Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

the resultant reduction in viral density and thereby contagion dissemination. However, it appears plausible at this stage that the addition of NaOCl disinfectant in the toilet flush could contain fecal virus-laden bioaerosols.

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In Reply — Neutralization of Fecal Aerosol-Laden SARS CoV-2: Public Health Implications

To The Editor: The authors of "Neutralization of Fecal Aerosol-Laden SARS CoV-2: Public Health Implications" make an interesting and important suggestion for containing the spread of coronavirus disease 2019 (COVID-19).[1] In response to our article about infectious fecal bioaerosols contributing to COVID-19 outbreaks,[2] Immanuel et al[1] rightly point out that chlorination of toilet water could reduce the spread of infectious fecal bioaerosols in the hospital setting. This is an important consideration for community spreading, especially in countries with high population density. Furthermore, the effects of inadequate disinfection of the plumbing systems and wastewater facilities on fomite transmission have received little attention so far.

Immanuel et al[1] propose that chlorination may be accomplished by addition of tablets or household bleach to toilet tanks. This is a reasonable suggestion for private homes and shared living facilities. We propose several additional considerations for implementation of such a toilet water treatment program to prevent the spread of COVID-19. Using a disinfecting apparatus or extended-release tablet is probably more practical than adding household bleach repeatedly to the tank. An extended-release disinfectant may also be preferable because it is unclear how much contact time would be required to inactivate the virus in a toilet bowl.

Additionally, we propose that a 1% concentration of disinfectant may be higher than necessary, as water chlorination at 0.17 to 1.0 mg/L inactivates a variety of viruses including noroviruses and poliovirus.[4] A 0.1% solution of household bleach has been recommended to achieve surface disinfection without causing irritation.[3] Because not all toilet tanks and bowls are the same size, it could be difficult for private residences to achieve the correct concentration by diluting a household bleach solution. However, using the correct concentration is important for both households and commercial facilities and should be done in concert with facility engineering experts, as oxidizing disinfectants may erode important plumbing components, and inhalation of chlorinated bio-aerosols may irritate the respiratory tract of sensitive residents or patients.

Some barriers exist to disinfecting the water source for commercial buildings. Facilities such as hospitals may have tankless toilets; thus, chlorinating the water supplying the toilet may require a facility

operation to separate the water supply for the toilet and chlorinate it, perhaps with a hypochlorite generator. This could be prohibitively expensive. In these cases, using a disinfectant-releasing apparatus in toilet bowls may be more practical.

Locations that allow recirculation of lavatory air should be considered high-risk areas for infectious bio-aerosol exposure. The methods suggested by Immanuel et al[2] may be well suited for such areas in public restrooms, assisted living facilities, schools, and other buildings. Disinfecting toilet water in the manner suggested by the authors could protect people in shared residences where one or more residents are positive for COVID-19.

The COVID-19 pandemic is the third novel coronavirus outbreak of the 21st century, following on the heels of the severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus outbreaks. Still, little has been done to create preventive interventions in public health infrastructure. More research is needed to determine efficacy of the proposed approach against severe acute respiratory syndrome coronavirus 2 infection transmission, and such research is warranted in case of expected future similar outbreaks.

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COVID-19, the Female Immune Advantage, and Cardiovascular Impact

To The Editor: The article by Ritter and Kararigas[1] is a welcome addition to the coronavirus disease 2019 (COVID-19) medical literature, as significant physiologic variations across multiple systems exist between the sexes, yet are often neglected.[1] Although we applaud the hypotheses on differing male and female responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, with emphasis on cardiac vulnerabilities, some additional key potential mechanisms with respect to the role of the "sex hormones" estradiol, progesterone, and testosterone require consideration.

Estradiol supports immune system modulation, amplifying innate and humoral immune responses, whereas testosterone is overall an immunosuppressant, in particular inhibiting differentiation of naive CD4+ T cells into T helper type 1 cells, impeding cell-mediated immunity. Estradiol helps initiate a robust innate immune response to pathogens via augmented toll-like receptor 7 (TLR7), an endosomal innate immune sensor recognizing RNA viruses such as SARS-CoV-2, inducing a type 1 interferon response, suppressing viral replication, and amplifying host antiviral response.[2] Subsequently, estradiol helps switch to a state of inflammatory resolution and healing. Progesterone also has substantial immunomodulatory effects on female immune systems.[3] These significant hormonal effects may result in dramatic sex differences in immune response to infection, and in turn, likely alter inflammatory-mediated cardiovascular impacts from SARS-CoV-2.

All immune cells have receptors for estradiol, enabling direct immunomodulation. This is complemented by the influence of estradiol on the renin-angiotensin-aldosterone system (RAAS), a second important immunomodulatory system.[4] Severe acute respiratory syndrome coronavirus 2 uses angiotensin-converting enzyme 2 (ACE2) as a functional receptor to infect cells, destroying its anti-inflammatory capabilities in the process. Females replete with estradiol have greater number and functionality of ACE2, likely a factor in their greater ability to handle SARS-CoV-2 infections. Additional estradiol-mediated RAAS modulatory actions provide further cardiovascular protection. Despite SARS-CoV-2–induced ACE2 deficiency, estradiol supports an anti-inflammatory state by facilitating angiotensin II