Environmental Science & Technology Letters

pubs.acs.org/journal/estlcu

Letter

Are Animal Disease Reservoirs at Risk of Human Antiviral Exposure?

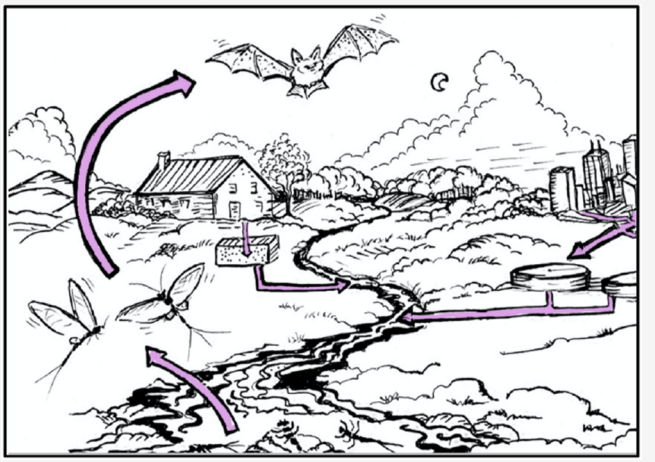
Emma J. Rosi,* Jerker B. Fick, and Barbara A. Han

Cite This: *Environ. Sci. Technol. Lett.* 2023, 10, 439−445

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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, they can 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 scientific research, antiviral development, and use.



KEYWORDS: *bats, antivirals, pandemics, emerging insects, antiviral resistance, wastewater*

INTRODUCTION

Environmental contamination by diverse synthetic chemicals, including pharmaceuticals,[1,2] has increased exponentially and compromises the "safe operating space" for life on Earth.[3−5] The current SARS-CoV-2 (COVID-19) pandemic underscores the need for pharmaceuticals to fight disease. A range of existing antiviral compounds were tested for efficacy in treating COVID-19,[6] with 11 currently in use.[7] Here, we explore the risk that antivirals may be transferred from aquatic ecosystems to animal disease reservoirs by emerging aquatic insects and thereby lead to evolution of antiviral resistant pathogens that pose risks for human health.

Antiviral compounds have been used to treat influenza and other viral infections, and when new viral threats emerge, these compounds are often rapidly repurposed while targeted antiviral therapies and vaccines are developed. For example, remdesivir was originally used to treat Ebola, but its use increased substantially because of its early efficacy against COVID-19.[6] From December 2021 to May 2022, over 1 million courses of antivirals to treat COVID-19 were dispensed in the U.S. alone.[8]

Antivirals are incompletely metabolized by humans, leading to potentially high concentrations in wastewater.[7] For example, 10% of remdesivir is excreted unchanged, and 49% is excreted as the active metabolite GS-451524.[9] Widespread use of antivirals may result in excretion of both unmetabolized compounds and active metabolites. Human wastewater is often directly released into aquatic environments with little or no treatment;[7] the UN estimates that nearly 4 billion people do not have wastewater treatment.[10] A recent global assessment estimates that approximately 1.2 million km of river reaches contain wastewater effluent.[11] In ∼5% of the world's rivers, roughly half of the water by volume is wastewater effluent during low flow conditions[11] suggesting that concentrations of antiviral compounds in surface waters can become quite high, especially in arid locations.

Wastewater treatment technologies vary widely,[11] but even the most advanced technologies do not remove all antiviral compounds.[7,12] Wastewater treatment plants remove ∼2% of remdesivir and its active metabolite GS-451524.[7] 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 antiviral concentrations are likely elevated.

Received: March 17, 2023
Revised: March 30, 2023
Accepted: March 31, 2023
Published: April 5, 2023

https://doi.org/10.1021/acs.estlett.3c00201
Environ. Sci. Technol. Lett. 2023, 10, 439−445

Predicted concentrations of compounds used to treat COVID-19 in surface waters range from low (ng L^{-1})[7] to very high (mg L^{-1}).[13] Concentrations of pharmaceuticals in surface waters typically occur in the ng L^{-1} range; however, they can be much higher in densely populated dry regions with limited wastewater treatment, in the μg L^{-1} range.[2] In Wuhan, China, 2 weeks after the initial SARS-CoV-2 outbreak, antivirals in rivers ranged from 2.1 to 24.5 ng L^{-1} [14]. During the 2009 H1N1 (swine flu) pandemic in the U.K., the antiviral oseltamivir carboxylate was 30−60 ng L^{-1} across the Thames catchment, with a maximum concentration of 193 ng L^{-1}.[15]

Manufacturing facilities can also be hotspots of surface water contamination by pharmaceuticals, including antivirals. Rivers receiving waste from pharmaceutical manufacturing facilities have concentrations of pharmaceuticals orders of magnitude higher than municipal effluents, in the mg L^{-1} range.[2,14,16] During a pandemic, increased production may lead to significant releases of pharmaceuticals. During the H1N1 outbreak of 2009, the antiviral oseltamivir in the Rhine River below a manufacturing plant in Basel, Switzerland, exceeded 1000 ng L^{-1}.[17]

Once released into surface waters, many types of pharmaceuticals bioaccumulate in aquatic insect larvae including mayflies, caddisflies, stoneflies, and true flies.[18−21] Bioaccumulation is the net result of a dynamic equilibrium between uptake and elimination and is affected by toxicokinetic parameters and the physicochemical properties of the chemicals. Bioaccumulation factors (BAFs) of pharmaceuticals can be modeled based on the structural properties of the compound (e.g., log(K_{ow}) values), though structure-based models do not correlate well with empirical measurements.[22] The best current models are based on compounds with very different chemical structures and use fish rather than invertebrates to estimate BAFs.[22] While the extent of antiviral bioaccumulation in invertebrates remains understudied, it is strongly suspected given the observed bioaccumulation of numerous other pharmaceuticals in aquatic invertebrates.[18−21]

Pharmaceutical contamination extends to terrestrial systems because many aquatic insects emerge as aerial adults, transporting bioaccumulated contaminants across ecosystem boundaries.[23] The retention or elimination of pharmaceuticals during metamorphosis from aquatic to aerial terrestrial life stages is generally understudied.[24] In one study, spiders that primarily consume emerged aquatic insects had high concentrations of a wide variety of pharmaceuticals in their tissues,[21] illustrating that some pharmaceuticals were transferred during metamorphosis to adults and bioavailable to predators.

Bats, which harbor many viruses, are a major consumer of emerged aquatic insects, an unexplored pathway of exposure to antiviral compounds. Although a recent study highlighted the concern for bats being exposed to antivirals,[25] to our knowledge the mechanism of exposure to bioaccumulated antivirals via aquatic insect consumption has not been proposed. We posit that 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.[26,27] It is also an ongoing concern for novel viruses discovered in bats, as for example a closely related sarbecovirus found in a Russian horseshoe bat demonstrated resistance to existing SARS-CoV-2 vaccines.[28]

Some bat species are estimated to consume at least a third of their body weight per day of prey, on the order of hundreds to several thousands of insects per individual per night.[29] Many bats forage over water bodies, especially on evenings with high aquatic insect emergence.[30] Some species feed over wastewater treatment lagoons.[31,32] Perhaps unsurprisingly, bats have also been reported to contain a range of pharmaceutical compounds in their tissues.[33]

Bats may also be exposed to pharmaceuticals through drinking contaminated water,[25] though this exposure route is estimated to be of less concern, as surface waters are not predicted to have high concentrations, even in close proximity to wastewater effluents.[7,34] Indeed, one study concluded that antiviral concentrations in wastewater are 1000-fold lower than what is likely to elicit the evolution of antiviral resistance in bats ingesting contaminated water.[7] We propose an alternative, heretofore unexplored mechanism—that the consumption of emerged aquatic insects containing bioaccumulated antiviral compounds is a more consequential route of exposure for bats.

The potential for emerging aquatic insects to serve as a vector of antivirals to bats and other disease reservoirs remains a research frontier. However, the concern that resistant pathogens will arise from animal reservoirs exposed to antivirals is not new.[25] For example, previous research demonstrated that dabbling ducks exposed to oseltamivir (commercially sold as Tamiflu) rapidly developed oseltamivir-resistant strains of influenza.[35] This resistant strain continued to spread in duck populations even after oseltamivir was no longer detectable in the environment.[36] This resistant strain found in ducks was unlikely to pose a threat to humans,[37] underscoring an important proviso—that the evolution of an antiviral-resistant strain is not necessarily a zoonotic threat. There is, however, accumulating evidence that unchecked transmission of SARS-CoV-2 in animal hosts will lead to the establishment of long-term endemic reservoirs of SARS-CoV-2 (e.g., white-tailed deer[38]) or may lead to the evolution of novel variants capable of transmission back into human populations,[39,40] against which existing vaccines are less effective.[41]

METHODS

We examined the spatial overlap between pharmaceutical concentrations and the occurrence of bat species throughout the world. Using recent data collected from rivers throughout the world on pharmaceutical concentrations[2] and information about the distribution of bat species[42] that are reservoirs of betacoronaviruses, we mapped the overlap among these two global data sets to explore the potential exposure of bats to pharmaceutical pollution.

We used two models to examine the potential for antiviral compounds to bioaccumulate in insects and expose bat species. In the first model, we began by calculating the concentration of each antiviral in insect tissues (B, in ng g^{-1}) as

$$B = \mathrm{PEC} \times \frac{1\,\mathrm{L}}{1000\,\mathrm{g}} \times \mathrm{BAF} \quad (1)$$

where PEC is the predicted environmental concentration in ng L^{-1}, and BAF is the bioaccumulation factor. Published estimates of drugs to treat COVID-19 include a worst-case scenario where 100% of a human population is taking antivirals[13] and an assumption of a smaller fraction of a population taking antivirals[7] (see Table S1). Bioaccumulation factors (BAFs) for antivirals have not been quantified, but

https://doi.org/10.1021/acs.estlett.3c00201
Environ. Sci. Technol. Lett. 2023, 10, 439−445

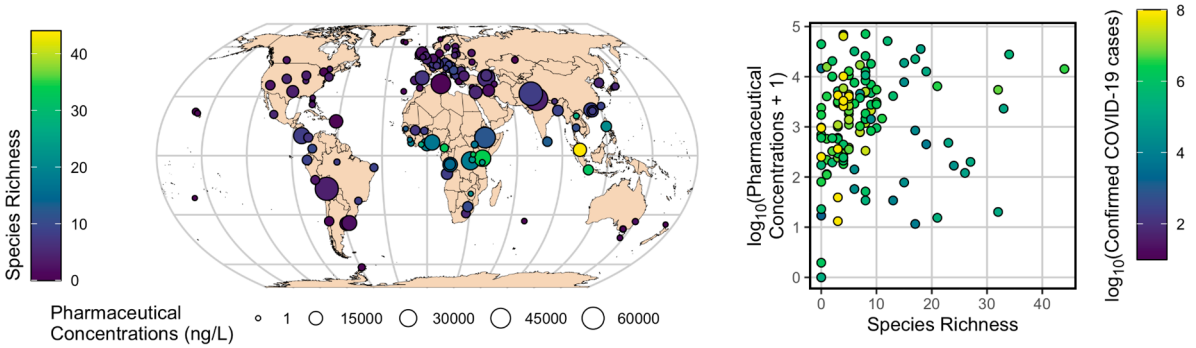


Figure 1. Geographic overlaps between insectivorous bat species confirmed to harbor betacoronaviruses (data from ref 42) and estimated pharmaceutical concentrations in surface waters globally. A map illustrating bat species richness and pharmaceutical concentrations (left panel) and bat species richness, pharmaceutical concentrations,[2] and estimated COVID-19 cases in regions around the world depicted (right panel).

Table 1. Percent of a Human Daily Dose ($\%DDD_m$) That Small and Large Bats May Receive from Eating Emerged Aquatic Insects Using Predicted Environmental Concentrations (PEC) in Surface Waters[13] and Bioaccumulation Factors (BAF) of 1 and 1000 for Compounds with Documented Usage for Treatment of COVID-19[a]

Pharmaceutical compound	PEC (mg L^{-1})	$\%DDD_m$ in small bats (BAF = 1)	$\%DDD_m$ in large bats (BAF = 1)	$\%DDD_m$ in small bats (BAF = 1000)	$\%DDD_m$ in large bats (BAF = 1000)
Hydroxychloroquine[b]	0.12	0.14	0.17	140	165
Chloroquine[b]	0.06	0.07	0.08	70	83
Ivermectin[b]	0.0015	0.06	0.07	58	69
Dexamethasone[c]	0.003	0.23	0.28	233	275
Azithromycin[b]	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

[a]See Table S1 for the percent of a human dose based on predicted environmental concentrations presented in ref 7. [b]These pharmaceuticals are not antiviral compounds and are less likely to result in antiviral resistant viruses. [c]Dexamethasone is a steroid used to treat COVID-19 symptoms and increases 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.

BAFs for other pharmaceuticals range from 1 to 1000.[43,44] We used BAFs of 1 and 1000 to constrain the range of possibilities.

We then calculated the consumption of antivirals by bats (C in ng g^{-1} day^{-1}):

$$C = (B \times I)/M_b \quad (2)$$

where I is the ingestion rate of insects by bats (in g d^{-1}), and M_b is the mass of the bats. Average insect consumption by bats (I) is 0.4 and 2.2 g d^{-1} ,and M_b is 6 and 28 g for small and large species, respectively.[29]

The human daily defined dose per mass of human tissue for each compound (DDD_m in ng g^{-1}) was estimated as follows:

$$DDD_m = (DDD/M_h) \quad (3)$$

where DDD is the daily defined dose for humans for each compound (in ng d^{-1}), and M is the average adult human mass (70,000 g).

The fraction of a daily defined dose that bats would be exposed to ($\%DDD_m$) for each compound was determined as

$$\%DDD_m = (C/DDD_m) \times 100 \quad (4)$$

where DDD_m and C were calculated as in eqs 2 and 3.

In the second model, we calculated the therapeutic concentration in bats (Bat_{DDD}) based on the corresponding human therapeutic dose for each drug:

$$Bat_{DDD} = \frac{DDD}{70} \times 0.028 \quad (5)$$

where human DDD is adjusted for the body weight of bats assuming 70 kg for humans and 28 g for bats.[29] Using an average daily consumption of 2.2 g of invertebrates by bats,[29] eq 6 yields the concentration needed in invertebrates to achieve a daily dose for exposed bats:

$$Inv_{Load} = \left(\frac{BatDDD}{2.2}\right) \times 1000 \quad (6)$$

where Inv_{Load} is the load of pollutants in invertebrates needed to achieve a Bat_{DDD} in $\mu g/g$, based on the previous assumptions. The predicted environmental concentration in the water (PEC in ng L^{-1}) necessary to achieve the relevant contaminant load in invertebrates is

$$PEC = (Inv_{Load}/BAF) \times 1000 \times 1000 \quad (7)$$

https://doi.org/10.1021/acs.estlett.3c00201
Environ. Sci. Technol. Lett. 2023, 10, 439−445

Table 2. Estimated Predicted Environmental Concentration Necessary to Achieve a Human Therapeutic Dose (DDD) in Large Bats, Based on Four Different BAFs

Pharmaceutical compound	Inv_{Load}[a] ($\mu g\ g^{-1}$)	PEC-1 eq 1[b] (ng L^{-1})	PEC-2 ACD/Laboratories[c] (ng L^{-1})	PEC-3 (BAF = 1)[d] (ng L^{-1})	PEC-4 (BAF = 1000)[e] (ng L^{-1})
Hydroxychloroquine[f]	94	53,000	12,000	94,000	94
Chloroquine[f]	91	7600	35,000	91,000	91
Ivermectin[f]	2.2	0.25	0.071	2200	2.2
Dexamethasone[g]	0.27	310	16	270	0.27
Azithromycin[f]	91	29,000	42,000	91,000	91
Remdesivir	20	3400	18,000	18,000	18
Lopinavir	150	2200	26	150,000	150
Ritonavir	220	4300	50	220,000	220
Oseltamivir	27	35,000	24,000	27,000	27
Darunavir	220	240,000	1700	220,000	220
Cobicistat	27	790	17	27,000	27
Umifenovir	150	4100	820	150,000	150

[a]Concentration in feed which will cause therapeutic daily dose in bats, based on human daily defined dose, adjusted for body weight, see Table S2. [b]PEC-1 values calculated on BAF values using equation log Pblood:water = 0.73 × log K_{ow} − 0.88.[50] [c]PEC-2 values calculated on BAF values by ACD/Laboratories Percepta Platform−PhysChem Module, acquired through the Chemspider database (http://www.chemspider.com/). [d]PEC-3 values calculated based on BAF value set to 1. [e]PEC-4 values calculated based on BAF value set to 1000. [f]These pharmaceuticals are not antiviral compounds and are less likely to result in antiviral resistant viruses. [g]Dexamethasone is a steroid used to treat COVID-19 symptoms and increases 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 include compounds used to treat COVID-19 across the world. This list does not represent a recommendation for their use.

where Inv_{Load} is calculated above, and BAFs were either modeled (see Table S2) or set to 1 and 1000.

RESULTS

There is significant overlap between pharmaceutical concentrations in surface waters around the world and the distributions 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)[42] (Figure 1). Although this study[2] did not measure SARS-CoV-2 antivirals, antivirals and pharmaceutical concentrations likely covary because conditions for high concentrations are likely similar (e.g., high human population, ineffective wastewater treatment, low dilution). A number of locations with a high diversity of insectivorous bats overlap with high concentrations of pharmaceuticals (Figure 1), suggesting that bat reservoirs of betacoronaviruses may be routinely exposed to pharmaceuticals, including antivirals, either directly through drinking water or via consumption of emerged aquatic insects. It is likely that potential antiviral exposure is exponentially greater downstream of manufacturing facilities, but these locations remain undisclosed to the public.

Antivirals in surface waters could potentially expose bats to *therapeutic concentrations*, corresponding to a human daily defined dose (DDD) (Table 1). In our first model, the fraction of a human DDD that bats would be exposed to is a combination of (1) published estimates of concentrations of pharmaceuticals used to treat COVID-19 in aquatic ecosystems,[13,7] (2) an estimated range of antiviral bioaccumulation factors (BAF) by aquatic insects,[43,44] and (3) estimated rates of insect consumption by bats[29]. For the antiviral remdesivir, if BAF = 1, small and large bats may consume 0.23% and 0.28% of a human dose, respectively (Table 1) from eating emerged aquatic insects. At BAF = 1000, the case for numerous pharmaceutical compounds,[21] small bats may consume 233% of a dose, and large bats may consume 275% of a dose. Exposures of bats to other drugs currently being used to treat COVID-19 were similarly influenced by BAF. More conservative predictions of environmental concentrations[7] 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 model, the water concentrations needed to deliver therapeutic doses in bats were scaled down from human therapeutic doses. We calculated these values based on the partitioning coefficient (log K_{ow}) and modeled estimates of BAFs (Table 2). In the case of remdesivir, if BAF= 1, for bats to obtain the equivalent of a human dose, the water concentration would need to be 18 $\mu g\ L^{-1}$, an unrealistically high water concentration. Other antiviral compounds modeled showed similarly high required concentrations. However, if BAFs in aquatic insects is 1000, the water concentrations would only need to be 18 ng L^{-1}, a concentration already reported for many pharmaceuticals including antivirals.[15,45]

DISCUSSION

Our conservative mapping and modeling exercises highlight the potential for bats to be at risk for exposure to antivirals via consumption of emerging aquatic insects. Our results demonstrate significant overlap between high concentrations of pharmaceuticals in surface waters and the distribution of bats that are reservoirs for beta coronaviruses. Importantly, our modeling demonstrates that the risk of exposure to antivirals is strongly dependent on the extent to which antivirals bioaccumulate in aquatic insects, which is currently not known. In addition to dose, the duration of exposure is important, because antivirals are prescribed in doses for a treatment period (days to weeks) to prevent evolution of antiviral resistant viruses.[46] Thus, a worst-case scenario may be intermittent exposure of bats to subtherapeutic 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.

Even if the likelihood of bat exposure to antivirals is small or isolated, the consequences for human populations could be severe. As demonstrated by SARS-CoV-2,[47,48] spillover from

https://doi.org/10.1021/acs.estlett.3c00201
Environ. Sci. Technol. Lett. 2023, 10, 439−445

animals to humans in one location can lead to rapid viral transmission worldwide. There are plausible scenarios in which the continued unchecked usage of antivirals could diminish our capacity to respond effectively to emerging pathogens, for instance, if a viral disease outbreak led to a spike in antiviral usage within a dense human population with limited wastewater treatment capacity. If such an outbreak occurred during a dry season with low wastewater dilution, concentrations of antivirals in surface waters would likely be high, with aquatic insects bioaccumulating antivirals and potentially exposing bats to subtherapeutic doses. A pharmaceutical manufacturing facility releasing antiviral compounds to surface waters where insectivorous bats routinely forage for emerged aquatic insects would be similarly problematic. Antiviral resistance evolving in these scenarios could subsequently spread through bat populations and increase the risk of spillover transmission of a virus that is challenging to treat.

A CALL TO ACTION

Mitigating risks associated with antiviral contamination requires understanding of how antivirals behave in the environment, including the degree of bioaccumulation and transfer from aquatic insect larvae to aerial adults, and their bioavailability to insectivorous bats. These investigations would be improved by better understanding the dietary range and foraging ecology of insectivorous bats. While many insectivorous bat species are generalist foragers, for example, others specialize on insects whose larvae do not develop in aquatic environments (e.g., dung beetles[49]), and variation in bat diets likely mediates their exposure to antivirals through prey. Increased understanding of the antiviral toxicokinetic properties, especially uptake rates and elimination efficiencies, in bats and insects is also needed.

While our proposed ecological hypotheses and modeled estimates of antiviral exposure present immediate research priorities, concomitant preventative actions would reduce the risk of bat exposure to antivirals. These include (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 of pharmaceuticals, including antivirals, by wastewater treatment plants, (4) increasing access to wastewater treatment technologies globally, and (5) investigating bioaccumulation and degradability of antivirals in natural systems and using this information to develop criteria for antivirals to advance to human trials.

CONCLUSIONS

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

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.3c00201.

Fraction of human doses that bats may be exposed to using PECs from Kuroda et al.[7] and parameters used to calculate estimated PEC necessary to achieve a human therapeutic dose in bats (PDF)

AUTHOR INFORMATION

Corresponding Author

Emma J. Rosi − *Cary Institute of Ecosystem Studies, Millbrook, New York 12545, United States;* orcid.org/0000-0002-3476-6368; Phone: 1-845-677-7600; Email: rosie@caryinstitute.org; Fax: 1-845-677-5976

Authors

Jerker B. Fick − *Department of Chemistry, Umeå University, Umeå 907 36, Sweden;* orcid.org/0000-0002-3949-7371

Barbara A. Han − *Cary Institute of Ecosystem Studies, Millbrook, New York 12545, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.estlett.3c00201

Notes

Rosi, E. J.; Fick, J. B.; Han, B. A. Spillover of human antivirals may promote resistant pathogens in animal reservoirs. EcoEvoRxiv Preprint, 2022. https://ecoevorxiv.org/repository/view/3661/ (accessed March 30, 2023).

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge A. Castellanos for figure assistance. We thank D. M. Walters for suggestions on the manuscript. There was no funding associated with this manuscript.

REFERENCES

(1) Bernhardt, E. S.; Rosi, E. J.; Gessner, M. O. Synthetic Chemicals as Agents of Global Change. *Front Ecol Environ* **2017**, *15* (2), 84−90.

(2) Wilkinson, J. L.; Boxall, A. B. A.; Kolpin, D. W.; Leung, K. M. Y.; Lai, R. W. S.; Galbán-Malagón, C.; Adell, A. D.; Mondon, J.; Metian, M.; Marchant, R. A.; Bouzas-Monroy, A.; Cuni-Sanchez, A.; Coors, A.; Carriquiriborde, P.; Rojo, M.; Gordon, C.; Cara, M.; Moermond, M.; Luarte, T.; Petrosyan, V.; et al. Pharmaceutical Pollution of the World's Rivers. *Proc. Natl. Acad. Sci. U.S.A.* **2022**, *119* (8), No. e2113947119.

(3) Rockström, J.; Steffen, W.; Noone, K.; Persson, Å.; Chapin, F. S.; Lambin, E. F.; Lenton, T. M.; Scheffer, M.; Folke, C.; Schellnhuber, H. J.; Nykvist, B.; de Wit, C. A.; Hughes, T.; van der Leeuw, S.; Rodhe, H.; Sörlin, S.; Snyder, P. K.; Costanza, R.; Svedin, U.; Falkenmark, M.; et al. A Safe Operating Space for Humanity. *Nature* **2009**, *461* (7263), 472−475.

(4) Persson, L.; Carney Almroth, B. M.; Collins, C. D.; Cornell, S.; de Wit, C. A.; Diamond, M. L.; Fantke, P.; Hassellov, M.; MacLeod, M.; Ryberg, M. W.; Søgaard Jørgensen, P.; Villarrubia-Gomez, P.; Wang, Z.; Hauschild, M. Z. Outside the Safe Operating Space of the Planetary Boundary for Novel Entities. *Environ. Sci. Technol.* **2022**, *56* (3), 1510−1521.

(5) Carlson, C. J.; Albery, G. F.; Merow, C.; Trisos, C. H.; Zipfel, C. M.; Eskew, E. A.; Olival, K. J.; Ross, N.; Bansal, S. Climate Change Increases Cross-Species Viral Transmission Risk. *Nature* **2022**, *607*, 555.

(6) Nippes, R. P.; Macruz, P. D.; da Silva, G. N.; Neves Olsen Scaliante, M. H. A Critical Review on Environment al Presence of

Pharmaceutical Drugs Tested for the Covid-19 Treatment. *Process Safety and Environmental Protection* **2021**, *152*, 568−582.
(7) Kuroda, K.; Li, C.; Dhangar, K.; Kumar, M. Predicted Occurrence, Ecotoxicological Risk and Environmentally Acquired Resistance of Antiviral Drugs Associated with COVID-19 in Environmental Waters. *Science of The Total Environment* **2021**, *776*, No. 145740.
(8) Gold, J. A. W.; Kelleher, J.; Magid, J.; Jackson, B. R.; Pennini, M. E.; Kushner, D.; Weston, E. J.; Rasulnia, B.; Kuwabara, S.; Bennett, K.; Mahon, B. E.; Patel, A.; Auerbach, J. Dispensing of Oral Antiviral Drugs for Treatment of COVID-19 by Zip Code−Level Social Vulnerability — United States, December 23, 2021−May 21, 2022. *MMWR Morb. Mortal. Wkly. Rep.* **2022**, *71* (25), 825−829.
(9) Buckingham, R. *Martindale: The Complete Drug Reference*, 40th ed.; Pharmaceutical Press: London, 2020.
(10) *WHO/UNICEF Joint Monitoring Programme for Water Supply: Sanitation and Hygiene*. https://www.unwater.org/publication_categories/whounicef-joint-monitoring-programme-for-water-supply-sanitation-hygiene-jmp/ (accessed 2022−04−26).
(11) Ehalt Macedo, H.; Lehner, B.; Nicell, J.; Grill, G.; Li, J.; Limtong, A.; Shakya, R. Distribution and Characteristics of Wastewater Treatment Plants within the Global River Network. *Earth Syst. Sci. Data* **2022**, *14* (2), 559−577.
(12) Fick, J.; Lindberg, R. H.; Tysklind, M.; Haemig, P. D.; Waldenström, J.; Wallensten, A.; Olsen, B. Antiviral Oseltamivir Is Not Removed or Degraded in Normal Sewage Water Treatment: Implications for Development of Resistance by Influenza A Virus. *PLoS One* **2007**, *2* (10), No. e986.
(13) Tarazona, J. V.; Martínez, M.; Martínez, M.-A.; Anadón, A. Environmental Impact Assessment of COVID-19 Therapeutic Solutions. A Prospective Analysis. *Science of The Total Environment* **2021**, *778*, No. 146257.
(14) Fick, J.; Söderström, H.; Lindberg, R. H.; Phan, C.; Tysklind, M.; Larsson, D. G. J. Contamination of Surface, Ground, and Drinking Water from Pharmaceutical Production. *Environ. Toxicol. Chem.* **2009**, *28* (12), 2522.
(15) Singer, A. C.; Järhult, J. D.; Grabic, R.; Khan, G. A.; Lindberg, R. H.; Fedorova, G.; Fick, J.; Bowes, M. J.; Olsen, B.; Söderström, H. Intra- and Inter-Pandemic Variations of Antiviral, Antibiotics and Decongestants in Wastewater Treatment Plants and Receiving Rivers. *PLoS One* **2014**, *9* (9), No. e108621.
(16) Scott, T.-M.; Phillips, P. J.; Kolpin, D. W.; Colella, K. M.; Furlong, E. T.; Foreman, W. T.; Gray, J. L. Pharmaceutical Manufacturing Facility Discharges Can Substantially Increase the Pharmaceutical Load to U.S. Wastewaters. *Science of The Total Environment* **2018**, *636*, 69−79.
(17) Prasse, C.; Schlüsener, M. P.; Schulz, R.; Ternes, T. A. Antiviral Drugs in Wastewater and Surface Waters: A New Pharmaceutical Class of Environmental Relevance? *Environ. Sci. Technol.* **2010**, *44* (5), 1728−1735.
(18) Jonsson, M.; Fick, J.; Klaminder, J.; Brodin, T. Antihistamines and Aquatic Insects: Bioconcentration and Impacts on Behavior in Damselfly Larvae (Zygoptera). *Science of The Total Environment* **2014**, *472*, 108−111.
(19) Heynen, M.; Fick, J.; Jonsson, M.; Klaminder, J.; Brodin, T. Effect of Bioconcentration and Trophic Transfer on Realized Exposure to Oxazepam in 2 Predators, the Dragonfly Larvae (*Aeshna Grandis*) and the Eurasian Perch (*Perca Fluviatilis*): Species-Specific Bioconcentration and Trophic Transfer. *Environ. Toxicol. Chem.* **2016**, *35* (4), 930−937.
(20) Sedvall, E.; Fick, J.; Pettersson, C.; Hedeland, M. Pharmaceuticals Are Identified in Insects in River Fyris − A Study with Both Tandem Quadrupole and Quadrupole-Time-of-Flight Mass Spectrometry. *Environmental Advances* **2022**, *8*, No. 100194.
(21) Richmond, E. K.; Rosi, E. J.; Walters, D. M.; Fick, J.; Hamilton, S. K.; Brodin, T.; Sundelin, A.; Grace, M. R. A Diverse Suite of Pharmaceuticals Contaminates Stream and Riparian Food Webs. *Nat. Commun.* **2018**, *9* (1), 4491.
(22) Miller, T. H.; Gallidabino, M. D.; MacRae, J. I.; Owen, S. F.; Bury, N. R.; Barron, L. P. Prediction of Bioconcentration Factors in Fish and Invertebrates Using Machine Learning. *Science of The Total Environment* **2019**, *648*, 80−89.
(23) *Contaminants and Ecological Subsidies: The Land-Water Interface*; Kraus, J. M., Walters, D. M., Mills, M. A., Eds.; Springer International Publishing: Cham, 2020. DOI: 10.1007/978-3-030-49480-3.
(24) Kraus, J. M.; Walters, D. M.; Wesner, J. S.; Stricker, C. A.; Schmidt, T. S.; Zuellig, R. E. Metamorphosis Alters Contaminants and Chemical Tracers in Insects: Implications for Food Webs. *Environ. Sci. Technol.* **2014**, *48* (18), 10957−10965.
(25) Kumar, M.; Kuroda, K.; Dhangar, K.; Mazumder, P.; Sonne, C.; Rinklebe, J.; Kitajima, M. Potential Emergence of Antiviral-Resistant Pandemic Viruses via Environmental Drug Exposure of Animal Reservoirs. *Environ. Sci. Technol.* **2020**, *54* (14), 8503−8505.
(26) Han, H.-J.; Wen, H.; Zhou, C.-M.; Chen, F.-F.; Luo, L.-M.; Liu, J.; Yu, X.-J. Bats as Reservoirs of Severe Emerging Infectious Diseases. *Virus Research* **2015**, *205*, 1−6.
(27) Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; Chen, H.-D.; Chen, J.; Luo, Y.; Guo, H.; Jiang, R.-D.; Liu, M.-Q.; Chen, Y.; Shen, X.-R.; Wang, X.; Zheng, X.-S.; et al. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature* **2020**, *579* (7798), 270−273.
(28) Seifert, S. N.; Bai, S.; Fawcett, S.; Norton, E. B.; Zwezdaryk, K. J.; Robinson, J.; Gunn, B.; Letko, M. An ACE2-Dependent Sarbecovirus in Russian Bats Is Resistant to SARS-CoV-2 Vaccines. *PLoS Pathog* **2022**, *18* (9), No. e1010828.
(29) Moiseienko, M.; Vlaschenko, A. Quantitative Evaluation of Individual Food Intake by Insectivorous Vespertilionid Bats (Chiroptera, Vespertilionidae). *Biology Open* **2021**, *10* (6), bio058511.
(30) Anthony, E. L. P.; Kunz, T. H. Feeding Strategies of the Little Brown Bat, Myotis Lucifugus, in Southern New Hampshire. *Ecology* **1977**, *58* (4), 775−786.
(31) Park, K. J.; Cristinacce, A. Use of Sewage Treatment Works as Foraging Sites by Insectivorous Bats. *Animal Conservation* **2006**, *9*, 259−268.
(32) Park, K. J.; Müller, C. T.; Markman, S.; Swinscow-Hall, O.; Pascoe, D.; Buchanan, K. L. Detection of Endocrine Disrupting Chemicals in Aerial Invertebrates at Sewage Treatment Works. *Chemosphere* **2009**, *77* (11), 1459−1464.
(33) Secord, A. L.; Patnode, K. A.; Carter, C.; Redman, E.; Gefell, D. J.; Major, A. R.; Sparks, D. W. Contaminants of Emerging Concern in Bats from the Northeastern United States. *Arch. Environ. Contam. Toxicol.* **2015**, *69* (4), 411−421.
(34) Biswas, P.; Hasan, M. M.; Dey, D.; dos Santos Costa, A. C.; Polash, S. A.; Bibi, S.; Ferdous, N.; Kaium, Md. A.; Rahman, MD. H.; Jeet, F. K.; Papadakos, S.; Islam, K.; Uddin, Md. S. Candidate Antiviral Drugs for COVID-19 and Their Environmental Implications: A Comprehensive Analysis. *Environ. Sci. Pollut Res.* **2021**, *28* (42), 59570−59593.
(35) Järhult, J. D.; Muradrasoli, S.; Wahlgren, J.; Söderström, H.; Orozovic, G.; Gunnarsson, G.; Bröjer, C.; Latorre-Margalef, N.; Fick, J.; Grabic, R.; Lennerstrand, J.; Waldenström, J.; Lundkvist, Å.; Olsen, B. Environmental Levels of the Antiviral Oseltamivir Induce Development of Resistance Mutation H274Y in Influenza A/H1N1 Virus in Mallards. *PLoS One* **2011**, *6* (9), No. e24742.
(36) Gillman, A.; Muradrasoli, S.; Söderström, H.; Holmberg, F.; Latorre-Margalef, N.; Tolf, C.; Waldenström, J.; Gunnarsson, G.; Olsen, B.; Järhult, J. D. Oseltamivir-Resistant Influenza A (H1N1) Virus Strain with an H274Y Mutation in Neuraminidase Persists without Drug Pressure in Infected Mallards. *Appl. Environ. Microbiol.* **2015**, *81* (7), 2378−2383.
(37) Norberg, P.; Lindh, M.; Olofsson, S. Published Sequences Do Not Support Transfer of Oseltamivir Resistance Mutations from Avian to Human Influenza A Virus Strains. *BMC Infect Dis* **2015**, *15* (1), 162.

(38) Chandler, J. C.; Bevins, S. N.; Ellis, J. W.; Linder, T. J.; Tell, R. M.; Jenkins-Moore, M.; Root, J. J.; Lenoch, J. B.; Robbe-Austerman, S.; DeLiberto, T. J.; Gidlewski, T.; Kim Torchetti, M.; Shriner, S. A. SARS-CoV-2 Exposure in Wild White-Tailed Deer (*Odocoileus Virginianus*). *Proc. Natl. Acad. Sci. U.S.A.* **2021**, *118* (47), No. e2114828118.
(39) Oreshkova, N.; Molenaar, R. J.; Vreman, S.; Harders, F.; Oude Munnink, B. B.; Hakze-van der Honing, R. W.; Gerhards, N.; Tolsma, P.; Bouwstra, R.; Sikkema, R. S.; Tacken, M. G.; de Rooij, M. M.; Weesendorp, E.; Engelsma, M. Y.; Bruschke, C. J.; Smit, L. A.; Koopmans, M.; van der Poel, W. H.; Stegeman, A. SARS-CoV-2 Infection in Farmed Minks, the Netherlands, April and May 2020. *Eurosurveillance* **2020**, *25* (23), 2001005.
(40) Wei, C.; Shan, K.-J.; Wang, W.; Zhang, S.; Huan, Q.; Qian, W. Evidence for a Mouse Origin of the SARS-CoV-2 Omicron Variant. *Journal of Genetics and Genomics* **2021**, *48* (12), 1111−1121.
(41) Wilhelm, A.; Widera, M.; Grikscheit, K.; Toptan, T.; Schenk, B.; Pallas, C.; Metzler, M.; Kohmer, N.; Hoehl, S.; Helfritz, F. A.; Wolf, T.; Goetsch, U.; Ciesek, S. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. *medRxiv Preprint*, 2021. DOI: 10.1101/2021.12.07.21267432.
(42) Becker, D. J.; Albery, G. F.; Sjodin, A. R.; Poisot, T.; Bergner, L. M.; Chen, B.; Cohen, L. E.; Dallas, T. A.; Eskew, E. A.; Fagre, A. C.; Farrell, M. J.; Guth, S.; Han, B. A.; Simmons, N. B.; Stock, M.; Teeling, E. C.; Carlson, C. J. Optimising Predictive Models to Prioritise Viral Discovery in Zoonotic Reservoirs. *Lancet Microbe* **2022**, *3*, e625.
(43) Miller, T. H.; Bury, N. R.; Owen, S. F.; MacRae, J. I.; Barron, L. P. A Review of the Pharmaceutical Exposome in Aquatic Fauna. *Environ. Pollut.* **2018**, *239*, 129−146.
(44) Duarte, I. A.; Fick, J.; Cabral, H. N.; Fonseca, V. F. Bioconcentration of Neuroactive Pharmaceuticals in Fish: Relation to Lipophilicity, Experimental Design and Toxicity in the Aquatic Environment. *Science of The Total Environment* **2022**, *812*, No. 152543.
(45) Zhang, Z.; Zhou, Y.; Han, L.; Guo, X.; Wu, Z.; Fang, J.; Hou, B.; Cai, Y.; Jiang, J.; Yang, Z. Impacts of COVID-19 Pandemic on the Aquatic Environment Associated with Disinfection Byproducts and Pharmaceuticals. *Science of The Total Environment* **2022**, *811*, No. 151409.
(46) Drusano, G. L. Prevention of Resistance: A Goal for Dose Selection for Antimicrobial Agents. *Clinical Infectious Diseases* **2003**, *36*, S42−S50.
(47) Worobey, M.; Levy, J. I.; Malpica Serrano, L.; Crits-Christoph, A.; Pekar, J. E.; Goldstein, S. A.; Rasmussen, A. L.; Kraemer, M. U. G.; Newman, C.; Koopmans, M. P. G.; Suchard, M. A.; Wertheim, J. O.; Lemey, P.; Robertson, D. L.; Garry, R. F.; Holmes, E. C.; Rambaut, A.; Andersen, K. G. The Huanan Seafood Wholesale Market in Wuhan Was the Early Epicenter of the COVID-19 Pandemic. *Science* **2022**, *377* (6609), 951−959.
(48) Pekar, J. E.; Magee, A.; Parker, E.; Moshiri, N.; Izhikevich, K.; Havens, J. L.; Gangavarapu, K.; Malpica Serrano, L. M.; Crits-Christoph, A.; Matteson, N. L.; Zeller, M.; Levy, J. I.; Wang, J. C.; Hughes, S.; Lee, J.; Park, H.; Park, M.-S.; Ching Zi Yan, K.; Lin, R. T. P.; Mat Isa, M. N.; Noor, Y. M.; Vasylyeva, T. I.; Garry, R. F.; Holmes, E. C.; Rambaut, A.; Suchard, M. A.; Andersen, K. G.; Worobey, M.; Wertheim, J. O. The Molecular Epidemiology of Multiple Zoonotic Origins of SARS-CoV-2. *Science* **2022**, *377*, eabp8337.
(49) Aguilar-Rodriguez, P. A.; Mendez-Rodriguez, A.; Ospina-Garces, S. M.; MacSwiney G., M. C.; Yovel, Y. Free-Ranging Van Gelder's Bat *Bauerus Dubiaquercus* (Chiroptera: Vespertilionidae) Preying on Dung Beetles in Southern Mexico. *Mammalia* **2022**, *86* (3), 252−256.
(50) Fitzsimmons, P. N.; Fernandez, J. D.; Hoffman, A. D.; Butterworth, B. C.; Nichols, J. W. Branchial Elimination of Superhydrophobic Organic Compounds by Rainbow Trout (Oncorhynchus Mykiss). *Aquatic Toxicology* **2001**, *55* (1−2), 23−34.

https://doi.org/10.1021/acs.estlett.3c00201
Environ. Sci. Technol. Lett. 2023, 10, 439−445