A RECIPE FOR SUPERBUGS: SURFACE WATER SCREENING IN BANGLADESH REVEALS PREVIOUSLY-UNDETECTED ANTIBIOTICS, ANTIFUNGAL COMPOUNDS, AND METABOLITES

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I. MULTIDRUG-RESISTANT ORGANISMS ARISE FROM HEALTH INEQUITIES AND THREATEN PUBLIC HEALTH EVERYWHERE

For those with access to a good health care system, treatment of a bacterial or fungal infection is generally an uncomplicated inconvenience: following diagnosis, one takes a prescription antibiotic or antifungal medication and after the course of treatment, the infection subsides. However, through clinical and agricultural overuse, lack of adherence to treatment protocols, poor sanitation practices, and other factors, bacterial and fungal pathogens develop resistance to our arsenal of prescription medications. This phenomenon—antimicrobial resistance (AMR), which gives rise to multidrug-resistant "superbugs"—is predicted to be a leading cause of death by 2050 because pathogens develop resistance to drugs faster than new pharmaceutical medications can be developed.

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This policy brief highlights recent findings on environmental AMR from an interdisciplinary team of researchers from the University at Buffalo's Community for Global Health Equity (CGHE) and the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), and provides suggestions for controlling the development and spread of multi-drug resistant pathogens in the environment.

Bangladesh continues to make progress in increasing access to safe water and improved sanitation due to the ongoing efforts of public health experts and scientists like those at icddr,b. However, the physical geography, infrastructure issues, and institutional and public health challenges of Bangladesh all contribute to a serious environmental AMR problem. As is the case in many low- and middle-income countries (LMICs), the sale of antimicrobials and antifungal medications in Bangladesh is not regulated, so these medications can be acquired without prescriptions and health worker oversight. Agricultural run-off and the release of hospital and municipal wastewater treatment plant effluents into Bangladesh's web-like network of surface waters result in the broad circulation and aquatic intermingling of bacterial and fungal pathogens with antimicrobial and antifungal medications. The waterborne "superbugs" that result from this intermingling can infect people and livestock whose waste products, in turn, can harbor drug-resistant pathogens that add to the contamination of surface waters.

To determine the occurrence of antimicrobials in water, the CGHE/icddr,b team uses state-of-the art liquid chromatography with a high resolution mass spectrometry (LC-MS) instrument to identify and quantify these contaminants in environmental samples. By contrast, previous efforts to identify aquatic antimicrobials in Bangladesh have used the "target analysis" approach, in which the researcher essentially asks: "Are contaminants X, Y, and Z in the samples?" To answer this question, the water samples are processed to detect the "targeted" chemical contaminants, which are then compared to known amounts of "reference standards" to determine the accurate concentrations of the contaminants.

For example, as ciprofloxacin is the most frequently-prescribed antimicrobial in Bangladesh, it is obviously important that researchers track how much ciprofloxacin is ending up in the environment by including a ciprofloxacin standard in the target analysis of water samples. At the same time, microbial isolates are collected and tested for their resistance towards the antimicrobials commonly used in the area. It is not surprising that out of a total of 46 microbial isolates identified by the CGHE/icddr,b team, 3 were resistant to ciprofloxacin.

While target analysis is of enormous benefit to environmental health research, it inherently yields an incomplete picture, as it may miss the detection of significant contaminants that are not in the targeted list. Therefore, in addition to conducting target analysis, the CGHE/icddr,b team sought to augment previous research by conducting "non-target" analysis of surface water samples. Rather than the closed question posed by target analysis, LC-MS non-target analysis asks an open-ended question: "What contaminants are present in the samples?"

Using non-target analysis of surface water samples collected in Bangladesh, the team identified a total of seven antimicrobials that had not previously been included in target analysis: clindamycin, lincomycin, linezolid, metronidazole, moxifloxacin, nalidixic acid, and sulfapyridine. Further, two antifungal agents with clinical applications (fluconazole and climbazole) were detected, as well as one antifungal agent used in agriculture (carbendazim). The presence of these antibiotics and antifungals in surface waters is of concern because of the potential for pathogens to develop resistance to these drugs. Thus, the identification of these chemicals signals the need for: (a) their inclusion in future target analysis of surface waters samples collected in Bangladesh, and (b) efforts to regulate and encourage more careful drug stewardship of these chemicals by practitioners and stakeholders.

II. PRACTICAL TAKEAWAYS

1. Effluents from hospitals and farms with livestock can contain antimicrobials, antifungals, and other drugs and compounds that can cause serious harm to human health. These compounds found in the environment contribute to the development of multi-drug resistant microorganisms, or "superbugs."

2. Drug-resistant pathogens do not recognize geopolitical borders. Therefore, evidence of antimicrobials and antifungals in Bangladesh surface waters is of international significance.

3. Several factors make LMICs vulnerable to emergence and spread of AMR: insufficient regulation of antimicrobial drug use; high volume of antimicrobials used in human medicine and agricultural production; and inadequate hygiene and wastewater management systems.

4. The CGHE/icddr,b team identified microbial strains that were resistant to ciprofloxacin, the most frequently-prescribed antibiotic in Bangladesh. Health care professionals in Bangladesh, including pharmacists and technicians, should be advised to use ciprofloxacin sparingly.

III. POLICY TAKEAWAYS

1. Further research to study and characterize environmental AMR is critical to controlling this serious threat to global public health. Non-target analysis is more costly than target analysis, but it provides a better, more complete picture of the occurrence of antimicrobials in the environment.

2. Funding to support AMR monitoring of surface waters in Bangladesh and other LMICs is warranted.

3. The antimicrobials, metabolites, and antifungal agents that the CGHE/icddr,b team identified should be added to the target analysis list for future testing of surface waters in affected regions.

4. International investment in industrial and municipal wastewater treatment plants in Bangladesh and other LMICs is crucial to contain the emergence and global spread of multi-drug resistant organisms.

5. To protect local as well as international public health, tighter control mechanisms must be implemented in countries where antimicrobials and antifungal compounds can be purchased without a prescription.

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ORIGINAL RESEARCH

Angeles, Luisa F, Shamim Islam, Jared Aldstadt, Kazi Nazmus Saqeeb, Munirul Alam, Md Alfazal Khan, Fatema-Tuz Johura, Syed Imran Ahmed, and Diana Aga. (2020). Retrospective suspect screening reveals previously ignored antibiotics, antifungal compounds, and metabolites in Bangladeshi surface waters. Science of the Total Environment, 712(2020)136285. doi:10.1016/j.scitotenv.2019.136285

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