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COVID-19, antibiotics and One Health: a UK environmental risk assessment

Sean D. W. Comber[1]*, Mathew Upton [2], Shaun Lewin[1], Neil Powell[3] and Thomas H. Hutchinson[1]

[1]*School of Geography, Earth and Environmental Sciences, University of Plymouth, Drake Circus, Plymouth PL4 8AA, UK;* [2]*School of Biomedical Sciences, University of Plymouth, Drake Circus, Plymouth PL4 8AA, UK;* [3]*Pharmacy Department, Royal Cornwall Hospital Trust, Truro TR1 3LJ, UK*

*Corresponding author. E-mail: sean.comber@plymouth.ac.uk

Sir,

There is growing interest in the role of secondary bacterial and fungal infections as a cause of increased morbidity and mortality in COVID-19 patients,[1] with reports of up to 95% of COVID-19 inpatients being prescribed antibiotics.[2] Concerns have been raised over the environmental implications of such a large-scale drug administration[3] and statements made about the potential impacts of COVID-19-related antibiotic prescription on antimicrobial resistance (AMR) and other toxicological effects on the environment.[4]

The UK National Strategy aims for a world in which AMR is effectively contained, controlled and mitigated by 2040.[5] Taking a 'One Health' approach to effective stewardship in settings such as those being experienced in the current pandemic will be key to minimizing the negative impacts of antibiotic use. A large proportion of some drugs (and metabolites) are excreted by patients into wastewater treatment works (WwTW), leading to release of drug residues into effluent-receiving rivers and coastal waters. Environmental concentrations and impacts will be greatest where drugs are used in high volumes, pass through WwTW largely undegraded and are discharged into rivers with limited dilution.

Since 2006, the EMA has required risk assessments of human medicines to allow standardized quantification of the environmental impact of pharmaceuticals. Consequently, the pharmaceutical industry has developed a database to provide Predicted No Effect Concentrations as Minimum Inhibitory Concentrations (PNEC-MIC) for active ingredients that may select for AMR, or levels hazardous to fish and other environmental species (PNEC-ENV).[6] Combined with Predicted Environmental Concentrations (PEC), generated using monitoring and modelling data, a risk assessment may be carried out. Should the PEC of individual drugs exceed either the PNEC-MIC or PNEC-ENV, further investigations are required.

To examine the potential impact of antibiotic prescribing in COVID-19 patients in the UK, we have undertaken a risk assessment based on established principles.[7] Patient numbers were obtained for UK emergency hospitals set up temporarily around the country to receive COVID-19 patients, with one chosen for illustrative purposes, and details of WwTW capacity and river water dilution serving the emergency hospital and associated town were available from previous research.[8] Antibiotic excretion rates were obtained from the open literature. These data allowed estimation of antibiotic loads entering the WwTW, over and above the expected baseline (non-COVID-19) use for UK patients.[9] A freely available and validated wastewater process model (SimpleTreat 4.0) was used to predict removal rates, which allowed predictions of effluent concentrations for antibiotics of interest being discharged to surface waters. Based on known dilution estimates, a PEC:PNEC ratio was derived to provide a risk ratio.

We illustrate here data relevant to a single UK emergency hospital (Harrogate, with 500 beds; see Figure S1, available as Supplementary data at *JAC* Online) in different COVID-19 scenarios, providing environmental assessments relevant to designing optimal drug use and waste management systems in a One Health context. NICE COVID-19 guidance was followed, which suggests that the first-line antibiotic should be doxycycline, with amoxicillin as second line. NICE guidelines for secondary care suggest doxycycline or a combination of clarithromycin and co-amoxiclav. Clavulanic acid does not have a PNEC value, so data presented here are for the impact of amoxicillin alone. Use of antibiotics in COVID-19 patients in hospitals will lead to the release of drug residues into UK rivers or coastal waters from any WwTW (Figure S1). Under pandemic scenarios, the use of antibiotics will obviously increase dramatically, thus increasing the overall burden on WwTW and potentially the receiving waters. Data available for the UK make it possible to carry out a risk assessment for site-specific areas.[10] To examine more focused regional impacts, we have calculated PEC data for the UK emergency hospital at Harrogate (Figure 1) based on modelling tools developed through the UK water industry-sponsored Chemical Investigation Programme and briefly described above.[7] We predict PEC:PNEC risk ratios of <1.0 for doxycycline and up to 5.70 for amoxicillin under two COVID-19 scenarios (all beds occupied and 70% or 95% of patients prescribed antibiotics, with all patients receiving either doxycycline or amoxicillin). The data for amoxicillin indicate a potential environmental concern for selection of AMR, but not toxicity to fish and other environmental organisms.

We have not modelled scenarios for hospitals where different proportions of patients receive one or other antibiotic, though in future this may inform best practice for minimizing selection for AMR or causing toxic environmental effects.

North of England Emergency Hospital case study	Amoxicillin	Doxycycline
Baseline river PEC (μg/L)	0.03	0.003
95% treated: river PEC (μg/L)	0.4	0.02
PNEC-ENV (μg/L)	0.6	25.1
PNEC-MIC (μg/L)	0.3	2.0
Risk ratio assessment (PEC/PNEC-MIC)		
Baseline PEC/PNEC-MIC	0.1	0.001
95% of hospital patients on antibiotics	**1.7**	0.010
Risk ratio assessment (PEC/PNEC-ENV)		
Baseline (pre-COVID-19 epidemic)	0.06	0.0001
95% of hospital patients on antibiotics	0.7	0.001

Figure 1. Environmental risk assessments for amoxicillin and doxycycline for a worst-case COVID-19 scenario for patients in an emergency hospital in Harrogate with risk ratios >1 highlighted in red. PNEC-MIC, Predicted No Effect Concentration, Minimum Inhibitory Concentration; PNEC-ENV, Predicted No Effect Concentration, Environmental; PEC, Predicted Environmental Concentration. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

We recommend more extensive environmental assessments be undertaken for all antimicrobial medicines used during pandemics. This will facilitate development of a robust evidence base in order to guide antibiotic prescribing choices that are less likely to increase AMR[11] and have the least environmental impact, thus supporting the UK National Strategy.[5] Such information could also inform future decisions on the location of emergency hospitals and wider drug and waste management to ensure optimal patient and environmental outcomes during pandemics.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

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