the migration of viruses in surface and subsurface systems include temperature, rate of adsorption, virus aggregation, moisture content, pH, the concentration of salts, properties of soil, organic matter, strains of the virus, and hydraulic condition (Bosch et al., 2006).

3.1. Adsorption

Being amphoteric in nature, coronaviruses are expected to be attracted and trapped by both positively and negatively charged soil colloids and humus species. Major adsorption is expected to occur in soil having a high concentration of clay. Bacteriophages that are considered to be surrogates for enteric viruses and also used as a process control in the detection of SARS-CoV-2 have shown greater adsorption potential to polyelectrolytes (Dang and Tanabara, 2019; Park et al., 2017) and minerals (Walsh et al., 2010). However, soil is a mixture of minerals, organic compounds, and living microorganisms thereby constituting a tri-dimensional structure with many particularities affecting retention potential where diffusive and convective fluxes are crucial. Thus, it would be difficult to predict the adsorption of SARS-CoV-2 to soil without field data. According to the Derjaguin–Landau–Verwey–Overbeek (DVLO) theory, at higher pH, viruses are weakly adsorbed to soil particles due to an increase in electrostatic repulsion (Armanious et al., 2016). Experiments conducted for adsorption study of human enteroviruses and bacteriophages onto different soils illustrated that decrease in pH increased the adsorption of the most viruses (Goyal and Gerba, 1979; Walsh et al., 2010). The presence of envelope (lipoproteinaceous membrane) and spike proteins, makes SARS-CoV-2 surface property significantly different from non-enveloped viruses (Walls et al., 2020). Presence of various functional groups along with characteristics spike proteins are expected to govern the adsorption, fate and transport of the novel virus in the environment. Despite the lipid layer is significantly vulnerable to several impurities present in the soil, enveloped viruses, such as mouse hepatitis virus (MHV- a murine coronavirus) and Pseudomonas phase (φ6) have shown high adsorption potential onto wastewater solid fractions. Such a difference in adsorptive behaviour of enveloped viruses was possibly due to the dominance of both hydrophobic effects and electrostatic force amidst sorbent surface and capsid protein (Ye et al., 2016; Armanious et al., 2016). Similar force of attraction would play a vital role in the transport of amphoteric SARS-CoV-2 in the aqueous medium. Howbeit, saturated soils filled with water during monsoon season and subsequently increased flow rate reported to increase the virus transport due to less interaction time with soil particles (Funderburg et al., 1981; Jin et al., 2000; Williamson et al., 2005; Betancourt et al., 2019; Yates et al., 1987). Similarly, smaller-sized viruses migrate at a faster rate due to lesser entrapment in the soil pore. Virus transport in fine-grained soil is expected to be slower due to its higher probability in virus retention than in coarse-grained soil. A typical diameter of a SARS-CoV-2 virion is 100 nm (Bar-On et al., 2020), which is larger than many of non-enveloped viruses (Table 2). Therefore, lesser mobility in soil is expected for SARS-CoV-2 owing to its size than that of enveloped viruses which is yet to be demonstrated.

3.2. Persistence

While there is a debate about whether virus inactivation follows first-order or time-dependent processes, several factors including temperature, conductivity, and water quality parameters are reported to inactivate the virus by disrupting the protein coat and nucleic acid. Again, the extent of inactivation of enveloped viruses is found to be high compared to the non-enveloped viruses in surface water, groundwater, and wastewater (Table 1). With an increase in temperature, the rate of enveloped virus inactivation reported to increase compared to non-enveloped viruses. Surrogate coronaviruses are known to retain their infectivity in water from days to several weeks depending upon the surrounding temperature. At low temperature viruses are expected to survive for longer duration and subsequently migrate to a greater distance (Casanova et al., 2009). However, an association of viruses with the colloidal and particulate materials can protect the virus from inactivation and such phenomena were observed for poliovirus Type 1 and bacteriophages (Kapuscinski and Mitchell, 1980; Xing et al., 2020). Similarly, clay minerals are reported to protect adsorbed bacteriophages from UV radiation (Vettori et al., 2000). Several authors also highlighted the importance of nutrients such as phosphorus and metals towards the inactivation of viruses (Bahich and Stotzky, 1979). Organometallic complexes are reported to alleviate the toxicity of heavy metals towards virus inactivation.

In many cases, septic tank effluents, leachate from sludge disposal sites, and direct land application of wastewater effluents considerably contribute to the groundwater contamination. However, the transportation of viruses in subsurface systems is a function of their retention time, nature, and geology of aquifer. Both efficacy and transport of virus are controlled by soil water content, temperature, sorption and desorption, pH, salt content, type of virus, and hydraulic stresses (Azadpour-Keeley and Ward, 2005). As discussed, both adsorption and inactivation collectively govern viruses transport during soil passage. While advection and dispersion control the virus spread, attenuation of virus concentrations. Irreversible reaction assumes no detachment of virus, and reversible reactions involve equilibrium and kinetics of adsorption. Thus in a subsurface system, adsorption and desorption are rapid in reference to flow velocity, favouring faster equilibrium. There might be another scenario where adsorption is kinetically limited in reference to the flow velocity, with a fixed adsorption and desorption rate coefficients. Hence the corresponding kinetic equations of solute transport must take into account dispersion, advection, and inactivation while modeling virus transport in a three-dimensional saturated flow condition (Schijven and Hassanizadeh, 2000).

Various models were proposed to study the transport phenomena of viruses in environmental matrices. Some of them were VIRAL, working on the principle of irreversible sorption phenomena (Yates and Jury, 1995), VIRULO based on Monte Carlo simulation to predict attenuation of virus in the unsaturated zone (Park et al., 2010; Park et al., 2011) and HYDRUS-2D working based on virus kinetics of deposition, surface chemistry of the sorption sites (Simunek et al., 2016). While enveloped viruses like SARS-CoV-2 may have notable mobility in the environment, further studies are needed to appraise its persistence and transport. Those above-developed models for non-enveloped viruses may be used to have a conservative estimation of enveloped virus transport. However, additional research is required to model SARS-CoV-2 transport in the soil, which can be used to model the transport of other enveloped viruses.

4. Inactivation mechanism

Viruses that are small and elliptical in shape are considered to be highly infectious. Even a small amount of viral load is enough to cause gastroenteritis. Compared to non-enveloped norovirus, a significant number of enveloped viruses were found in vomit and excreta of infected persons. Infections by most of the viruses are transmitted through contact, fecal-oral route, droplets, or aerosols (Weber and Stilianakis, 2008). Viral particles are also transmitted via contaminated surfaces, clothes, food, water, and fomites (Andersen, 2019). It is reported that SARS-CoV can survive on the surface for several days and could retain its infectivity up to 9 days (Rabenau et al., 2005). Similarly, Otter et al. (2016) revealed that other enveloped viruses, such as MERS and SARS viruses, could survive up to several months. Various factors that govern the survival of viruses are i) type of strain ii) load of titer iii) type of surface and v) environmental condition (Otter et al., 2016).

Disinfection plays an important role in controlling microbial infection in medical settings, such as, health care facilities, and nursing homes (Pfaender et al., 2015). Also, it helps in controlling microbial infections.
infection in water treatment plants and WWTPs by destroying or deactivating pathogenic microorganisms (Macinga et al., 2008). Disinfection is one of the most fundamental ways of disrupting virus spread by reducing or inactivating their infectious nature (Hijnen et al., 2006). In this section, different modes of virus inactivation such as, UV, alcohol, heat treatment, and other conventional and advanced methods, are discussed. Possible inactivation mechanism for SARS-CoV-2 has also been presented by referring to the available literature on other envelope viruses and non-enveloped viruses, as shown in Table 2 and Fig. 2.

4.1. UV-based inactivation

UV-based disinfection technique is profoundly used in the medical sectors to sterilize medical equipment, and PPEs (Vaidya et al., 2018). UV(C) rays were proven to be more efficient than the UV(A) and UV(B) in inactivating viruses, as they possess high energy and are most absorbed by the DNA and RNA (Ravanat et al., 2001). Darnell et al. (2004) compared the efficiencies of UV(A) and UV(C) to inactivate the viruses within a limited period. UV(C) could increase the rate of virus inactivation to 400 times within 6 min, while UV(A) showed no effects when the experiment was extended up to 15 min. The UV-based disinfection involves the absorption of UV rays by DNA/RNA bases followed by fusion with pyrimidines into covalently linked dimmers, which later becomes non-pairing bases (Perdiz et al., 2000). DNA can absorb UV(C) in the range of 245–285 in the most propitious way and thus proves to be suitable to disinfect microbes (Pratelli, 2008).

4.2. Alcohol

Disinfection by means of alcohol is considered an important measure for the inactivation of viruses. Alcohol-based sanitizers (a mixture of polyquaternium and organic acid) are used to inactivate non-enveloped viruses such as human rotavirus, poliovirus type 1, human norovirus, and murine norovirus that are inactivated by a factor of $10^3$ times within 30 s (Macinga et al., 2008). Ethanol and propanol were also found to inactivate feline calicivirus (norovirus’ surrogate) by 4 log units within 30 s (Gehrke et al., 2004). A notable study by Kampf et al. (2020) reported an efficient method to disinfect SARS-CoV-2 in less than 60 s using ethanol [C$_2$H$_5$OH (65%)], hydrogen peroxide [H$_2$O$_2$ (0.5%)] and sodium hypochlorite [NaClO (0.1%)] (Kampf et al., 2020). Hulkanower et al. (2011) reported the reduction of infectivity by $>3$ log units with ethanol. Generally, inactivation of viruses by alcohol-based disinfectants involves disruption of the virus envelope within the capsid, without targeting the RNA (Pfaender et al., 2015). Kratzel et al. (2020) evaluated two of the alcohol-based disinfectants based on WHO formulation for the inactivation of SARS-CoV-2, namely, ethanol and 2-propanol, along with glycerol and H$_2$O$_2$. Both the formulations resulted in the reduction of the viral titers in 30 s.

4.3. Chemical-based disinfection

Chemical-based inactivation is also an important tool for disinfecting viruses. Jelsma et al. (2019) studied the effect of sodium chloride (NaCl) and phosphate-based (P-salt) salts on enveloped swine fever viruses present in the porcine intestines. The reduction values were determined at four different temperatures, namely, 4, 12, 20, and 25 $^\circ$C. Compared to sodium-based salt, phosphate-based (P-salt) salts were found to be more effective across all the studied temperatures. Virus titers showed a reduction of 99% from its initial concentration. One of the enveloped viruses, HSV (Herpes Simplex Virus) was inactivated using zinc gluconate and zinc lactate salts in vitro. The former salt showed inactivation for 80% of the virus particles with more than 98% reduction, while the later inactivated 90% of the samples with more than 97% reduction. The reduction was found to be proportional to the concentration of salt used (Arens and Travis, 2000). Kampf et al. (2020) studied the effect of several biocidal agents on the inactivation of SARS-CoV-2. Ethanol (62–71%), sodium hypochlorite (0.1–0.5%), glutardialdehyde (2%) were found to reduce the titers by 2–4 log$_{10}$ while on contrary, benzalkonium chloride (0.04%) and ortho-phthalaldehyde (0.55%) were less effective in inactivating SARS-CoV-2.

4.4. Chlorination

Inactivation of many viruses in the drinking water treatment plants is usually done by chlorination. Cromeans et al. (2010) studied the effect of monochloramine on human adenoviruses, enteroviruses, and murine norovirus. Agolini et al. (1999) studied the effect of chlorine disinfectant on HCV (hepatitis C virus) inactivation. Ogata and Shibata (2008)
studied the effect of chlorine dioxide (ClO₂) gas against Influenza A virus, an enveloped virus. The mechanism involves denaturing of viral envelope proteins, which are responsible for the infectious nature of the virus by ClO₂. SARS-CoV-2 has already been detected in many of the untreated wastewater samples at Australia (positive in 22% samples), Netherland (58%), USA(71%), France (100%), and USA (100%) (Ahmed et al., 2020; Medema et al., 2020; Wu et al., 2020; Wurtzer et al., 2020; Nemudryi et al., 2020). Thus, it becomes ever important to disinfect the viruses before they contaminate surface water bodies and enter into urban water cycle. Chlorination is the most common wastewater disinfection method. A 2.8 log-unit inactivation by chlorination was reported for poliovirus (Tree et al., 2003). Although information regarding the portion of infectious SARS-CoV virus in feces is still emerging, reports of RNA of SARS-CoV-2 in the feces of infected patients raise the importance of being extra vigilant about management of undiluted hospital wastewater (Wang et al., 2020b). Liquid chlorine, chlorine dioxide, and sodium hypochlorite are some of the mostly used disinfectants at health facilities (Lizasoain et al., 2018; Yu et al., 2014). All these chlorine based disinfectants offer several advantages over UV/Ozone and other inactivation processes like i) low power consumption ii) low toxicity iii) simple equipment iv) need no skilled labor v) low set-up and operational cost (Fan et al., 2017). The effective product which inactivates the pathogen during chlorine-based disinfection is HClO (Wang et al., 2020b). Also, due to 80% similarity between SARS-CoV-2 and SARS-CoV-1, the disinfection process of the latter could be well approximated to the former one. Chen et al. (2006) studied the complete inactivation of SARS viruses by adding free Cl (0.5 mg/L) or ClO 2 (2.9 mg/L) after a heat treatment of 30 °C for half an hour. Therefore, it may be an effective wastewater disinfection method for the COVID-19, too; however, further studies are required to ascertain the dose response relationships (Chen et al., 2006).

4.5. Thermal inactivation

Heat treatment for virus inactivation has been in use for decades. Seo et al. (2012) studied the effect of temperature on the virus inactivation. A 10² times reduction was noticed at 24 °C within 12 days; 4 log unit reduction at 70 °C within 2.5 min in human/murine norovirus and a 3 log reduction at 71 °C in feline calicivirus within 2 days. Inactivation involves denaturing viral capsid proteins, which in turn creates gaps in the viral particles making it more vulnerable to proteinase K and RNase treatment (Seo et al., 2012). Recently, Hu et al. (2020) studied the thermal inactivation of SARS-CoV-2 by heating human serum contaminated with the virus at 56 °C for 30 min. In another approach, 90% inactivation of the virus was achieved within 7 and 14 min when experiments were conducted in simulated saliva and culture media, respectively (Ratnesar-Shumate et al., 2020).

4.6. Other inactivation mechanisms

Several studies have reported instances of using microorganisms as an important tool for inactivating enterovirus (Toranzo et al., 1983).
Toranzo and Metricic (1982) reported the antiviral properties of isolated marine bacteria. Photocatalysis is an alternative to chemical disinfection. He et al. (2004) studied the efficiencies of Ag/Al₂O₃ and Cu/Al₂O₃ on SARS-CoV inactivation and observed complete inactivation in 5 min and 20 min (He et al., 2004). Kingsley et al. (2002) studied the effect of hydrostatic pressure on the inactivation of hepatitis A virus (HAV) virus and observed successful inactivation at high pressure (> 450 MPa) within 5 min. Similarly, poliovirus was inactivated at a pressure of 600 MPa within 5 min (Kingsley et al., 2002). Hydrostatic pressure might have damaged the capsid proteins, which led to virus inactivation. Breidablik et al. (2019) devised ozonized water as an alternative for the alcohol-based disinfectant. After SARS outbreak, several chemical disinfectants were used as potential inactivators (He et al., 2004).

5. Antiviral drugs: environmental occurrence and potential ecotoxicity

Several research groups around the globe are working to develop the vaccine for COVID-19, with an expected 12–18 months of timeline for production and delivery. In the meantime, researchers are also exploring potential antiviral drugs to minimize the mortality rate caused by SARS-CoV-2. Fig. 3 shows repurposed antiviral drug targets for SARS-CoV-2 infection. Development of drugs starts with the identification of interactions between a target virus and host receptor (Yang et al., 2017), as polymerase inhibition, budding inhibition, target sites for the virus, human-drug interaction, and a better strategy (Zumla et al., 2016). Drug repurposing is one of the most crucial steps in finding the drug from the already existing drugs, which saves both time and cost during drug development (Zhou et al., 2020). Table 3 summarizes various human viruses, including SARS-CoV-2, and their effective antiviral drugs.

Lin et al. (2018) studied the effect of disulfiram drug for the inhibition of SARS and MERS coronaviruses (Lin et al., 2018). It behaves as an allosteric inhibitor for MERS and a competitive inhibitor for SARS by inhibiting the papain-like proteases. Zhou et al. (2020) studied the probability of 16 potential drugs for the SARS-CoV-2 after observing a similarity index of 89.6% and 96% in the nucleocapsid proteins and envelope, respectively, with SARS-CoV. The drugs were mesalazine, toremifene, eplerenone, paroxetine, sirolimus, dactinomycin, irbesartan, mercaptopurine, melatonin, quinacrine, carvedilol, colchicine, camphor, equaline, oxymetholone, and emodin. Additionally, a combination of sirolimus and dactinomycin, toremifene and emodin, and mercaptopurine and melatonin were found to be potential drug combinations against SARS-CoV-2 (Zhou et al., 2020). Some of the old drugs (such as ribavirin, interferon, lopinavir, and ritonavir), formerly used for SARS and MERS, are currently under trial repurposing against SARS-CoV-2 (Zumla et al., 2016).

Hydroxychloroquine (HCQ) was reported to be effective against COVID-19 (Liu et al., 2020). The production of cytokine was often observed in severely-ill COVID-19 patients (Sun et al., 2020) and HCQ was found to be successful in inhibiting the production of cytokine (Liu et al., 2020). Wang et al. (2020a) compared the several drugs for the in-vitro treatment of the virus and found out the remdesivir and chloroquine to be highly efficient and safe drugs. Choy et al. (2020) also observed the combination of remdesivir and emetine to be the most suitable combination for the inhibition of SARS-CoV-2 after trying a combination of 5 drugs. Ko et al. (2020) listed the favourable instances of making remdesivir as an inhibitor for COVID-19, namely, reduction of viral load in SARS-CoV-2, safety i.e., nontoxic effects on infected patients. Similarly, Caly et al. (2020) studied the application of FDA-approved Ivermectin drug in reducing the viral RNA by 5,000 times.

Table 3

| Human viruses | Disease caused | Antiviral drugs against the virus | Ecotoxicological effects | Side effects on human |
|---------------|----------------|---------------------------------|-------------------------|-----------------------|
| Influenza A   | Flu epidemics  | Tamiflu/Oseltamivir ethyl ester | Toxic effects on bacteria, algae, water fleas, fish, planktonic crustaceans | G: Gastroenteritis symptoms (Pain, diarrhea, nausea, vomiting, fever, headache, chills, sweating); F: Fatigue; L: Liver problems; K: Kidney problem; V: Visionary problems; T: Throat problems; A: Antiangiogenic effects; C: Cytotoxic effects; N: Neutropenia; P: Pancytopenia; LA: Loss of appetite; S: Sleep disorder (Insomnia, strange dreams, mood change); B: Behavioral changes (feeling irritable, drowsiness, anxiety, mood change). |
| HIV           | Acquired immunodeficiency syndrome (AIDS) | Adefovir, Tenofovir, Entecavir | Harmful to green algae, crustaceans, and diatoms | |
| Herpes simplex | Cold sores, Genital herpes | Acyclovir, Famciclovir | Toxic effects on bacteria | |
| Hepatitis A, B, C & E | Liver infection, jaundice | Ribavirin, Efavirenz | Liver damage in fish, fatal for fishes | |
| Zika virus    | Zika fever     | Delphinidin, Sofosbuvir | Fungicide, microbicidal, carcinogenicity in mice | |
| Ebola virus   | Hemorrhagic fever | Galidesivir, Remdesivir | Behavioral depression and hematopathology changes in rhesus monkeys and cynomolgus monkeys | |
| SARS-CoV-2    | Pneumonia, COVID-19 | Ivermectin, Hydroxychloroquine | Toxic to albino rats, microalgae, daphnia, zebrafish, springtails, and other soil invertebrates | |
within 48 h.

Immediately after consumption, antiviral drugs undergo series of biotransformation such as glucuronidation, sulfoxidation, dimethylamino N-demethylation, and sulfate conjugation and finally excreted from the human body to the greater extent as metabolites, including active ones, mostly in urine (Nannou et al., 2020). Therefore, the drug residues and metabolites can be continuously transported through hospital and household wastewater to WWTPs and may pose additional challenges in their detection in complex environmental matrices (Mohapatra et al., 2018). Since WWTPs are not specifically designed to remove such drug residues, WWTPs become a major source of antivirals (Mohapatra et al., 2020). In this section, fate, transport, and occurrence of antiviral drugs with their seasonal variation, and ecological activity, turbulence, mixing, and rate of exfiltration and infiltration can significantly vary depending on seasons. Thus, seasonality influences the fate and transport of antiviral in the aquatic environment. To study the seasonal variation in the concentration of antiviral drugs such as ganciclovir, ribavirin, acyclovir, stavudine, oseltamivir, zidovudine and oseltamivir carboxylate, Peng et al. (2014) analysed the influent and effluent wastewater samples of a WWTP, landfill leachate, groundwater, reservoir water, and surface water from river Pearl and its tributaries in China. The concentrations of anti-influenza drugs were monitored during a period of 9 months. Except for favipiravir, laninamivir, and laninamivir octanoate, most of the studied antivirals were found to be persistent and could travel from upstream to downstream in chemically unchanged form. While the majority of antivirals are resistant to photodegradation, favipiravir, which is under clinical trial against SARS-CoV-2, is reported to be removed through photodegradation (Azuma et al., 2017). Kolpin et al. (2004) and Yu et al. (2011) evaluated the transport of a set of antiviral drugs by studying their photodegradation, biodegradation, and sorption behaviours in a river receiving active antiviral drugs from the manufacturing industries along the river course as reported elsewhere (Prasse et al., 2010).

5.2. Occurrence and seasonal variation of antiviral drugs in the environment

The occurrence of antiviral drugs in environmental waters is largely affected by seasonality of diseases, corresponding consumption of antiviral drugs, and environmental factors. The common physical and biological parameters such as water flow rate in the river, penetration depth of sunlight, depth of water column, ambient temperature, biological activity, turbulence, mixing, and rate of exfiltration and infiltration can significantly vary depending on seasons. Thus, seasonality influences the fate and transport of antiviral in the aquatic environment. In the case of Nairobi River in Kenya, the highest concentration for zidovudine (9 pg L$^{-1}$) was detected due to high consumption of antiviral drugs in that season. Kolpin et al. (2004) and Yu et al. (2011) studied the effect of river flow/discharge on several antiviral drugs. The drug acyclovir was detected at the highest concentration in winter (17 ng L$^{-1}$) than in spring (14 ng L$^{-1}$), summer (11 ng L$^{-1}$), and fall (7 ng L$^{-1}$). Its concentration in the effluent did not show statistically significant seasonal variation over one year of sampling. An antiviral drug oseltamivir, and its metabolite oseltamivir carboxylate were detected in a river during the flu epidemic in Japan (Azuma et al., 2012). The maximum concentration of oseltamivir carboxylate was found to be 288 ng L$^{-1}$, and the concentration trend corresponded with the number of influenza patients obtained from sentinel surveillance (Azuma et al., 2012).

5.1. Fate and transport of antiviral drugs

In general, pharmaceuticals are expected to be attenuated via hydrolysis, sorption photodegradation, and biodegradation in the natural environment (Mohapatra et al., 2020). Similar mechanisms are expected for attenuation of antiviral drugs in the environment. Pharmaceuticals have a large range of Log $K_{ow}$ (octanol-water partition coefficient) from –4–8, indicating various absorptive nature in the environment (Fig. 4); antiviral drugs have relatively small Log $K_{ow}$ of –0.3 ± 0.3 (mean ± standard error), suggesting a hydrophilic nature. Azuma et al. (2017) evaluated the transport of a set of antiviral drugs by studying their photodegradation, biodegradation, and sorption behaviours in a river for a period of 9 months. Except for favipiravir, laninamivir, and laninamivir octanoate, most of the studied antivirals were found to be persistent and could travel from upstream to downstream in chemically unchanged form. While the majority of antivirals are resistant to photodegradation, favipiravir, which is under clinical trial against SARS-CoV-2, is reported to be removed through photodegradation (Azuma et al., 2017). Most of these antiviral drugs were weakly adsorbed to sediment and sludge samples, indicating removal via sorption is not the primary removal mechanism. Except for laninamivir and oseltamivir, no other antivirals were found to be removed through biodegradation.

While there is no extensive study reported on the transport of antiviral drugs in the natural environment, available data on other drugs suggests that river’s hydrogeological conditions, dissolved organic matter, and physical conditions prevailing in an aquatic environment may control the attenuation of antivirals (Yang et al., 2017). However, it would be difficult to predict the actual attenuation of such drugs in surface water receiving active antiviral drugs from the manufacturing industries along the river course as reported elsewhere (Prasse et al., 2010).
pharmaceuticals has been well studied, but similar study for antiviral drugs is still lacking (Vieno et al., 2005). Kumar et al. (2020a) studied the seasonal trend in the occurrence of fluoroquinolone drugs viz., levofloxacin, norfloxacin and ciprofloxacin in Kelani and Brahmaputra rivers from Sri Lanka and India, respectively. It was found that concentration of drugs declined significantly in summer compared to the winter season. Similarly, the occurrence of naproxen, diclofenac, ibuprofen, bezafibrate, and ketoprofen was studied in the influent and effluent streams of a WWTP and nearby drinking water treatment plant (DWTP), as well as at downstream of a river in summer, spring and winter seasons (Vieno et al., 2005). Poor removal for the pharmaceuticals was noticed during the winter season (~25%) attributed to slow microbial activity compared to summer and spring seasons. The mean concentration of the studied drugs was found to increase by 3–5 times in the winter season compared to other seasons. These results suggest that cold/winter seasons adversely elevate the probability of pharmaceutical contamination in environmental water and escalate the chances of their occurrence in drinking water (Vieno et al., 2005).

Collectively, in winter, human immunity tends to be low, especially in colder countries, thus viral infection cases and consumption of antiviral drugs increases. Together with the low flow rate in winter, antiviral concentration levels in environmental waters are typically high in winter. Additional studies may be conducted as a priority basis, especially during this pandemic, to understand occurrence, fate, persistence, transport, and seasonal variation of antivirals, including the ones considered for the application to COVID-19 patients, in the environment.

5.3. Ecotoxicity of antiviral drugs

Like several other pharmaceuticals, antiviral drugs are prognosticated to be one of the most perilous among the therapeutic group, with the help of quantitative structure activity relationship (QSAR) modeling, in terms of their toxicity with regard to fishes, crustaceans, common water fleas and algae (Sanderson et al., 2004; Menon et al., 2020). The ecotoxicological effects of various antiviral drugs, together with their side effects on human are summarized in Table 3.

Prasse et al. (2012) reported the toxicity of the oxidation product of the drug acyclovir, N-(4-carbamoyl-2-ino-5-oximidazolidolin) for-mamido-N-methoxyacetic acid (COFA) on Aliivibrio fischeri bacteria. Diverse reports are available on the ecotoxic nature of antiviral drugs, ibuprofen, bezafibrate, and ketoprofen was studied in the influent and rivers from Sri Lanka and India, respectively. It was found that concentration ecotoxicity was observed even at concentrations 0.1 mM. Inhibition of viral replication with Tamiflu or oseltamivir ethyl ester was reported to be even more toxic in the presence of metabolites and oxidation/transformation products; those compounds can be as biologically active as their parent compounds. This gives rise to the major concern of the development of antiviral drug-resistant viruses within wild animals, such as bats, pigs, camels, etc., which are natural reservoirs of the viruses (Kumar et al., 2020c). The potential pathways and origins of antiviral drug-resistant viruses through environmental waters are depicted in Fig. 6.

In the case of influenza virus, water fowls are known animal reservoirs (Wallensten et al., 2007). As for SARS-CoV-2, bats and pangolins are considered as wild animal reservoirs (Kumar et al., 2020c; Zhang et al., 2020). Recently, the novel coronavirus has also been detected in eight lions and tigers at New York’s Bronx Zoo (Naquin, 2020). Development of antiviral drug-resistant viruses is concerned when those animals with viruses ingest the contaminated environmental waters, then the viruses are continuously exposed to the high loads of antiviral drug residues and their metabolites/transformation products and, thus gain resistance through mutations. This potential development of antiviral drug-resistant viruses within animal reservoirs and their subsequent transmission to humans will compromise the treatment of the viral disease (Kumar et al., 2020c). This all will cause more severity to human being for the current and future pandemic control.

6.2. Clinical implications, management and preventive/control measures against antiviral resistance

When the antiviral resistance is suspected, proper management in terms of clinical treatments, therapies, and laboratory testing can
Fig. 5. Global Occurrence and prevalence of antiviral resistance in the viruses (Influenza, Human immunodeficiency virus: HIV, Hepatitis B virus: HBV, Hepatitis C virus: HCV, Herpes simplex virus: HSV, and Human Cytomegalovirus: HCMV) and virally infected patients.

Fig. 6. Probable antiviral drug resistant virus mutation in animal reservoirs.
minimise the risk of severe consequences (Strasfeld and Chou, 2010). To guide the therapeutic decisions, an accessible and authorised database about the mutations of drug resistant viruses should be developed (Strasfeld and Chou, 2010). Less toxic and potent antiviral drugs should be developed which can reduce the risk of cross-resistance and simultaneously target the different aspects of viral replications. Understanding the kinetics of emergence of antiviral resistance in the host population (from minor to predominant) is now possible due to the contemporary next-generation sequencing (van der Vries and Ison, 2017). Administration of genetic screening for pre-existing resistant mutants with respect to the particular drugs before the onset of treatments proves to be beneficial as observed in the case of HIV and HCV (Irwin et al., 2016). Such genomic data obtained for screening helps to scan the already known mutants and to detect new resistant mutations. Moreover, for management of antiviral resistant viruses, following actions can be summarised: 1) Discontinuation of ongoing monotherapies: If the ongoing drug therapy is stopped, then generally the resistant virus returns to its wild-type, which can be then easily treated with new drugs or vaccination. 2) Switching to a new antiviral agent or therapy: This will help when the virus is resistant against some particular drug. 3) Adding another drug to the current treatment: New drugs can be more effective against the known resistant mutants than repurposed drugs. 4) Using combination chemotherapies: patient with advanced critical disease/infections can be treated with proper combinations of antiviral agents (Bartholomeusz and Locarnini, 2006).

Management is mainly associated with the already developed resistant mutants or viruses. But following preventive measures can be effective against the development of antiviral resistance as well as for the remediation of environmental pollution by anti-viral drugs:

- **Prevention from the infection and transmission:** Most of the viral infections can be prevented and their transmission can be reduced by using simple, inexpensive and effective measures such as hand washing, vaccination, unnecessary injections, use of bed nets, and contraceptives (Drexler, 2014). The general public should be made aware and educated through media and campaigns which clearly emphasize the message regarding the dangers caused by overuse of antiviral or anti-infective drugs.
- **Authorised guidelines:** The national (such as https://www.mygov.in/covid-19/) and local authorities should develop and provide the clinical guidelines for different diseases, recommended drug dosage and duration for certain infection treatments. Also, guidelines for the selection of combination therapies and proper antiviral agents should be recommended by the respective authorities and must be communicated effectively to the healthcare personals. Nevertheless, people should be educated with the help of authorised guidelines for proper disposal of the unused and expired drugs.
- **Block interspecies transmission of resistant viruses:** Viruses in their natural hosts (animals) can be exposed to antiviral drugs via water that contains residues and metabolites of antiviral drugs, and can subsequently develop antiviral resistance. Although this mechanism is hypothesized and is debatable, natural recombination of genetic materials of different viral strains and drug exposure-induced resistant viral strains can reach human population through direct contact with such natural hosts (reservoirs) or via the intermediate hosts. Thus, avoiding the direct contact with the natural-hosts and to some extent intermediate host species, the transmission of resistant viruses can be blocked. For example, in the case of coronaviruses, bats, rats, camels, and pangolins are known natural hosts (Zhang et al., 2020). Thus, identification of their intermediate host species and avoiding contact with them can block the transmission of such coronaviruses to humans.
- **Effective wastewater treatment facilities:** A systematic study on the requirement of barriers additional to the conventional wastewater disinfection techniques is recommended. Potential technologies for further assessment include advanced treatment technologies, such as advanced oxidation processes, adsorption, membrane separation processes, and/or hybrid treatment systems, (Nannou et al., 2020; Dhargar and Kumar, 2020; Jain et al., 2013; Thakur et al., 2020), which may achieve the required level of SARS-CoV disinfection and also remove the antiviral drug residues and their harmful metabolites/formation products from treated effluent.

### 7. Conclusions

While vaccine development against SARS-CoV-2 is underway, the number of confirmed cases has globally crossed 20 million, as of the second week of August, 2020. In such an unprecedented scenario where several countries have already experienced the second wave, the use of alcohol, and chlorine-based disinfectants has been found to be promising to inactivate the virus from various surfaces. Compared to UV-based disinfection, chlorination seems to be a more suitable means for the developing countries due to the low cost and ease of handling. Currently, there is no publication related to persistence and transport of SARS-CoV-2 in land surface and subsurface medium (soil and ground water). However, it is essential to research these aspects of SARS-CoV-2, which particularly critical for the developing countries where lack of sanitation and inadequate management of biomedical wastes are prevalent. It is also imperative to take initiatives to find the answer of questions such as: What will be the different scenarios in case of such a high use of antivirals during this ongoing pandemic of SARS-CoV-2? Can we deny the possibility of the development of stronger viruses, causing severe pandemics than COVID-19 in the near future? What will be the occurrence scenarios of environmental pollution by antiviral drugs and antiviral resistance in different parts of the world? Will there be any correlation of drug residue and antiviral resistance occurrence in the ambient water and the number of infected person reported from that region or it will be governed by the capabilities of WWTP infrastructure present in that country?. Finally, how to minimise the pollution of natural waterbodies by antiviral drugs and viruses, especially these antiviral drug concentrations to go the ambient waters like river especially in developing countries where WWTPs are scarce and not even integrated in the hospital effluent?

### CRediT authorship contribution statement

**Manish Kumar:** Conceptualization, Visualization, Writing - original draft, Revision, and Response. **Payal Mazumder:** ADR first draft and related illustrations. **Sanjeeb Mohapatra:** Inactivation Part. **Alok Kumar Thakur:** Transport portion first draft. **Kiran Dh炀arg:** Spread and Seasonality first draft. **Kaling Taki:** Illustrations and Revision. **Santanu Mukherjee:** Revision and Response. **Arbind Kumar Patel:** Environmental Fate. **Prosun Bhattacharya:** Revision and Improvement. **Pranab Mohapatra:** Transport portion. **Jorg Rinkelbe:** ADR and related revisions. **Masaaki Kitajima:** Revision. **Faisal I Hai:** Inactivation part and revision. **Anwar Khursheed:** Writing - review & editing. **Hiroaki Furumai:** Overall read, revision and response. **Christian Sonne:** Expressions and Revision. **Keisuke Kuroda:** Visualization, Writing - review & editing.

### 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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