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Potential emergence of antiviral-resistant pandemic viruses via environmental drug exposure of animal reservoirs

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A continuous leak of antiviral drugs into the environment leads to antiviral resistance which compromises the treatment of human viral diseases.^{1,2} As the intense search for effective drugs against the novel coronavirus (SARS-CoV-2) is progressing world-wide, several antiviral and anti-parasitic drugs, including those for Ebola (remdesivir), influenza (favipiravir, oseltamivir), HIV (lopinavir/ritonavir) and malaria (chloroquine), have undergone clinical trials on COVID-19 patients.^{3,4} Since these drugs and their metabolites are mostly excreted in urine, there is the potential for discharge to the environment depending on removal efficiency at wastewater treatment plants (WWTPs).^{1,2,5,6} For example, our preliminary worst-case (treatment by activated sludge process only) estimation shows that rivers and lakes receive 430–2120 ng/L favipiravir hydroxide, the major metabolite of influenza drug favipiravir (Avigan®), or 54–270 ng/L GS-441524, the active form of ebola drug remdesivir, from WWTP effluents if 100 new patients per 1 million capita are added every day to existing patients who are treated with the drugs (estimated based on Singer et al. 2007² and Azuma et al. 2012⁵). Animals that are a natural reservoir of viruses, including bats, camels, cats, pangolins, and pigs, may then be exposed to the river water containing antiviral drugs (Fig. 1), inducing antiviral selective pressures and mutations in the virus leading to anti-viral drug resistance.

Viruses are known to rapidly undergo genome mutations with successive replications, increasing the chances of resistance to existing antiviral treatments.⁷ To date, antiviral drug resistance has been reported for human viral diseases including AIDS, hepatitis B and C, herpes,

37 and influenza.⁷ Likewise, antiviral drug resistance could be accelerated by exposure of animal
38 reservoirs to environmental waters containing antiviral drugs. For example, for influenza
39 viruses, multiple studies^{1,2,5} have alarmed the risk of anti-influenza drug resistance in the body
40 of water fowls, which are known as natural reservoirs of influenza virus⁸. During influenza
41 pandemic, water fowls, such as ducks, may ingest anti-influenza drugs and metabolites in
42 environmental waters. In Japan, oseltamivir carboxylate, the active metabolite of oseltamivir
43 (Tamiflu®), was detected in river water at concentrations up to 864.8 ng/L⁶ during the past
44 pandemic of novel influenza, exceeding the concentration that inhibits 50% of *in vitro* growth
45 (IC₅₀) of influenza-A virus (97–210 ng/L)⁹. This suggests contaminated natural waters could
46 initiate antiviral selective pressure in animal reservoirs during a pandemic with high rates of
47 anti-viral drug use. Similarly, SARS-CoV-2 is potentially capable of acquiring antiviral drug
48 resistance in its animal reservoirs (e.g., bats and pangolins)¹⁰ in the event of exposure to
49 surface waters contaminated with antiviral drugs during the COVID-19 pandemic. As of May
50 14, 2020, the average mutation rate of SARS-CoV-2 is 25.3 substitutions per year, which equals
51 approximately one in 14 days.¹¹ Considering this mutation rate and the numerous populations
52 of wild animal reservoirs, the emergence of antiviral drug-resistance to SARS-CoV-2 during the
53 current waves of COVID-19 could generate challenges for human treatment in the post COVID-
54 19-pandemic Anthropocene.

55

56 The unprecedented mass use of antiviral drugs is looming as global researchers race to develop
57 them for COVID-19 applications, alongside vaccine development. In March 2020, U.S. health
58 officials estimated that it may take 12 to 18 months for production and delivery of effective
59 vaccines for COVID-19,¹² with many hurdles to overcome, placing greater pressure on anti-viral
60 drug development. The urgent question to understand is to what extent wild animal reservoirs
61 could be exposed to anti-viral drug residues in environmental waters, and how that may induce
62 antiviral drug-resistant viruses in the future that then challenge the existing treatments for
63 COVID-19-like pandemic diseases.

64

65 Presumptive actions are required to study the occurrence, behavior and fate of various
66 antiviral drugs and their metabolites during wastewater treatment and into receiving waters
67 during pandemic events. In addition, the susceptibility of SARS-CoV-2 to antiviral drugs needs
68 an urgent evaluation of potential antiviral drug resistance development in wild animal

69 reservoirs. Perhaps this current COVID-19 crisis may become an opportunity to invest in
70 upgrading WWTPs with advanced treatment capabilities such as ozonation for the enhanced
71 removal of pharmaceuticals, including antiviral drugs.^{1,5} Lack of proper sanitation
72 infrastructure in less developed countries is also a challenge in terms of antiviral spread control
73 in the environment, and thus additional investments in this area is needed as a global
74 responsibility to maintain the efficacy of anti-viral drugs. We believe that significant research is
75 required to safeguard the efficacy and longevity of anti-viral treatments. By responsibly
76 understanding their environmental fate in WWTP and environmental settings, accelerated
77 anti-viral resistance may be avoided, and treatment tools for future viral pandemics preserved.

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79 **615 words; 12 references**

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81 **Notes:**

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83 The authors declare no competing financial interest.

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