Title: Spillover of human antivirals may promote resistant pathogens in animal reservoirs

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Abstract

Novel viral pathogens are causing diseases to emerge in humans, a challenge to which society has responded with technological innovations such as antiviral therapies. Antivirals can be rapidly deployed to mitigate severe disease, and with vaccines, save human lives and provide a long-term safety net against new viral diseases. Yet with these advances come unforeseen consequences when antivirals are inevitably released to the environment. Using SARS-CoV-2 as a case study, we identify global patterns of overlap between bats and elevated pharmaceutical concentrations in surface waters. We model how freshwater contamination by antivirals could result in exposure to insectivorous bats via consumption of emergent insects with aquatic larvae, ultimately risking the evolution of antiviral-resistant viruses in bats. The consequences of widespread antiviral usage for both human and ecosystem health underscore urgent frontiers in both scientific research and sustainable development.

Keywords: antivirals, bats, emerging aquatic insects, wastewater

In a nutshell

- Humans have developed antiviral therapies that are often repurposed for multiple viral diseases.
- Antiviral compounds are incompletely metabolized during human use and enter surface waters via wastewater effluents.
- Although aquatic insects are known to bioaccumulate some pharmaceuticals by multiple orders of magnitude, antiviral bioaccumulation has not been quantified.
- When insect predators such as bats are also reservoirs of viral pathogens, exposure to bioconcentrated antivirals may result in viruses that are resistant to antiviral drugs.
- We outline a research frontier to examine the potential for these effects and a call to action to minimize risks for human health.

The Anthropocene is marked by an exponential increase in environmental contamination by diverse human-manufactured chemicals, including pharmaceuticals (Bernhardt *et al.* 2017; Wilkinson *et al.* 2022), compromising the 'safe operating space' for humanity and life (Rockström *et al.* 2009; Persson *et al.* 2022; Carlson *et al.* 2022). The current SARS-CoV-2 (COVID-19) pandemic, with over 589 million cases and the loss of over 6.4 million human lives, underscores the value of pharmaceuticals to fight disease. In response, a range of existing antiviral compounds was tested for efficacy in treating COVID-19 (Nippes *et al.* 2021), leading to 11 pharmaceuticals currently being used (Kuroda *et al.* 2021).

Antiviral compounds have been used to treat influenza and other viral infections. Oseltamivir is a widely prescribed antiviral for seasonal influenza, and acyclovir is used to treat infections caused by varicella-zoster virus. Antivirals are developed to target particular viruses, but when new viral threats emerge these compounds are often rapidly repurposed while targeted antiviral therapies are developed. For example, remdesivir was originally used to treat Ebola, and its use increased substantially throughout the world because of its early efficacy against COVID-19, which led to its approval for use in treating then-dominant variants of SARS-CoV-2 (Nippes *et al.* 2021). Antivirals are very effective at treating viral infections when given early in the course of infection. The "test and treat" initiative in the US allows patients to be tested in pharmacies and immediately

treated with antivirals. From Dec 2021 to May 21, 2022, over 1 million courses of antivirals to treat COVID-19 were dispensed in the US alone (Gold *et al.* 2022).

Warnings in wastewater

Antiviral compounds are incompletely metabolized by humans, leading to potentially high environmental concentrations in wastewater (Kuroda *et al.* 2021). For example, humans excrete 15% of oseltamivir and 80% of its metabolite oseltamivir carboxylate, the prodrug and active ingredient, respectively (He *et al.* 1999; Buckingham 2020). Ten percent of remdesivir is excreted unchanged and 49% is excreted as the active metabolite GS-451524 (Buckingham 2020). Increasingly widespread use of SARS-CoV-2 antivirals could similarly result in widespread excretion of unmetabolized antiviral compounds and active metabolites in waste. Human wastewater is often directly released into aquatic environments with little or no treatment (Kuroda *et al.* 2021). Indeed, the UN estimates that nearly half of the 8 billion people on the planet do not have access to wastewater treatment (WHO and UNICEF 2022). In urban areas, wastewater may be treated before discharge, but a recent global assessment estimates that approximately 1.2 million km of river reaches contain wastewater treatment effluent (Ehalt Macedo *et al.* 2022). Incomplete wastewater treatment is further exacerbated when effluent is poorly diluted by receiving waters, such as in dry regions of the world with lower volumes of freshwater. In ~5% of the world's rivers, roughly half of the water by volume is wastewater effluent during low flow conditions and 17% of global rivers contain about 10% effluent (Ehalt Macedo *et al.* 2022) suggesting that concentrations of antiviral

compounds in surface waters may be quite high in many locations, at least during low flow.

Wastewater treatment technologies vary widely around the world (Ehalt Macedo *et al.* 2022), but even the most advanced technologies do not remove all antiviral compounds (Kuroda *et al.* 2021). For example, wastewater treatment plants remove ~2% of remdesivir and its active metabolite GS-451524 (Kuroda *et al.* 2021). Removal efficiencies also vary by compound with over 90% removal of lopinavir and ritonavir, used to treat HIV, and less than 2% removal for oseltamivir and ribavirin, used to treat influenza and hepatitis C, respectively (7). Antiviral contamination of surface waters associated with the current SARS-CoV-2 pandemic is not known, but increasing use, low metabolism by humans, and inefficient removal from wastewater suggest that antiviral concentrations are likely to be elevated.

Predicted concentrations of compounds used to treat COVID-19 in surface waters range from low ng L^{-1} (Kuroda *et al.* 2021) to very high concentrations in mg L^{-1} (Tarazona *et al.* 2021). For most pharmaceuticals in surface waters, concentrations typically occur in ng L^{-1} range; however, in dry locations with high population densities and limited wastewater treatment, pharmaceuticals occur in the 1000s of ng L^{-1} (i.e., μg L^{-1}) range (Wilkinson *et al.* 2022). Downstream of pharmaceutical manufacturing facilities, pharmaceutical concentrations can occur in the millions of ng L^{-1} (i.e., mg L^{-1}) range (Fick *et al.* 2009). Concentrations are influenced by the number of treated patients, the capacity for removal via wastewater treatment, and the dilution factor in the recipient waterbody. In Wuhan, China two weeks after the initial SARS-CoV-2 outbreak, antiviral concentrations increased in wastewater treatment effluent and in surface water ranged

from 2.1 ng L^{-1} to 24.5 ng L^{-1}(Fick *et al.* 2009). During the 2009 H1N1 (swine flu) pandemic, the intra- and inter-pandemic variation of an influenza antiviral, oseltamivir carboxylate, was at concentrations of 30-60 ng L^{-1} across the Thames catchment, with a maximum measured concentration of 193 ng L^{-1} (Singer *et al.* 2014).

Manufacturing facilities are hotspots of surface water contamination by pharmaceuticals, including antivirals. Rivers receiving waste from pharmaceutical manufacturing facilities have the highest concentrations of pharmaceuticals (Fick *et al.* 2009; Scott *et al.* 2018; Wilkinson *et al.* 2022), with concentrations many orders of magnitude higher than those present in municipal wastewater effluent (Scott *et al.* 2018). During a pandemic, ramping up production at a facility can result in significant releases of pharmaceuticals to the environment. For example, during the H1N1 outbreak of 2009, the antiviral oseltamivir was released from a manufacturing plant in Basel, Switzerland, and concentrations in the Rhine River exceeded 1000 ng L^{-1} (Prasse *et al.* 2010). Fortunately, in this case, the facility discharged into a very large river, which provided a high degree of dilution.

Consequences for ecosystems

Aquatic insects. Once released into surface waters, many types of pharmaceuticals have been empirically measured to bioaccumulate in aquatic insect larvae including mayflies, caddisflies, stoneflies and true flies (Jonsson *et al.* 2014; Heynen *et al.* 2016; Richmond *et al.* 2018; Sedvall *et al.* 2022). Bioaccumulation is the net result of a dynamic equilibrium between uptake and elimination and is affected by toxicokinetic parameters and the physico-chemical properties of the chemicals. When

empirical measurements are lacking, bioaccumulation factors (BAFs) of pharmaceuticals can be modeled based on the structural properties of the compound (e.g., $\log(K_{ow})$ values), but structure-based models do not correlate well with empirical measurements (Miller *et al.* 2019). To our knowledge BAFs of antiviral compounds have not been measured, and current models are based on compounds with very different chemical structure, and use fish rather than invertebrates (Miller *et al.* 2019). Therefore, the extent of antiviral bioaccumulation in invertebrates remains unknown; however, given that the concentrations of other pharmaceutical compounds in their tissues can exceed the concentrations in water by multiple orders of magnitude, similar bioaccumulation of antivirals is possible (Jonsson *et al.* 2014; Heynen *et al.* 2016; Richmond *et al.* 2018; Sedvall *et al.* 2022).

The impacts of pharmaceutical contamination reach beyond aquatic systems. To complete their lifecycles, many species of aquatic larval insects emerge as aerial (flying) adults, transporting bioaccumulated contaminants across ecosystem boundaries (Kraus *et al.* 2020). The extent to which aquatic insects retain or accumulate pharmaceuticals during metamorphosis from aquatic to aerial terrestrial life stages is generally understudied and is likely to be variable across different contaminants (Kraus *et al.* 2014). In one study, spiders that primarily consume emerged aquatic insects had high concentrations of a wide variety of pharmaceuticals in their tissues (Richmond *et al.* 2018), illustrating that these pharmaceuticals had been transferred during metamorphosis to aerial adults and were bioavailable to predators. Although antivirals were not included

in that study, it demonstrates a plausible mechanism of antiviral transfer from humans to surface waters to emerging aquatic insects.

Bats. The majority of bat species are insectivorous and many species are major consumers of emerged aquatic insects, but the consumption of emerged aquatic insects by bat species is an unexplored pathway of exposure to antiviral compounds (Figure 1). This is of particular concern for bats in which numerous zoonotic viruses naturally persist with occasional spillover transmission to humans, including Ebola virus, Nipah virus, SARS-1 and SARS-CoV-2 viruses (Han *et al.* 2015; Zhou *et al.* 2020).

Some bat species are estimated to consume at least a third of their body weight per day, on the order of hundreds to several thousands of insects per individual per night (Moiseienko and Vlaschenko 2021). Many bats forage over water bodies, especially on evenings with high aquatic insect emergence (Anthony and Kunz 1977). Some species feed over wastewater treatment lagoons (Park, K.J., A. Cristinacce 2006; Park *et al.* 2009). Perhaps unsurprisingly, bats have also been reported to contain a range of pharmaceutical compounds in their tissues, including several antibiotics, salicylic acid, and caffeine (Secord *et al.* 2015).

Bats may also be exposed to pharmaceuticals through drinking contaminated water, though this exposure route is estimated to be of less concern, as surface waters are not predicted to have high enough concentrations to cause toxicological effects, even in close proximity to wastewater effluents (Kuroda *et al.* 2021; Biswas *et al.* 2021). Indeed, one study concluded that antiviral concentrations in wastewater are 1000 times lower than what is likely needed to elicit the evolution of antiviral resistance in bats ingesting contaminated water (Kuroda *et al.* 2021). We posit that the consumption of emerged

aquatic insects containing bioaccumulated antiviral compounds is a more consequential route of exposure of bats to antiviral compounds than drinking the water, although direct exposure to contaminated water has not been measured and cannot be ruled out for non-insectivorous bats (e.g., nectivorous and frugivorous species).

While the potential for emerging aquatic insects to serve as a vector of antivirals to bats and other disease reservoirs remains a research frontier, the concern that resistant pathogens will arise from animal reservoirs exposed to antivirals is not new (Kumar *et al.* 2020). For example, previous research demonstrated that dabbling ducks exposed to oseltamivir rapidly developed oseltamivir-resistant strains of influenza (Järhult *et al.* 2011). This resistant strain continued to spread in duck populations even after oseltamivir was no longer detectable in the environment (Gillman *et al.* 2015). This resistant strain found in ducks was unlikely to pose a threat to humans (Norberg *et al.* 2015), underscoring an important proviso - that the evolution of an antiviral-resistant strain does not itself guarantee a zoonotic threat. In contrast, there is accumulating evidence that unchecked transmission of SARS-CoV-2 in farmed mink (Oreshkova *et al.* 2020), white-tailed deer (Chandler *et al.* 2021), and other species (e.g., (Wei *et al.* 2021)) may lead to the evolution of novel variants capable of transmitting back into human populations, against which existing vaccines are less effective (Wilhelm *et al.* 2021).

A confluence of evidence

Overlap of bat distributions and antiviral contamination: Recently available data on pharmaceutical concentrations in surface waters around the world (Wilkinson *et al.* 2022) allowed comparison with range maps of insectivorous bat species that are confirmed to carry one or multiple betacoronaviruses (the genus to which SARS-1,

SARS-CoV-2, and MERS belong) (Becker *et al.* 2022). Although Wilkinson et al. (Wilkinson *et al.* 2022) did not collate data on SARS-CoV-2 antivirals per se, it is reasonable to assume that antiviral and pharmaceutical concentrations covary since both come via wastewater, and the conditions leading to high concentrations of pharmaceuticals are expected to be similar for antivirals (e.g., ineffective wastewater treatment, low dilution). We observed a number of locations globally where a high diversity of insectivorous bats overlaps with high concentrations of pharmaceuticals in surface waters (Figure 2), highlighting particular regions where current evidence suggests that potential bat reservoirs of betacoronaviruses may be routinely exposed to pharmaceuticals, including antivirals, either directly or through the consumption of emerged aquatic insects. Antiviral exposure is expected to be exponentially greater in proximity to manufacturing and formulation facilities, but these locations remain undisclosed to the public.

How much exposure? We constructed two models to investigate whether the concentrations of antivirals in surface waters are in a range that would expose bats to *therapeutic concentrations* of antivirals, corresponding to a human daily defined dose (DDD). In the first model, we estimated the fraction of a human DDD that bats would be exposed to by combining 1) published estimates of concentrations of pharmaceuticals used to treat COVID-19 in aquatic ecosystems, 2) an estimated range of antiviral bioaccumulation by aquatic insects, and 3) estimated rates of insect consumption by bats.

For drugs used to treat COVID-19, published estimates of environmental concentrations (PECs) include a worst-case scenario where 100% of a population is taking antivirals (Tarazona *et al.* 2021) and a more conservative estimate of a smaller

fraction of a population taking antivirals (Kuroda *et al.* 2021). After consumption, these antivirals enter wastewater effluent where it is estimated that upon release into surface waters they are diluted to 10% of their original concentration based on recent global estimates of wastewater dilution in rivers worldwide (Ehalt Macedo *et al.* 2022).

Published estimates of average insect consumption by bats ranged between 0.4 and 2.2 g d^{-1} for small vs. large species, respectively (Moiseienko and Vlaschenko 2021). We estimated the fraction of a human dose that bats would be exposed to on a given night assuming they consume 100% emerged aquatic insect prey (which is possible when aquatic insect emergence rates are high).

While bioaccumulation factors (BAF) for antivirals have not yet been quantified, other pharmaceuticals measured in emerged aquatic insects typically range in BAF from 1-1000 (Miller *et al.* 2018; Duarte *et al.* 2022). This means that the concentrations for some compounds found in aquatic insects are similar to the concentration in the water (BAF=1), whereas others can reach tissue concentrations 1000x greater than water. We therefore provide estimates of the fraction of a human dose (using prescribed dosing for each drug, and the average human size of 70 kg) that a bat may be exposed to at BAFs of 1 and 1000 (Table 1, for full calculations Table S1 and supporting text).

In the case of the antiviral remdesivir, at BAF = 1, small and large bats may be exposed to 0.23 and 0.28% of a human therapeutic dose, respectively (Table 1). At BAF = 1000, which is the case for numerous pharmaceutical compounds (Richmond *et al.* 2018), small bats may be exposed to 206% of a therapeutic dose, and large bats may be exposed to 243% of a human therapeutic dose. Our calculations of exposure of bats to other drugs currently being used to treat COVID-19 were similarly dependent on the

BAF. For instance, calculations based on the more conservative predictions of environmental concentrations (Kuroda *et al.* 2021) suggest bats would be exposed to less than 1% percent of a human dose even if the BAF is 1000 (Table S1).

In our second approach, we calculated the water concentrations needed to deliver therapeutic doses in bats scaled down from human therapeutic doses (for full calculations see Table S2 and supporting text). We assigned BAFs of 1 and 1000, and calculated values based on the partitioning coefficient (log K_{ow}) and modeled estimates of BAFs (Table 2). In the case of remdesivir, if the BAF is 1 in aquatic insects, for bats to obtain the equivalent of a human therapeutic dose, the concentration in surface waters would need to be 18 μg L^{-1}, an unrealistically high concentration. Other antiviral compounds modeled showed similarly high required concentrations. However, if the BAF in aquatic insects is 1000, the water concentrations would only need to be 18 ng L^{-1}, which is in the range of concentrations reported for other pharmaceuticals throughout the world, including other antivirals (Singer *et al.* 2014; Zhang *et al.* 2022).

Both modeling approaches consider whether it is possible for bats to be exposed to a human therapeutic dose of antivirals. In both scenarios, as bioaccumulation factors of antivirals increase, exposure to human therapeutic doses become increasingly probable. In addition to dose, duration of exposure is important to consider. For effective treatment in humans it is vital to take antivirals at the recommended therapeutic doses for the recommended treatment period to prevent evolution of antiviral resistant viruses (Drusano 2003). Thus, a worst-case scenario may be intermittent exposure of bats to sub-therapeutic doses of antivirals, which may increase the risk of evolution of antiviral-resistant viral pathogens. Antiviral BAFs around 100 would expose bats to doses that are

approximately 10-20% of a human therapeutic dose. Continued widespread release of human antivirals into aquatic ecosystems and subsequent exposure in bats may lead to a cycle of antiviral resistant zoonotic viruses, potentially diminishing antiviral efficacy.

Even if the likelihood of such a scenario is small or isolated, the consequences for human populations could be severe. As demonstrated by SARS-CoV-2, spillover from an animal to humans in one location led to rapid viral transmission worldwide. Similar to antibiotic resistant bacteria, the continued unchecked usage of antivirals could diminish our capacity to respond effectively to emerging pathogens. The current pandemic underscores the plausibility of multiple scenarios. For instance, a viral disease outbreak causes a spike in antiviral usage at a location with a dense human population, limited wastewater treatment capacity, and low wastewater dilution in a dry season. The concentrations of antivirals in surface waters in this scenario would be relatively high. Aquatic insects bioaccumulate these antivirals, exposing local bats to sub-therapeutic doses of antivirals as they forage on emerged insects. Another possible route would be antivirals released from pharmaceutical manufacturing facilities, which are hotspots for pharmaceutical compounds in the environment (Prasse *et al.* 2010; Scott *et al.* 2018). A pharmaceutical manufacturing facility that releases antiviral compounds to a nearby surface water where insectivorous bats routinely forage for emerged aquatic insects creates a direct link from antivirals, emerging insects, and bats.

Antiviral resistance that evolves in these conditions could subsequently spread through bat populations, and increase the risk of spillover transmission of a virus that is novel and challenging to treat. This scenario appears to be a series of unlikely and unfortunate events, but we have witnessed the series of similarly unlikely events that

precipitated the current pandemic. Animals, potentially individuals from only 1-2 species, transmitted the SARS-CoV-2 virus to humans, potentially only to a few people (Pekar *et al.* 2022). The consequences of this seemingly random and isolated event continue to reverberate, causing a 3.9% drop in the global GDP (Oum, Stephanie, Jennifer Kates, Adam Wexler), and the tragic loss of at least 6.4 million lives (WHO International).

A call to action

Mitigating the risk of antiviral contamination will first require understanding how these compounds behave in the environment, including the degree of bioaccumulation and transfer from aquatic insect larvae to aerial adults, and their bioavailability to insectivorous bats. Our understanding of this background risk will be furthered by better understanding the dietary range and foraging ecology of insectivorous bats, which also remain understudied. While many insectivorous bat species are generalist foragers, e.g., (Brooke 1994), others specialize on insects whose larvae do not develop in aquatic environments (e.g., dung beetles, (Aguilar-Rodríguez *et al.* 2022)) and this variation in bat diets likely mediates both the degree and the phenology of their exposure to antivirals through their prey. Increased understanding of the antiviral toxicokinetic properties, especially uptake rates and elimination efficiencies, in bats and insects is also needed. Furthermore, we call on the global community to take immediate preventative actions to reduce the risks of bat exposure to antivirals. This includes 1) incentivizing the responsible use of antivirals to treat only the most at-risk individuals; 2) Enacting regulations to prevent antiviral release during manufacturing and conducting routine monitoring of antivirals in downstream receiving waters; 3) Quantifying and investing in increased removal efficiency of pharmaceuticals, including antivirals, by wastewater

treatment plants; 4) Improving wastewater treatment technologies globally to promote removal of antivirals and numerous co-benefits for human and environmental health; and 5) Investigating bioaccumulation and degradability of antivirals in natural systems, and including these explicitly as criteria for which new antivirals advance to human trials.

Conclusions

In an increasingly connected world, novel infectious diseases can spread rapidly to every country of the world. Widespread use and uncontrolled release of antiviral may pose unforeseen and potentially serious consequences to human health. Bioaccumulation of antivirals in aquatic insects and potential transfer to bats represents a gap in our understanding about the consequences of antiviral contamination of the environment. We need to exercise caution with our current arsenal of antiviral compounds to ensure that our actions today do not render treatments ineffective for the diseases of tomorrow.

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Figures and Tables

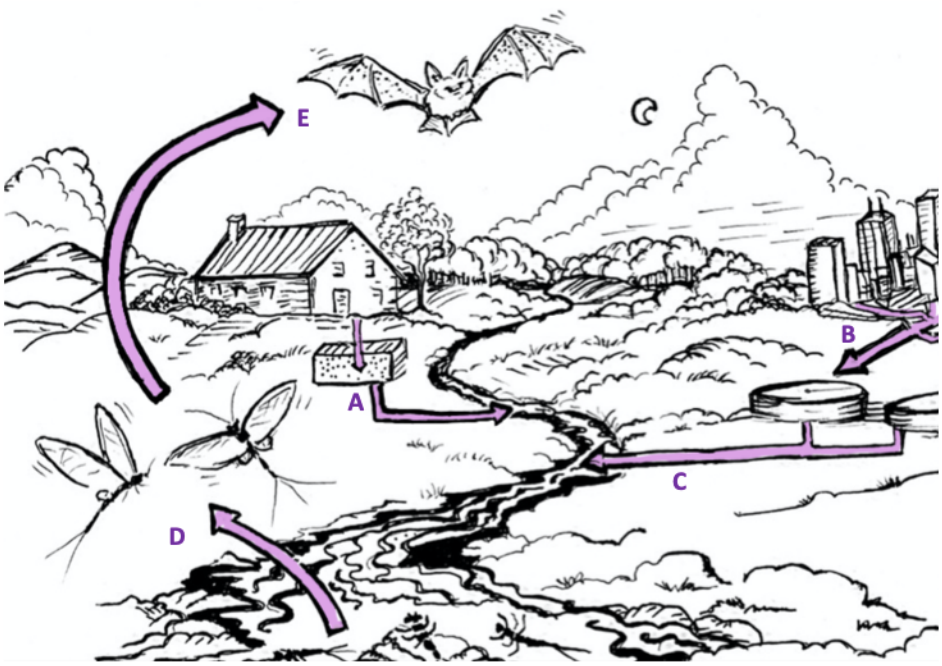

Figure 1. Plausible routes of transfer of antivirals from humans to bats: A) antivirals entering streams via septic systems; B) antivirals from urban areas entering wastewater treatment plants; C) antivirals from WWTPs entering the environment; D) bioaccumulated antivirals in emerging aquatic insects; E) bat exposure to antivirals in adult aquatic insects through predation.

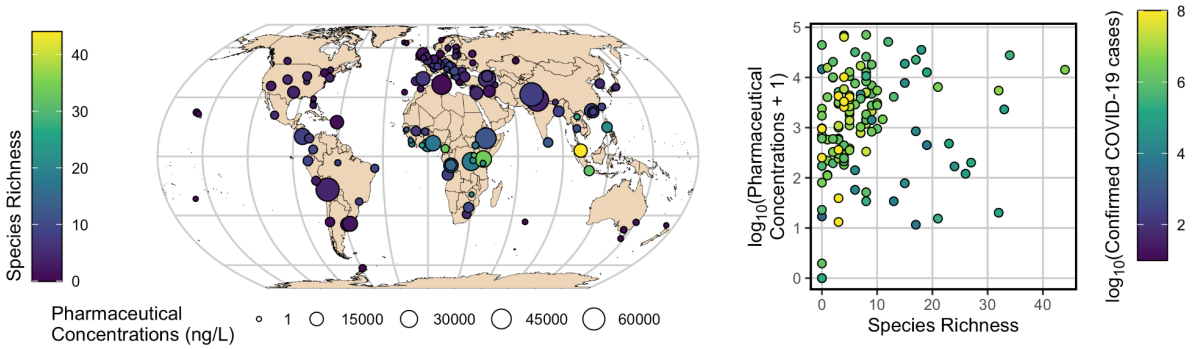

Figure 2. Geographic overlaps between insectivorous bat species confirmed to harbor betacoronaviruses (data from (Becker *et al.* 2022)) and estimated pharmaceutical concentrations in surface waters globally. A map illustrating bat species richness and pharmaceutical concentrations (left panel), and bat species richness, pharmaceutical concentrations and estimated COVID-19 cases in regions around the world depicted in right panel. (Pharmaceutical concentrations reported in (Wilkinson *et al.* 2022)).

Table 1. Percent of a human daily dose (%DDD) that small and large bats may receive from eating emerged aquatic insects using predicted environmental concentrations (PEC) in surface waters (Tarazona *et al.* 2021) and bioaccumulation factors (BAF) of 1 and 1000 for compounds with documented usage for treatment of COVID-19. See Table S1 for the percent of a human dose based on predicted environmental concentrations presented in (Kuroda *et al.* 2021).

Pharmaceutical compound	PEC (mg L^{-1})	%DDD in small bats BAF=1	%DDD in large bats BAF=1	%DDD in small bats BAF=1000	%DDD in large bats BAF=1000
Hydroxychloroquine*	0.12	0.14	0.17	140	165
Chloroquine*	0.06	0.07	0.08	70	83
Ivermectin*	0.0015	0.06	0.07	58	69
Dexamethasone#	0.003	0.23	0.28	233	275
Azithromycin*	0.12	0.11	0.13	112	132
Remdesivir	0.05	0.23	0.28	233	275
Opinavir	0.19-0.37	0.22	0.25	216	254
Ritonavir	0.07-0.10	0.23	0.28	233	275
Oseltamivir	0.04	0.25	0.29	249	293
Darunavir	0.54	0.21	0.25	210	248
Cobicistat	0.03-0.07	0.22	0.26	218	257
Umifenovir	0.30–0.13	0.23	0.28	233	275

*These pharmaceuticals are not anti-viral compounds and are less likely to result in anti-viral resistant viruses. # Dexamethasone is a steroid used to treat COVID-19 symptoms and increase survival rate and is not at all likely to result in antiviral resistant viruses. Please note that the therapies recommended for treatment of COVID-19 vary from nation to nation and we list those that are being used to treat COVID-19 across the world. This list does not represent a recommendation for their use nor does this list represent the current approval status of these therapies.

Table 2. Estimated predicted environmental concentration necessary to achieve a human therapeutic dose (DDD) in large bats, based on four different BAFs[a].

Pharmaceutical compound	Bat_{DDD} [b] ($\mu g\ g^{-1}$)	PEC-1 Eq 1.[c] ($ng\ L^{-1}$)	PEC-2 ACD/Labs [d] ($ng\ L^{-1}$)	PEC-2 BAF=1[e] ($ng\ L^{-1}$)	PEC-4 BAF=1000 [f] ($ng\ L^{-1}$)
Hydroxychloroquine*	0.094	53000	12000	94000	94
Chloroquine*	0.091	7600	35000	91000	91
Ivermectin*	0.0022	0.25	0.071	2200	2.2
Dexamethasone#	0.00027	310	16	270	0.27
Azithromycin*	0.091	29000	42000	91000	91
Remdesivir	0.020	3400	18000	18000	18
Lopinavir	0.15	2200	26	150000	150
Ritonavir	0.22	4300	50	220000	220
Oseltamivir	0.027	35000	24000	27000	27
Darunavir	0.22	240000	1700	220000	220
Cobicistat	0.027	790	17	27000	27
Umifenovir	0.15	4100	820	150000	150

[a] For full calculation of estimated predicted environmental concentrations necessary to achieve a human therapeutic dose, see supporting information, Table S2 and supporting text. [b] Concentration in bats for human therapeutic dose, based on human daily defined dose, adjusted for body weight, see Table S2 and supporting text. [c] PEC-1 values calculated on BAF values using equation log Pblood:water = 0.73 x log Kow - 0.88 (Fitzsimmons et al., 2001), [d] PEC-2 values calculated on BAF values by ACD/Labs Percepta Platform - PhysChem Module, acquired through the Chemspider database (http://www.chemspider.com/)[e] PEC-3 values calculated based on BAF value set to 1, [f] PEC-4 values calculated based on BAF value set to 1000.

*These pharmaceuticals are not anti-viral compounds and are less likely to result in anti-viral resistant viruses. # Dexamethasone is a steroid used to treat COVID-19 symptoms and increase survival rate and is not at all likely to result in antiviral resistant viruses. Please note that the therapies recommended for treatment of COVID-19 vary from nation to nation and we list those that are being used to treat COVID-19 across the world. This list does not represent a recommendation for their use nor does this list represent the current approval status of these therapies.