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Making waves: How does the emergence of antimicrobial resistance affect policymaking?

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Abstract

This article considers current trends in antimicrobial resistance (AMR) research and knowledge gaps relevant to policymaking in the water sector. Specifically, biological indicators of AMR (antibiotic-resistant bacteria and their resistance genes) and detection methods that have been used so far are identified and discussed, as well as the problems with and solutions to the collection of AMR data, sewage surveillance lessons from the COVID-19 pandemic, and the financial burden caused by AMR, which could be synergically used to improve advocacy on AMR issues in the water sector. Finally, this article proposes solutions to overcoming existing hurdles and shortening the time it will take to have an impact on policymaking and regulation in the sector.

Keywords

AMR surveillance, microbial indicators, precautionary approach, regulation, water sector

1. Introduction

Antimicrobials and, specifically, antibiotics have become one of the main pillars of modern medicine, saving millions of lives since they were first introduced in the 1940s. Antibiotics are essential in treating bacterial infections in both humans and animals, but the emergence of antimicrobial resistance (AMR) has limited their effectiveness (Nathan, 2020). As a result, governments, industry, and scientists are adamant the AMR crisis is one of the most pressing global threats. Several initiatives are in place to deal with this, mainly in clinical and environmental settings. In clinical settings, the focus has been on surveillance, reducing the use of existing drugs, establishing incentives for the discovery and production of new antibiotics, implementing global guidelines, and, when possible, local regulations. In environmental settings, the focus has predominantly been on research initiatives to monitor the presence and impact of antibiotics, decreasing antimicrobial therapy in agriculture and livestock, determining minimal acceptable thresholds for antibiotics in treated effluents, and exploring the potential role of wastewater treatment to reduce antibiotics and AMR determinants in treated water (Hong et al., 2018; Stanton et al., 2020; Murray et al., 2021). However, the ability to monitor how AMR spreads from the environment to clinical settings is limited (Hofer, 2019) due to the lack of a single or set of universal biological indicators that can establish the rate of AMR spread in environmental settings and their potential risk to human health. The only short-term solution repeatedly recommended is the precautionary approach (Manaia, 2017).

In this article the precautionary principle has been expanded with the following objectives: (i) exploring how AMR surveillance has been implemented and data has been generated in both clinical and water/environmental settings; (ii) discussing how biological indicators related to AMR have been used in pilot surveillance efforts and how data has been generated and shared; (iii) reflecting on sewage surveillance lessons from the

COVID-19 pandemic and how this could help better manage AMR in water; and (iv) commenting on the financial burden of AMR and how this could be used to drive change in policymaking. The aim of this article is therefore to highlight current knowledge gaps, anticipate future trends, and suggest actionable insights to advance AMR regulation in the water sector.

2. AMR in the water sector

Antimicrobial resistance is complex to define and quantify. Broadly speaking, AMR is an intrinsic or acquired ability of microorganisms to resist an antimicrobial. In the latter case, they can acquire resistance to antimicrobials by either genetic mutation or by accepting AMR genes from other bacteria. In fact, AMR genes are considered as environmental pollutants if anthropogenic disturbances increase their prevalence above the usually occurring background levels (Martinez, 2009). Moreover, bacteria associated with hospital acquired infections and their ability to resist antibiotic treatment are under the spotlight in the AMR crisis (Chandler, 2019). AMR extends not only to antibiotics but to a number of chemical classes, including heavy metals and disinfectants/biocides (Singer et al., 2016).

The accepted framework for dealing with AMR is the “One Health” approach. Fundamental to this is interdisciplinary collaboration and communication on health in the human, animal, and environmental sectors. Areas of action include monitoring targets known to decrease infectious risk, such as improving sanitation, providing access to clean water, improving medical care, tackling environmental pollution, and managing the overuse of antimicrobials in both human healthcare and animal husbandry (Essack, 2018; Jovanovic et al., 2021).

As water bodies frequently receive treated and untreated wastewater effluents and anthropogenic pollution, water is an ideal environment for the acquisition and spread of AMR. In fact, this impact can be exacerbated in developing countries where the presence of wastewater treatment is limited or even absent (Pandit and Kumar, 2015; Pandey et al., 2021). Consequently, the “One Water” approach has been suggested to complement the One Health framework in order to monitor and manage AMR in the water sector. The One Water approach proposes that drinking and wastewater are interconnected and need to be managed holistically. Both the One Health and the One Water frameworks guide us to holistically manage wicked problems – such as global water supply, climate change, and the AMR crisis – while considering the environment, and human and animal health (Shafer and Fox, 2016; Hong et al., 2018). Moreover, considering that the United Nations Sustainable Development Goals (SDGs) will be the point of reference for any strategy or policy towards a more sustainable future, those goals relating to water and sanitation should be taken into account in formulating effective policies. The SDGs include eight targets that address drinking water, sanitation and hygiene services, wastewater treatment, water quality, water use, water management, transboundary cooperation, water-related ecosystems, official development assistance and participation of local communities (WHO-UNICEF, 2021).

3. Surveillance as a tool for AMR containment

AMR cannot be eradicated either in clinical or environmental settings. The containment of AMR, however, is possible (Jovanovic et al., 2021), and to achieve this the World Health Organization (WHO) has highlighted that surveillance of AMR is essential. Data acquired through surveillance can be used to monitor the development and spread of AMR, and also to measure the impact of strategies and interventions to mitigate it (Smith and Coast, 2002). Although the consensus that resistance development, rather than just transmission, exists in environmental settings and is vital to AMR containment, this precautionary topic has been extremely difficult to advocate and gain the attention of policymakers (Wellcome Trust, 2020). In order to address this, several AMR databases and data collection initiatives have been revisited to better connect the resulting data, thereby generating new insights and influencing policymaking.

4. Databases generated on AMR surveillance

The major surveillance programs targeting AMR at global scale have placed emphasis on monitoring of clinically relevant pathogens (such initiatives are listed below). Surveillance of AMR emergence and spread in water/environmental settings has been more consistently done in research at local level (Rodriguez-Mozaz et al., 2015; Majeed et al., 2021), regional/continental monitoring campaigns (Cacace et al., 2019; Pärnänen et al., 2019) or selected countries at global scale (Hendriksen et al., 2019), targeting particular antimicrobial resistance ‘hotspots’, such as wastewater treatment plants (Lekunberri et al., 2017), contaminated watersheds (Koczura et al., 2016), soil/agricultural land (Singer et al., 2016), and seawater ecosystems (Blanco-Picazo et al., 2020). Moreover, there is insufficient or no information from other countries or regions, especially from low-income and middle-income countries where the AMR surveillance in water is limited.

The global open-access triple antimicrobial resistance database led by the WHO, the Food and Agriculture Administration (FAO) and the World Organisation for Animal Health (OIE) provides access to information on the status of countries’ implementation of the global action plan and actions to address antimicrobial resistance across all sectors. Data collection here is based on a country self-assessment questionnaire, the *Global Database* *for the Tripartite Antimicrobial Resistance AMR Country Self-assessment Survey* (TrACSS) (https://amrcountryprogress.org/). A second database of interest is the Global Antimicrobial Resistance Surveillance System (GLASS) (https://www.who.int/glass/en/), which focuses on eight target pathogens detected in four human specimen types (blood, urine, stool, and genital swabs) (https://www.who.int/glass/en/). A third initiative, led by the US based Centre for Disease Dynamics, Economics & Policy (CDDEP), put together a resistance map using data collected from North America, more than 30 European countries, and several low and medium-income countries (https://resistancemap.cddep.org/). This database monitors resistance of principal pathogens versus various classes of antibiotics. Others include the US Centers for Disease Control (CDC), which has its own database (https://arpsp.cdc.gov/profile/geography) that maps various statistics on pathogens per US state; and the European Centre for Disease Prevention and Control (ECDC), which has a "surveillance atlas" on a country-by-country basis (https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc). The most recent input date in the atlas is 2019. The ECDC is also focused on producing surveillance reports for the continent. The Sweden based Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) – an international collaborative platform engaging 28 nations and the European Commission to curb antimicrobial resistance (AMR) – has various funding and project consortium initiatives to fund AMR research globally and has gathered a collection of multipurpose databases (https://www.jpiamr.eu/).

The recently formed Global AMR R&D Hub is a knowledge center focused on monitoring R&D and investment initiatives to address challenges and improve coordination and collaboration in global AMR research development using the One

Health approach. It is a partnership of countries, non-governmental, and intergovernmental organizations (https://globalamrhub.org/). Other organizations include PAR, The Foundation to Prevent Antibiotic Resistance (https://parfoundation.org/); the industry consultancy-led AMR Insights (https://www.amr-insights.eu/); and the STAR-IDAZ International Consortium on Animal Health (https://www.star-idaz.net/).

These various initiatives are encouraging; however, in order to fully extract and utilize the value and meaning of their data, these databases need to be harmonized so that trends can be truly observed, actions be taken, and overarching environmental AMR regulations implemented (Aarestrup and Koopmans, 2016; WHO, 2015). Recently, it has been suggested that data technologies, such as blockchain, IoT (Internet of Things) and others, may help to achieve better management and use of AMR data globally (https://www.amr-insights.eu/). For that to occur, however, legal barriers impeding data sharing between countries and organizations will need to be tackled at governmental levels.

5. How far advanced are biological indicators for AMR in water?

For implementing impactful surveillance of AMR in environmental settings, a standard methodology should be selected, as well as a set of relevant biological indicators, to be able to establish an economically feasible and long-term sustainable monitoring regime. Although standard culture-based methods used to evaluate microbial safety of drinking water and wastewater have provided valuable information (Marano et al., 2020), these methods have limited applicability in AMR surveillance and are biased towards cultivable organisms. AMR is mostly related to microorganisms harboring antibiotic resistance genes (ARGs), for which the detection depends almost exclusively on molecular methods (Gao and Sui, 2020).

Cutting-edge genomics (e.g., microarray technology) and metagenomics have been proposed as a possible next step to achieve global monitoring of AMR in water/environmental settings (Duarte et al., 2020; Hendriksen et al., 2019; Hong et al., 2018). They have been successfully used in sewage surveillance and have proven to be flexible, scalable, relatively easy to implement and standardize – features that could potentially benefit also their application in low and medium-income countries (MacLean and San Millan, 2019). However, these methods are not exempt from disadvantages and limitations, such as how the complexity in sequence assembly and/or functional genes of one microorganism cannot be fully linked to its phylogeny (Forbes et al., 2017; Cheng et al., 2019). The joint use of standard culture-based methods and cutting-edge genomics can therefore overcome these limitations. Trends observed using these methods need to be correlated with observations in clinical settings so that insightful correlations can be established between the emergence of antibiotic-resistant pathogens and ARGs encountered in the environment.

Such evidence is essential to persuade both the public and policymakers of the urgent need to act on AMR (Jovanovic et al., 2021). Specific examples that establish how the spread of ARGs occurred from water/environmental sources to impact on clinical settings are starting to emerge. These include the mobility of $bla_{\text{CTX-M}}$ (gene encoding resistance for β-lactamases responsible for inactivating third generation cephalosporins) (Cantón, 2009; Jovanovic et al., 2021), *mcr*-1 (resistance to colistin or polymyxins), $bla_{\text{NDM-1}}$ (resistance to a large range of *β*-lactamases, including carbapenems) (Jovanovic et al., 2021). The risk of the spread of ARGs from antibiotic-resistant bacteria to final consumers has recently been established in animal farming settings (Van Gompel et al., 2020).

Recommended approaches to determine biological indicators for AMR surveillance in water include monitoring resistance in: (i) microorganisms watched by official lists (WHO, UNESP, USCDC, ECDC, etc.) (Jovanovic et al., 2021); (ii) faecal and other benchmark microbial indicators (such as bacteriophages) routinely monitored in drinking and wastewater facilities (Larsson et al., 2018); (iii) clinical relevant antibiotic-resistant bacteria; and (iv) the general presence of ARGs in the target water setting, also known as evaluation of the environmental 'resistome'.

While the correlations between the presence of these AMR 'precautionary microbial indicators' and the risk they may pose of migrating from water to a clinical setting are established, the precautionary approach can further inform improving water safety. In established high risk environments for AMR spread, such as effluents of hospital and antibiotic production facilities, wastewater treatment facilities need to be upgraded to reduce pollution and to more effectively remove not only antibiotics and antimicrobials but also AMR indicators such as resistant bacteria and ARGs (Hong et al., 2018). These changes, however, are only likely to occur with enforcement of stronger water regulations. Compliance here will depend upon the development and availability of fit-for-purpose and economically viable water treatment technologies (de Almeida Kumlien et al., 2021). An important case-study to help advance AMR regulations in water can be drawn from the latest pandemic, our views on which are discussed below.

6. Lessons from the COVID-19 pandemic

The COVID-19 pandemic has quickly advanced our knowledge and practice of sewage surveillance and epidemiology of SARS-CoV-2 studies in water, which has extensively benefited from wastewater-based epidemiology. This latter is a relatively new approach that has the potential to provide comprehensive health information using communityderived wastewater (Sims and Kasprzyk-Hordern, 2020). In fact, the European Commission has recently proposed recommendations for a common approach to establish a systematic surveillance of SARS-CoV-2 and its variants in wastewaters in the EU (European Commission, 2021), which would undoubtedly help to identify health-related relevant parameters to be regularly monitored in wastewaters. These initiatives represent an opportunity to implement their recommendations and advance AMR surveillance (Wilson et al., 2020).

Even though a conclusive quantitative microbial risk assessment (QMRA) to influence policymaking on AMR in water is needed given the threat AMR poses to public health, the case for using the precautionary approach should be considered, particularly when data is still not conclusive. Risks that cannot be calculated can be predicted, or at least estimated, by deploying data analytics, scientific leadership, and knowledge and, within local financial and technical limits, be corroborated on a pilot scale through multinational projects. This, however, needs to happen through parallel taskforces that also focus on driving changes in current water legislation.

Established networks and projects rapidly pivoted during the years 2020 and 2021, such as the Dutch led ‘Sewers for COVID’ (https://devpost.com/software/sewers4covid) and the Spanish ‘SARSAIGUA’ (https://sarsaigua.icra.cat/), and can be aligned with existing AMR surveillance initiatives to speed up AMR surveillance and containment in the environment (Singer et al., 2016). Using the precautionary approach, existing strategies to determine AMR precautionary indicators, even though not definitive, could be used to pilot more significant AMR surveillance schemes in water. One concrete way to drive that change is to add such indicators to watchlists and, with more aggressive advocacy by the right actors, to water regulations. Here, the ideal target monitoring sites would be

hospital and antibiotic facilities wastewaters, potentially regulated through changes in overarching and enforcing law, such as the Water Framework Directive in Europe.
The question that should be asked at this point is: how can actionable insights be created to influence policymaking with the data available now? For a vital issue such as AMR, advocacy on the theme is both relevant and recommended. The important action is to determine who are the actors at community, research, policymaking, and water utility levels that need to be involved, both in arguing for the AMR cause and in driving change. A way to bring these actor together is through smart specialization clusters, a collaboration strategy mediated by governmental funding schemes, well known to speed up innovation in the water sector (de Almeida Kumlien et al., 2019, 2018). Figure 1 illustrates a systematic process to develop policies that can address public health problems such as AMR.

7. Driving change in policymaking of AMR in water

Similarly to the dispersion of data collected in various AMR surveillance efforts, the current and future costs of the AMR crisis to countries are still only estimates. Apart from realizing robust QMRA data, a fundamental factor to drive change in AMR policymaking in water is by clearly demonstrating the financial losses caused by this crisis (Roope et al., 2019). Although data here is still approximate, estimates show a difficult scenario on the horizon for global economies. Recent estimates put the AMR cost globally at US$100 trillion through loss of productivity. In the USA, (data from 2019) more than 2.8 million multidrug-resistant bacterial infections occur annually, with an estimated 35,000 deaths and a US$20 billion health-care burden (Strathdee et al., 2020). In Europe, the annual economic cost associated with the treatment of antibiotic-resistant infections has been estimated to be around €1500 million. This figure includes the economic impact associated with the number of days of lost productivity, estimated to be approximately €450 million each year (Roca et al., 2015). AMR affects national budgets, mortality, and related disability-adjusted life-years (DALYs). In the EU and European Economic Area (EEA) its impact has been comparable to the combined effects of tuberculosis, influenza, and HIV (Cassini et al., 2019).

Progress has been made in establishing methodologies to determine AMR costs. A comprehensive framework for categorization of AMR costs, which evaluates human, animal, and environmental factors, and its effects up through societal levels is "The Global Antimicrobial Resistance Platform for ONE-Burden Estimates (GAP-ON€)". This initiative, funded under the JPIAMR, considers local direct and indirect epidemiological costs and data, and is adaptable for a broad range of etiological pathogens and geographic locations (Morel et al., 2020).

Recommendations by the WHO, or, in the absence of a central government that regulates AMR stewardship, by other organizations which act locally, have shown slow progress. Currently, only 5% of countries have a multisectoral AMR action plan that has been implemented with identified funding sources and monitoring processes in place (O'Neill, 2016). Compliance, even when it is attained in some countries, might not be possible to achieve due to lack of financial and human resources (Chandler, 2019; Roope et al., 2019). The cost of implementing AMR governance is considerable, and most likely unaffordable for developing nations. The cost of remediating the AMR crisis, however, will be much higher.

The WHO has recently highlighted the need to develop new AMR regulations with global reach (Hoffman et al., 2015). This could be achieved by revising the International Health Regulations (IHR), developing a new treaty on pandemics, or a separate agreement on

AMR. Regardless of the path of action chosen, we need to seize chances to achieve new regulations for AMR now.

Given this, scientific leadership is essential to advise policymakers on which are the best control points and methodologies for implementing regulation of AMR in the water sector. Among them, the following should be taken into consideration: (i) precautionary indicators to achieve more effective surveillance of AMR in water/environmental settings; (ii) harmonization and better accessibility of methodologies to detect AMR and data generated; (iii) reflecting on lessons learnt from the pandemics, especially regarding sewage surveillance schemes; and (iv) making the case on the financial impact of the AMR crisis.

These points need to be advocated, aligned, and incorporated in a centralized enforcing AMR regulation, pivoted by the right leadership (being at WHO or UN level), and only achievable with stronger collaboration between AMR stakeholders, at community/country, research, industry, water utility and policymaking levels.

8. Conclusions

- Polluted aquatic environments (e.g., wastewaters) present a potentially high risk of the spread of AMR affecting public health and thus should be carefully monitored.
- Scientific leadership needs to work with policymakers to advocate for immediate water regulation based on precautionary microbial indicators and methodologies to detect and evaluate the potential impact of AMR on human health.
- Harmonization of detection methodologies and indicators through the combined participation of research institutions worldwide is crucial to reach these goals.

- The generation of new data, improvements in existing data communication, accessibility, and harmonization between global AMR databases will help generate insights into the impact of AMR from the water environment on human health.
- Lessons on sewage surveillance learnt from the COVID-19 pandemic and the estimated financial impact of the AMR crisis can help drive better advocacy for new regulations in water.

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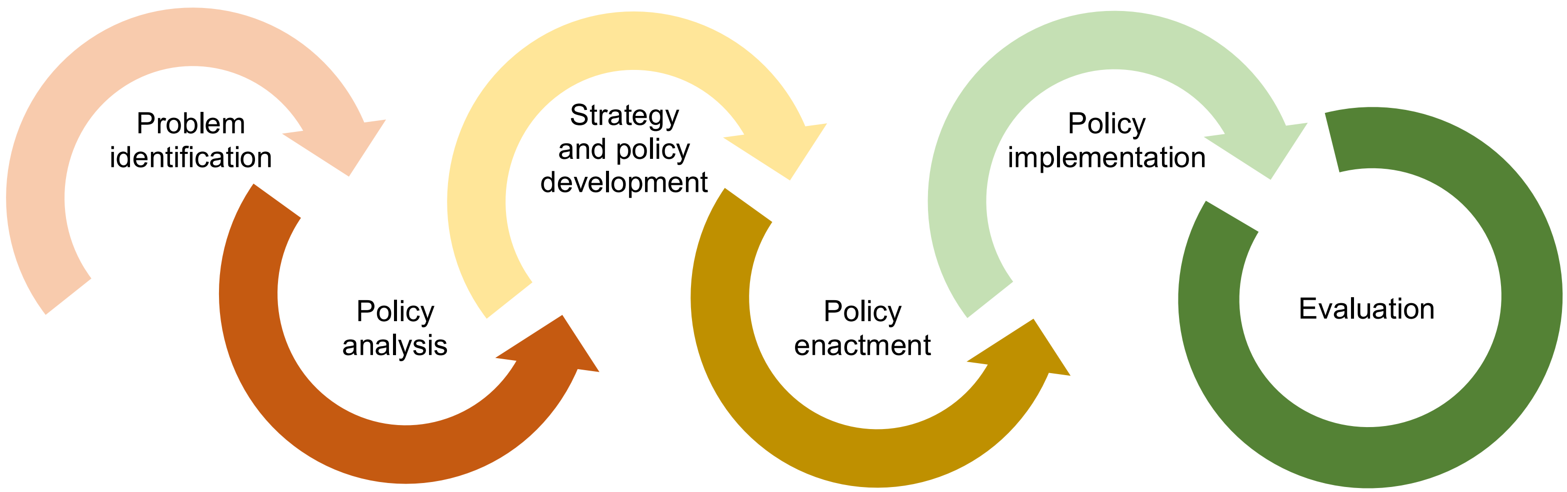

Figure 1. A proposed framework to identify the different actions and steps in the policy process. This figure has been adapted from the CDC's Policy Analytical Framework (https://www.cdc.gov/).