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Review

One Health and Global Health View of Antimicrobial Susceptibility through the "Eye" of *Aeromonas*: Systematic Review and Meta-Analysis

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ABSTRACT

Antimicrobial resistance (AMR) is one of the most pressing public health concerns; therefore, it is imperative to advance our understanding of the factors influencing AMR from Global and One Health perspectives. To address this, *Aeromonas* populations were identified using 16S rRNA gene libraries among human, agriculture, aquaculture, drinking water, surface water, and wastewater samples, supporting its use as indicator bacteria to study AMR. A systematic review and meta-analysis was then performed from Global and One Health perspectives, including data from 221 articles describing 15 891 isolates from 57 countries. The interconnectedness of different environments was evident as minimal differences were identified between sectors among 21 different antimicrobials. However, resistance to critically important antibiotics (aztreonam and cefepime) was significantly higher among wastewater populations compared with clinical isolates. Additionally, isolates from untreated wastewater typically exhibited increased AMR compared with those from treated wastewater. Furthermore, aquaculture was associated with increased AMR to ciprofloxacin and tetracycline compared with wild-caught seafood. Using the World Health Organization AWaRe classifications, countries with lower consumption of "Access" compared to "Watch" drugs from 2000 to 2015 demonstrated higher AMR levels. The current analysis revealed negative correlations between AMR and anthropogenic factors, such as environmental performance indices and socioeconomic standing. Environmental health and sanitation were two of the environmental factors most strongly correlated with AMR. The current analysis highlights the negative impacts of "Watch" drug overconsumption, anthropogenic activity, absence of wastewater infrastructure, and aquaculture on AMR, thus stressing the need for proper infrastructure and global regulations to combat this growing problem.

1. Introduction

Antimicrobials have undoubtedly revolutionized modern medicine. However, their imprudent application has propelled the rapid evolution of a natural phenomenon, antimicrobial resistance (AMR), amongst human and animal pathogens [1]. To meet the demands of an ever-increasing global human population, antimicrobial use remains on the rise. Between 2000 and 2015, worldwide antimicrobial consumption increased by 65% to 34.8 billion defined daily doses (DDD) [2]. Up to 90% of an antimicrobial dose may be excreted, unchanged, through feces and urine [3], where it can then interact with non-target microorganisms. With 1.7 billion people lacking basic sanitation, and over 10% of the world irrigating crops with wastewater [4], AMR transmission can occur between interconnecting ecosystems in many natural systems [5,6]. Additionally, multidrug-resistant strains in human and animal feces [7,8] are released into the environment and are another significant public health risk.

Increased international travel has 'decreased the distance' between humans and, accordingly, the microbes associated with them [9]. Emerging forms of AMR, including those from diverse aquatic and terrestrial habitats, foodstuffs, and water resources from vastly disparate nations, territories, and socioeconomic strata, are rapidly spreading around the world [10]. The myriad of settings

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in which new AMR variants arise necessitates a greater understanding of natural, agricultural, and human-impacted systems. Thus, multifaceted approaches must be taken by researchers and leaders alike to address this issue. In response, holistic approaches, such as One Health and Global Health, are now regularly employed to understand AMR [11].

Multidisciplinary and multisectoral concepts enable collaboration to develop comprehensive mitigation strategies for complex national and global health threats [12]. One strategy implemented by the World Health Organization (WHO) has been to classify the WHO Essential Medicines List of therapeutic antibiotics against 26 common clinical infections of children into three “AWaRe” categories (A: Access; Wa: Watch; Re: Reserve), based on their potential to induce and disseminate AMR. The goal is to prescribe more narrow-spectrum Access drugs as first and second choice against common pathogens, instead of higher resistance potential Watch and last-resort Reserve drugs. It is suggested that the latter drugs be closely monitored and used only for a limited number of severe infections [13]. The ratio of Access drugs to Watch drugs, known as the A:Wa index, can be used in national action plans for antimicrobial stewardship [14]. Application of these concepts to widespread AMR requires an equally omnipresent but tractable indicator species. A species found ubiquitously in multiple interconnected ecosystems is ideal to enable further understanding of antibiotic resistance genes (ARGs) transmission dynamics. *Escherichia coli* is a common indicator species used to monitor AMR, but the use of multiple indicators would strengthen the understanding of AMR dynamics and movement among environments. The genus *Aeromonas* has emerged as a potential candidate [15] because it lives in both natural and host-associated environments. The genus *Aeromonas* consists of oxidase-positive, Gram-negative, facultative anaerobic bacilli that commonly live in freshwater, wastewater, estuarine, and marine ecosystems; some members infect a broad range of host taxa from cold- to warm-blooded animals, including humans [16].

Aeromonas are common pathogens to both farm-raised and wild fish, and cause diseases such as furunculosis and septicemia [17]. These infections vary from acute to chronic, and can spread rapidly, depleting fish populations [18,19]. While the environmental impact alone is substantial, human reliance on wild and aquaculture seafood reserves means that *Aeromonas* spp. pose serious risks to global economies and food stocks [18]. The aquatic nature of *Aeromonas* spp. also provides potential for human contact and infection. *Aeromonas*-related disorders in humans include gastroenteritis, septicemia, necrotizing fasciitis, and myonecrosis, and are significant challenges for healthcare systems [18], particularly in the context of resistance to treatments.

Aeromonas spp. are common in wastewater [20,21], and within biofilms lining sewer pipes [22], and are often exposed to antimicrobials and other stressors, potentially increasing horizontal gene transfer (HGT) of ARGs [23]. The presence of AMR in *Aeromonas* residing in environmental, clinical and agricultural ecosystems, and the involvement of *Aeromonas* with intra- and inter-species HGT, position it as an indicator species that could expand the understanding of AMR dynamics [24]. Although interconnected ecosystems are pivotal in the global transmission of AMR [11], there is a lack of holistic studies of bacteria in these ecosystems that also consider economic, infrastructural, and ecopolitical factors and antimicrobial consumption at national level.

With its ubiquity in the aquatic and anthropogenic-impacted environments, ease of culture in the lab, resistance to critical antimicrobials, intra- and inter-species horizontal genetic exchange, and pathogenicity throughout the animal kingdom, *Aeromonas* offers a strong and important indicator bacteria for surveillance of AMR transmission dynamics from a One Health perspective [15]. The aim of this study was to apply *Aeromonas* as an indicator species for analysing global AMR patterns from a One Health perspective and to examine its AMR patterns in relation to environmental and socio-economic factors. To address this aim, the distribution of *Aeromonas* in 16S rRNA gene libraries derived from environments considered to be significant contributors to the development of AMR was examined. This distribution of *Aeromonas* was compared to that of *E.coli*, a typical AMR indicator, to support its utility in this role. A systematic review and meta-analysis was then performed of articles published between January 2000 and December 2020 containing AMR data against AWaRe drugs among *Aeromonas* spp., with a focus on isolates from sectors including clinical, wastewater, surface and drinking water, seafood, and agriculture. The objectives were: 1) To assess whether various sectors associated more strongly with specific resistance patterns; 2) To identify if Gross National Income (GNI) is associated with AMR; 3) To determine the impact of wastewater infrastructure and aquaculture on AMR; 4) To provide the first assessment of antimicrobial stewardship by comparing the change in a country’s AWaRe index scores from 2000 to 2015 to AMR levels; and 5) To determine whether environmental policy correlates with AMR. Together, this work provides a comprehensive analysis of AMR among *Aeromonas* populations globally from a One Health perspective and identifies potential targets to combat AMR.

2. Methods

2.1. 16S rRNA gene sequence dataset processing

Proportions of *Aeromonas* and *Escherichia/Shigella* in each sample from three datasets (Supplemental Methods) were calculated as the number of reads of the V4 region of the 16S rRNA gene assigned to the genus divided by the total number of reads in the corresponding sample. In total, 10 229 samples were obtained for further analyses. For all compiled data, the mean and standard deviations of *Aeromonas* and *Escherichia/Shigella* relative proportions were calculated with R v.4.1.0 [25]. Plots were generated with the R package ggplot2 [26]. Code, sample information, and ASV taxonomy and abundances are available on GitHub: https://github.com/NewtonLabUWM/Aeromonas_metanalysis. For a list of all SRA records included in the analysis see Supplemental Dataset 1. SRAList.

2.2. Search Method

As shown in Figure 2, this systematic review and meta-analysis was achieved in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [27]. Relevant sources were identified on the Web of Science (WOS) and PubMed databases using Boolean operators (AND/OR) and search terms that encompass six major themes: agriculture, seafood, clinical infections, drinking water, surface water, and wastewater. Each theme was searched individually to group relevant articles for syntheses. The search for every environment included the general search terms “aeromonas” AND (“antimicrobial resistance” OR “antibacterial resistance” OR “multi-drug resistance” OR “antimicrobial” OR “anti-bacterial” OR “drug resistant” OR “antibiotic resistance” OR “antibiotic resistant”) followed by AND with more specific environmental search terms – agriculture: “agriculture” OR “crops” OR “animals” OR “cattle” OR “ruminants” OR “meat” OR “food” OR “ready-to-eat” OR “abattoir” OR “chicken” OR “lamb” OR “pig” OR “cow” OR “mutton” OR “vegetable” OR “fruit” OR “poultry” OR “sprouts” OR “lettuce” OR “market”; surface water: “lake” OR “river” OR “surface water” OR “pond” OR “freshwater” OR “fresh water” OR “swimming” OR “pool”; wastewater: “wastewater” OR “hospital sewage” OR “sewage” OR “waste water”; clinical: “clinical” OR “diarrhea” OR “stool” OR “pneumonia” OR “gastroenteritis”

OR “septicemia” OR “bacteremia” OR “wound”; seafood: “fish” OR “aquaculture” OR “seafood” OR “shrimp” OR “sushi” OR “oysters” OR “scallops” OR “salmon” OR “food” OR “ready-to-eat”; drinking water: “drinking water” OR “well water” OR “tap water” OR “water distribution” OR “municipal” terms.

Primary and secondary database searches were performed independently by two separate researchers for each environmental theme to minimize the possibility of overlooking relevant articles. Publication date limits were set as January 1st, 2001, and December 31st, 2020. As this study was conducted from a One Health and Global Health perspective, no limits were set for geographical region during the literature search. Abstracts that reported original research on *Aeromonas* or Gram-negative bacteria in the context of the environmental theme being searched, as well as possible antibiotic susceptibility testing, were selected for further investigation. Disagreements about the inclusion of articles in the meta-analysis were resolved by consensus or third-party consultation when consensus was not achieved. These initial WOS and PubMed searches produced numerous articles for each environment. From these lists, full-text links were obtained using WOS, PubMed, and Google Scholar databases as well as by contacting authors directly.

2.3. Selection Process

Articles that met the initial screening criteria were subjected to full-text review with more stringent exclusion criteria. All criteria were required to be met before the article was considered for review. Articles were retained if the reviewers were able to find the full-text articles, published in English, with clearly defined methods for isolation and identification of *Aeromonas*. Identification based on biochemical tests, MALDI-TOFF, API-20E/NE, or other conventionally accepted means were necessary for article inclusion. Additionally, antibiotic susceptibility tested by methods adhering to either US Clinical and Laboratory Standards Institute (CLSI), US National Committee for Clinical Laboratory Standards (NCCLS), or European Committee on Antimicrobial Susceptibility (EUCAST) guidelines was required. Sources employing disc diffusion, minimum inhibitory concentration (MIC) methods, agar dilution, VITEK® AST cards, or other conventionally accepted means of antibiotic susceptibility testing were included in this systematic review and meta-analysis.

A minimum threshold of 10 isolates was deemed necessary for each article, apart from those investigating clinical *Aeromonas* spp., for which the minimum threshold was two. Studies were excluded if they did not clearly state the source of isolates or did not meet the minimum required threshold of *Aeromonas* isolates from the source being examined. Furthermore, if resistance and susceptibility data could not be determined with the information provided, the data were not included. This may have been due to reporting only collective resistance data, intentional isolation of only resistant strains, or infographics that did not enable precise data extrapolation.

2.4. Data extraction

Data for each respective environment were extracted and compiled independently by the primary reviewers (DJ, JL, AD, NH, TS) of each respective environment using Microsoft Excel on OneDrive. Spreadsheets included article title, authors, environmental sampling source, symptomatic expression (if defined), antibiotics tested, susceptibility patterns, number of *Aeromonas* isolated and analysed, isolation and identification methods, country of study, and the year of sampling and the year of article publication. Considering the susceptibility of some isolates at intermediate resistance levels after longer exposure or in certain anatomical regions [28], intermediate resistance was recorded as susceptible.

A defined list of antimicrobials was not a requisite for article inclusion. Therefore, data for all antibiotics were gathered from the articles, except for ampicillin because of its intrinsic resistance and inclusion in various *Aeromonas*-selective media. However, antimicrobials further examined within this study were selected based on their representative class and abundance of data available from all environmental sources. Information on the number of articles and isolates analysed within each respective antimicrobial and environment is provided in Supplementary Dataset 2. Multiple antimicrobial resistance (MAR) information was not analysed because it was not possible to identify whether articles included ampicillin resistance as part of their MAR index. Articles published by similar authors that contained identical isolate and resistance numbers were considered duplicates. Four articles were excluded because of this criterion (Figure 2).

2.5. Data acquisition from global databanks

Yearly gross-domestic product (GDP) information was acquired from The World Bank [29]. Antibiotic consumption information, given in daily ingested dose (DID), was gathered from Browne et al. [30], and national socioeconomic and anthropogenic environmental factor data were collected from the WHO and the 2020 Environmental Performance Index Report [31]. The latter report provides national performance rankings in areas such as air quality, sanitation and drinking water, heavy metal exposure, waste management, ecological biodiversity, habitat loss, fisheries, climate change, pollution, agriculture, and wastewater treatment. The Access-to-Watch index score was acquired from Klein et al. for the years 2000 and 2015 [32]. To assess a country’s antibiotic stewardship through the implementation of the WHO AWaRe recommendations of increasing Access drugs to Watch drugs, the Access-to-Watch index (ratio of Access drugs DID to Watch drugs DID) from 2000 was divided by the value in 2015 for each country. An increase in the A:Wa index ratio change from 2000 to 2015 indicates decreased use of Access compared with Watch drugs.

2.6. Statistical methods

Pooled prevalence with 95% confidence intervals (CIs) for susceptibility to each antibiotic within each of the six sectors was calculated using Comprehensive Meta-Analysis Version 3.3.070 software (Biostat, Inc) and the R package metafor [33], with I^2 used to identify heterogeneity between studies. Meta-analyses were performed using the Comprehensive Meta-Analysis Version 3.3.070 software and run separately for each search theme and for tri-source groupings, which combined the six search themes by industrial relatedness to give “clinical”, “agricultural” (aquaculture and agricultural), and “environmental” (wastewater, surface and drinking water) groups. Forest plots were constructed using R package metafor [33]. To assess systematic heterogeneity within the sectors, funnel plots were constructed using the ‘funnel.rma’ function of the ‘metafor’ R package. Following the recommendations of Sterne and Egger [34], the plots show the residuals of the fitted model on the x-axis with standard errors on the y-axis. Each funnel plot was adjusted for antibiotic and source (Supplemental Figure 18-20).

The heat map figure was created using R package ggplot2 [26], with results derived from the mixed-effect meta-analysis conducted in R package metafor [33]. The comparison of GNI with AMR was adjusted for outliers using 1/N and isolate source. Pearson correlation coefficient was used for analysis of resistance and anthropogenic environmental factor relatedness. Although fixed-effects summaries were also calculated, only mixed-effects results are presented in this analysis because of the high degree of heterogeneity throughout the study.

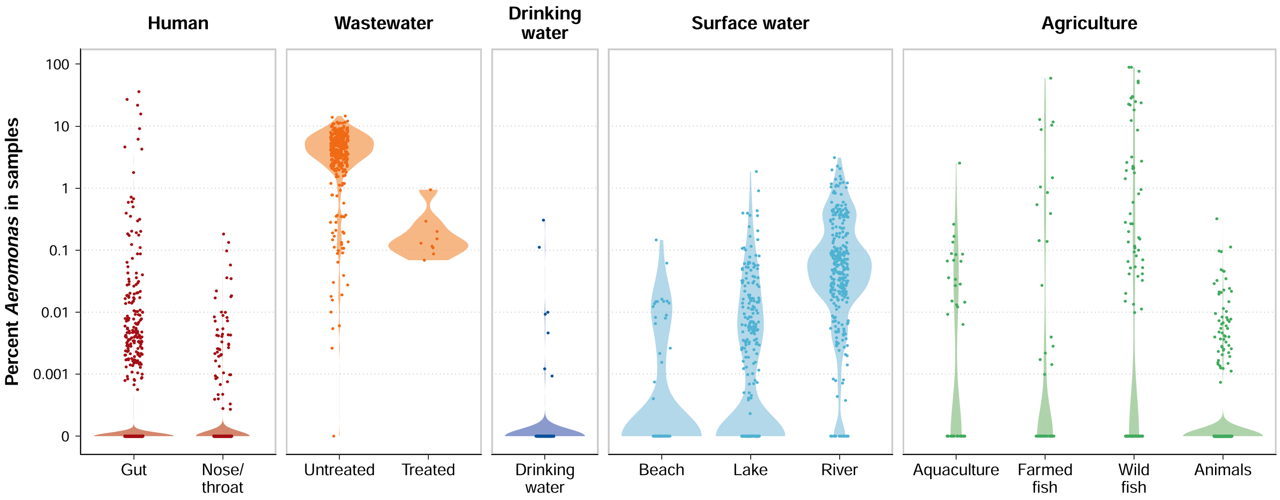

Figure 1. Log-transformed proportions of reads assigned to the genus *Aeromonas* in 16S rRNA gene sequence datasets visualized in violin plots. Each point represents the *Aeromonas* proportion in a sample, and the shape displayed for each category indicates the sample density at a given relative abundance, where more samples at given relative abundance will produce a wider shape. Samples were categorized according to the groupings depicted in the plot, and samples were assigned to groups by the environment descriptor for each sample in the Sequence Read Archive (SRA) or from their respective publication. The number of samples in each category is as follows: human gut = 6810, human nose/throat = 1086, untreated wastewater = 335, treated wastewater = 9, drinking water = 228, beach = 63, lake = 315, river = 320, aquaculture infrastructure = 51, farmed fish = 57, wild fish = 154, agriculture animals (cows and pigs) = 801.

The values and rankings from GDP, DID and environmental factor data were analysed using meta-regression against the calculated pooled prevalence (PP) of resistance for each country to identify statistically significant trends, while controlling for outliers using 1/N (N=total number of isolates in study) and other confounding factors.

3. Results

3.1. Prevalence of Aeromonas across environments

Aeromonas spp. have been isolated from many environments of primary concern (e.g., aquaculture, hospitals, wastewater) for the transport and dissemination of AMR; therefore, the genus *Aeromonas* has the potential to be used as an indicator species to track global antibiotic susceptibility patterns [35]. In an examination of *Aeromonas* distribution across aquatic and host-associated environments, the genus was found to be omnipresent in aquatic habitats and was the most prevalent in untreated urban wastewater samples as a proportion of the total microbial community (4.53% ± 2.81%; Figure 1). *Aeromonas* was identified in all but one of the 344 wastewater (untreated and treated) samples. *Aeromonas* was also abundant in samples associated with fish, both farmed and wild (Figure 1: present in 74 of 211 fish and 20 of 51 aquaculture samples). In some fish-associated samples, *Aeromonas* was dominant, comprising >20% of the recovered sequences. *Aeromonas* spp. were also common in natural water samples, particularly those collected from rivers (Figure 1), where, on average, the genus constituted 0.19% of the recovered sequences and was identified in 303 of 320 samples. *Aeromonas* was less common in lake and beach sand samples but was still regularly recovered from these habitats (149 of 315 lake samples and 19 of 63 beach sand samples).

In contrast to wastewater, fish-associated, and natural water samples, *Aeromonas* was absent in most samples collected from humans (gut and nose/throat) or domesticated pigs and cows, but was relatively abundant (≥0.01% of sequences) in a few (77) samples (Figure 1). In total, *Aeromonas* was identified in 242 of 7896 (2.4%) of all human samples and 59 of 801 (7.4%) cow/pig samples. Across the included aquatic environments, *Aeromonas* was least common in drinking water, where it was detected in only 7 of 228 (3.1%) samples (Figure 1).

Compared with *E. coli,* a common indicator species for AMR, *Aeromonas* populations were significantly more common among wastewater environments, surface waters, and farmed fish (Supplemental Figure 1A and B). Whereas *E. coli* was more common amongst human and animal samples and in drinking water (Supplemental Figure 1A and B).

3.2. Meta-analysis parameters

This systematic review screened a total of 7382 articles, of which 221 articles were eligible for meta-analysis (Figure 2). From these articles, AMR against 21 antibiotics (Supplemental Table 2), with 20 containing AWaRe classifications [13] (Access, Watch, Reserve), were obtained from 15 891 *Aeromonas* isolates representing clinical, environmental and agricultural ecosystems, with further subdivisions identified in Table 1.

Mixed-effect meta-analysis was performed on resistance patterns among *Aeromonas* populations reporting PP, 95% CIs and I^2. Table 2 shows the overall lowest resistance levels to aztreonam (6.9: 4.0–11.6) and ofloxacin (6.9: 3.7–12.3), followed by cefepime (7.7: 4.9–11.9), ciprofloxacin (8.0: 6.3–10.0), meropenem (8.7: 5.5–13.6), ceftazidime (8.7: 6.3–11.8), and gentamicin (9.7: 7.6–12.3). Overall, there were minimal differences for each antibiotic among the six primary sources (Table 2 and Figure 3). However, isolates from wastewater were significantly more resistant to nalidixic acid, cefepime (fourth-generation cephalosporin), and the WHO reserve drug aztreonam than their clinical counterparts (Table 2). Nalidixic acid resistance increased over two-fold, from 31.4% (95% CI, 24.2–39.6%) to 67.0% (95% CI 48.2–81.6) in wastewater. Cefepime increased over six-fold, from 6% (3.7–9.7%) to 37.5% (14.4–68.2%). Most strikingly, aztreonam resistance increased over eight-fold, from 3.8% (1.6–8.4%) in clinical isolates to 30.5% (13.3–55.6%) in wastewater.

A more detailed analysis was performed on the most studied antimicrobials from eight different antibiotic classes among the *Aeromonas* studies. Imipenem and meropenem have similar resistance mechanisms, so data for these drugs were grouped into a singular carbapenem (CBP) category. Cefotaxime and ceftriaxone

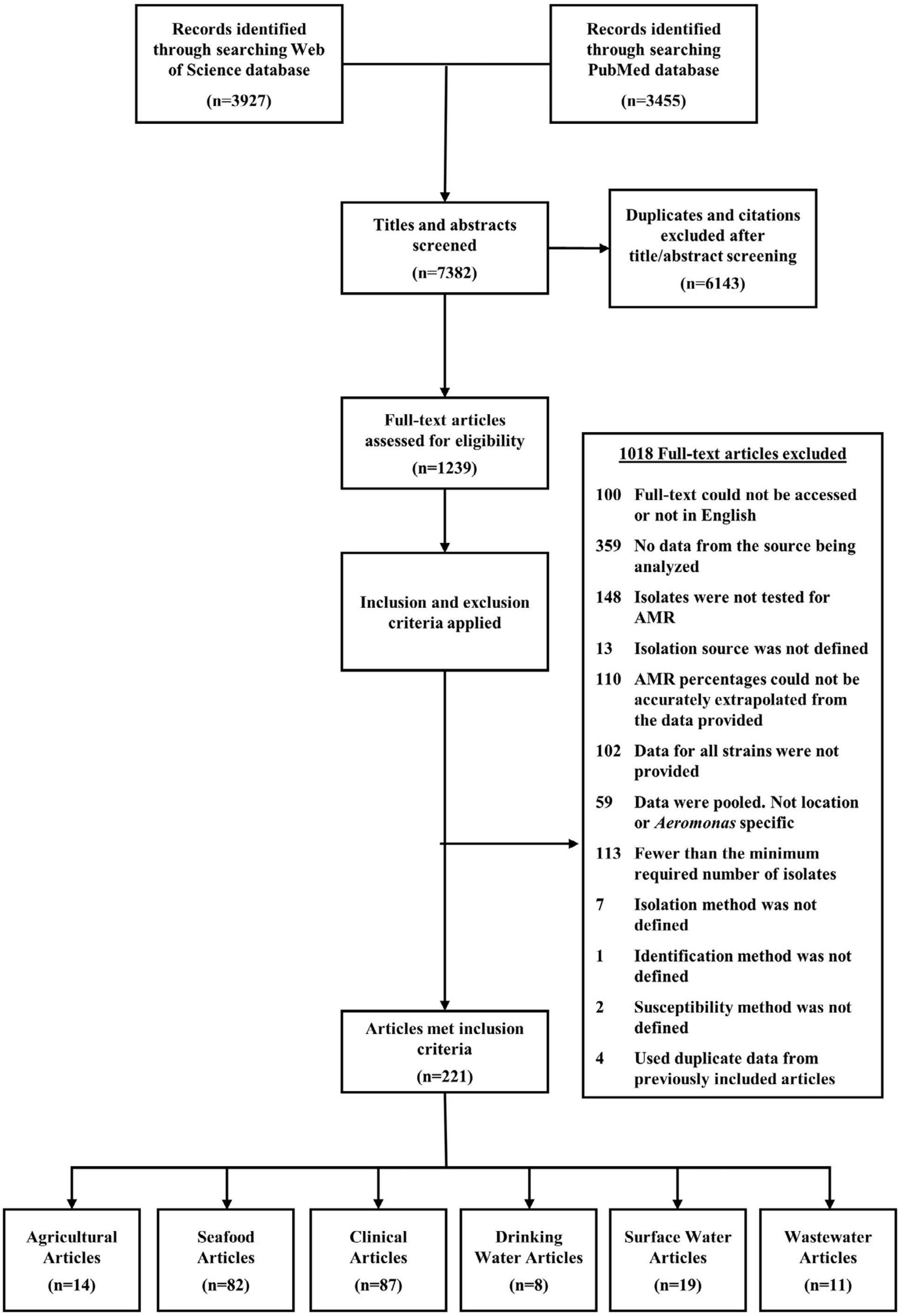

Figure 2. PRISMA flow chart of systematic review and meta-analysis.

were grouped into a category for third-generation cephalosporins (3CEF). For studies that tested both antimicrobials in each category, only imipenem and cefotaxime data were used due to larger datasets. Overall, the detailed analysis included resistance to four WHO "Access" and four WHO "Watch" drugs.

To identify predominant risk factors within these habitats, the major sources were further divided into subcategories. These refined susceptibility profiles within wastewater treatment (Figure 3, Supplemental Figures 2-9) and seafood (Figure 3, Supplemental Figure 10-17) identified large disparities. Untreated wastewater demonstrated higher AMR levels among *Aeromonas* isolates than those from treated wastewater, with significant differences among ciprofloxacin, 3CEF, gentamicin and tetracycline (Figure 3, Supplemental Figure 3, 5, 7 and 9, respectively, $P < 0.05$). When comparing seafood from wild vs. farmed sources, *Aeromonas* populations were more resistant to ciprofloxacin (Figure 3 and Supplemental Figure 13, $P < 0.05$) and tetracycline among farmed sources, with the latter exhibiting the largest difference (Figure 3 and Supplemental Figure 17: Wild 11.1% vs. Farmed 41.0%, $P < 0.05$).

3.3. Socioeconomic associations with AMR

Analysis of national AMR rates identified Saudi Arabia, Bhutan, and Ethiopia as having the highest resistance levels for all sources, after adjusting for antibiotic and microbial source (Figure 4). The

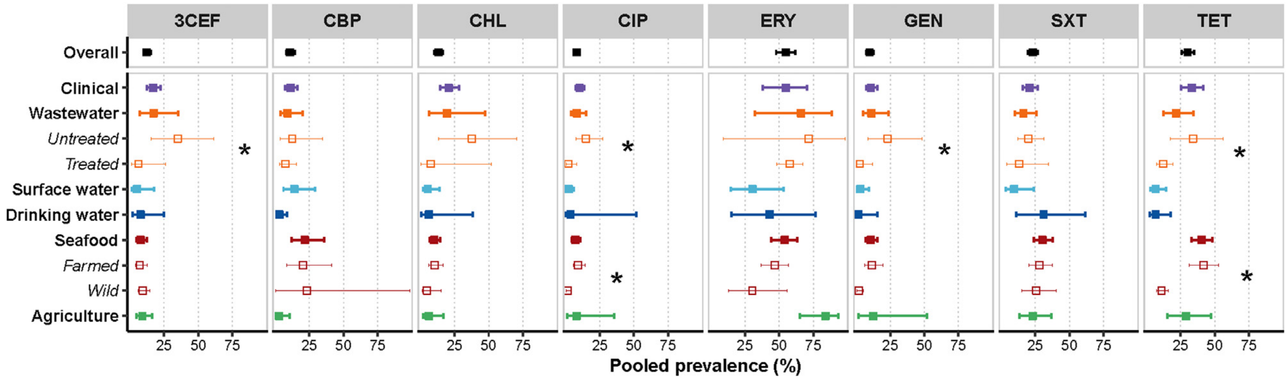

Figure 3. Pooled prevalence of antibiotic resistance among *Aeromonas* populations from each source. Data represent the pooled prevalence of AMR among *Aeromonas* populations from each sector and sub-sector. Bars represent the 95% confidence intervals. * $P < 0.05$.

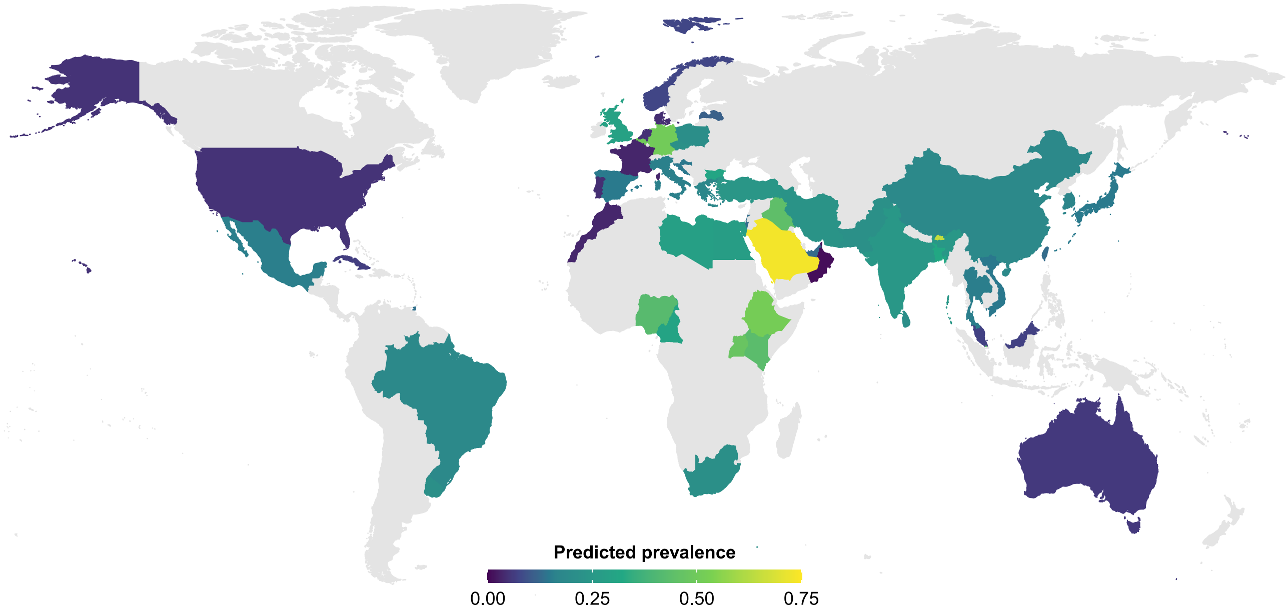

Figure 4. Correlation of the predicted prevalence of antibiotic resistance among *Aeromonas* populations from all sources. Predicted prevalence was determined by meta-regression while adjusting for all antibiotic/major source combinations.

World Bank Gross National Product (GNP) statistics were utilized to determine the correlation of economic activity with antimicrobial susceptibility [29]. Countries with low to middle national economic rankings (0–50%) harbored significantly higher AMR levels towards most antimicrobials (Supplemental Table 3: $P < 0.05$), except CBP and chloramphenicol, compared to high GNI (75–100%) after controlling for source and outliers (1/N) using meta-regression with random effects. These national income correlations were most pronounced within clinical and environmental sources, with minimal differences among agricultural isolates (Supplemental Table 3 and Figure 5). Countries with high GNIs (75–100%) had significantly lower resistance levels among clinical samples than countries with low GNI for 3CEF, ciprofloxacin, gentamicin, and sulfamethoxazole-trimethoprim (SXT) (Supplemental Table 3 and Figure 5, $P < 0.05$). Among environmental sources, mixed-effects meta-regression indicated high GNI countries have significantly lower resistance levels to CBP, 3CEF, SXT and tetracycline (Supplemental Table 3 and Figure 5, $P < 0.05$) after controlling for sub-source and 1/N. A significant correlation was only evident between national income levels and CBP resistance levels within agricultural sources where lower GNI was associated with increased resistance (Supplemental Table 3 and Figure 5, $P < 0.05$).

3.4. Correlation of AWaRe index on AMR

To assess the effect of each nation's consumption of Access to Watch drugs (A:Wa index), AMR was compared with the ratio of the A:Wa index from 2000 to 2015 using mixed effects meta-regression controlling for 1/N and source. A decrease in a country's AWaRe index over time from 2000 to 2015 (suggesting increased consumption of Watch drugs compared with Access drugs) correlated with significantly higher resistance levels to all Access and Watch drugs (Table 3: $P < 0.001$), with stronger associations to GEN, SXT, 3CEF, CIP, and ERY (Supplemental Table 4, $P < 0.05$).

3.5. Association of national environmental performance and AMR

Focusing on 32 environmental performance indicators, the Environmental Performance Index (EPI) gauges environmental impact within 11 categories amongst 180 nations [31]. Employing overall EPI rankings, univariable meta-analysis identified an inverse correlation between national EPI and AMR rates amongst grouped Access and Watch drugs (Table 3: $P < 0.001$), although CHL and CBP had minimal associations (Supplemental Table 5). Even after a multivariable analysis adjusted for source, A:Wa change and EPI,

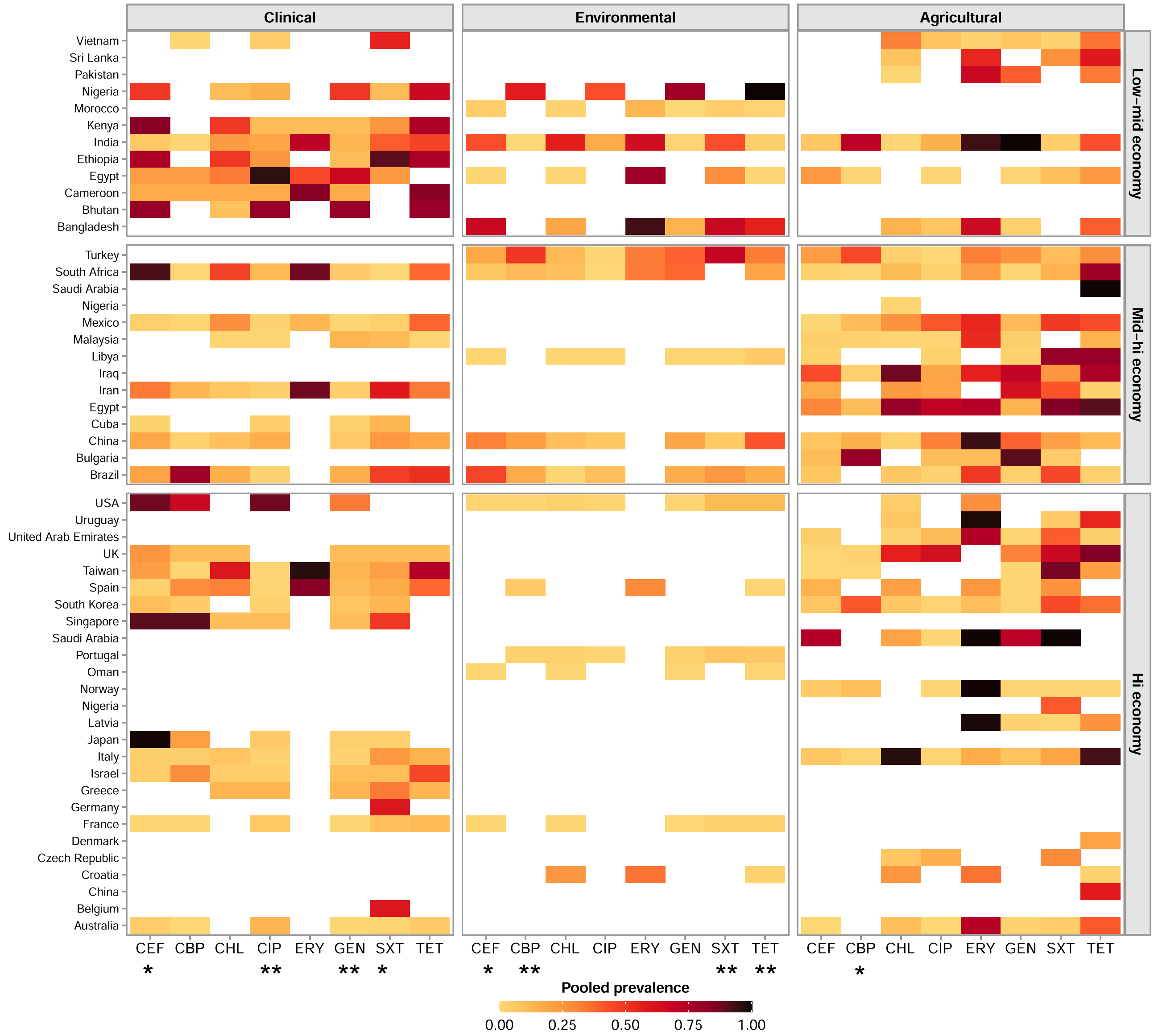

Figure 5. Heat map of Gross National Income with antibiotic resistance. All antibiotic resistance data from the various sources were grouped into either clinical, environmental, or agricultural. Clinical represents any strains isolated from humans. Environmental includes wastewater, drinking water and surface water sources. Agricultural includes any isolates obtained from seafood or other food sources identified within the search criteria. The heat map was derived from a mixed-effect meta-analysis on the country and antimicrobial resistance rate. Statistical differences between all national gross income levels were determined using mixed-effect meta-regression controlling for 1/N and sources within each environment. * $P < 0.05$ and ** $P < 0.005$. CEF: third generation cephalosporins; CAR: carbapenems; CHL: chloramphenicol; CIP: ciprofloxacin; ERY: erythromycin; GEN: gentamicin; SXT: sulfamethoxazole-trimethoprim; TET: tetracycline.

this strong correlation between EPI and AMR remained (Table 3: $P < 0.001$). National income was not included in this multivariable analysis due to the high correlation (R-squared=80%) between GDP and EPI. Amongst the individual environmental performance categories, the strongest correlations with increased antimicrobial susceptibility were countries with better environmental performance in environmental health, air quality, sanitation and drinking water, heavy metal exposure, waste management, climate change, and pollution emissions (Supplemental Table 6, $P < 0.05$).

4. Discussion

AMR is a significant threat to human and agricultural health; therefore, it is imperative to advance understanding of its driving factors. To aid this, a Global One Health indicator species is needed. *E. coli* is considered a prominent candidate organism to fill this role. Its prior establishment in AMR surveillance, as a measure of anthropogenic impact on ecosystems, and standardized culturing methods certainly position it as a good target [28]. However, *E. coli* is not commonly associated with fish and shellfish [36], nor is it a common inhabitant of aquatic ecosystems, so additional AMR indicator species could benefit the global understanding of AMR. *Aeromonas* is a pathogen of fish, shellfish and humans, a common inhabitant of aquatic ecosystems, and a readily culturable bacterium [16]; therefore, it fits the criteria as a Global One Health indicator. The current analysis of the distribution of *Aeromonas* across environmental sectors confirmed that it was regularly detected in community samples from the clinical, aquatic environmental, and agricultural sectors. *Aeromonas* was far more common than *E. coli* in wastewater, freshwater ecosystems, and aquaculture, which further supports the use of *Aeromonas* spp. as indicator bacteria to detect global AMR trends, particularly when considering connections between sanitary waste systems, aquaculture production, and natural aquatic environments.

Table 1
Details of AMR research articles included in meta-analysis.

Clinical source	**# of articles (# of isolates)**
Urine	1 (1)
Stool/Diarrhea	46 (2367)
Blood/CSF	18 (1133)
Wound/Tissue	16 (241)
Mixed/Undefined	25 (1821)
Total	**107 (5821)**
Wastewater source	
Raw	9 (799)
Treated	7 (483)
Total	**16 (1282)**
Surface water	
Lake	3 (351)
Rivers	14 (2175)
Mixed	2 (125)
Total	**19 (2651)**
Potable water	
Treated	6 (644)
Untreated	2 (246)
Total	**8 (890)**
Seafood	
Farm-Fish	51 (2298)
Farm-Shellfish	2 (94)
Farm-Mixed	6 (304)
Retail-Fish	13 (969)
Retail-Shellfish	7 (249)
Retail-Mixed	1 (43)
Wild-Fish	7 (466)
Wild-Shellfish	4 (165)
Total	**91 (4588)**
Agriculture	
Vegetables	1 (55)
Dairy	3 (86)
Animal Meat	6 (300)
Mixed	3 (218)
Total	**13 (659)**
TOTAL ISOLATES	**15 891**

The current systematic review and meta-analysis of AMR among *Aeromonas* populations from a global One Health perspective identified: 1) resistant strains to all 21 antimicrobials amongst all sectors, with minimal differences in AMR trends, supporting the interconnectedness of humans and animals with their environments; 2) countries with lower GDP associated with stronger AMR rates; 3) antimicrobial stewardship policies reducing Watch drug consumption and relying more on Access drugs linked to lower AMR trends; and 4) the strongest correlation with AMR is poor environmental performance, although EPI strongly correlates with GDP and A:Wa index.

One strategy proposed by the WHO to curb AMR was to assign drugs an AWaRe classification and set a national goal to have Access drugs comprise at least 60% of total antibiotic consumption [13]. Global antibiotic prescribing rates, however, do not align with this strategy [37]. For both community- and healthcare-acquired infections, penicillins with beta-lactamase inhibitors (Access drugs) are the most frequently prescribed antibiotics at 29.2% and 24.8%, respectively [38]. However, the second and third most prescribed antibiotics were Watch drugs, with third-generation cephalosporins (15.5%) and fluoroquinolones (14.0%) for community-acquired infections, and fluoroquinolones (12.8%) and carbapenems (12.2%) for healthcare-acquired infections [38]. Compounding this concern, global empirical prescription of antibiotics for community-acquired infections is typically double that of targeted therapy [38].

The current univariable analysis findings support that increased use of Watch drugs compared to Access drugs from 2000 to 2015 correlated with increased resistance to all Access and Watch drugs among *Aeromonas* populations. This significant effect was lost after multivariable analysis, which could be due to the strong correlation of A:Wa change to EPI (R-squared = 0.56). Overall, the least resisted of the 21 antimicrobials investigated was aztreonam. As a Reserve drug, the need to maintain low resistance levels cannot be understated and underscores the importance of the prudent control of the use of this drug [13].

Injudicious antibiotic application is not limited to healthcare, overapplication of antibiotics is also a cause for concern in agricultural industries [39]. Of particular concern is the abundant application of antibiotics in aquaculture. Asia is the leading producer of aquaculture products, with China generating 48.2 million tons (56.5% of total aquaculture production) per year, followed by India (9.1%), Indonesia (7.0%), and Vietnam (5.2%) [40]. In China and Vietnam particularly, antimicrobial usage has increased and broadened to a wider variety of antibiotics (∼15), with oxytetracycline, sulfadiazine, florfenicol, sulfadimethoxine, erythromycin, amoxicillin, and enrofloxacin comprising more than 54% of the antibiotics used [41]. Considering aquaculture provides roughly 40% of the growing fish market, with yearly growth in production (annual growth rate of 3.7–5.0% from 2011–2019), it is likely that antimicrobial use in the seafood industry will continue to rise [40].

Previous studies have documented the consequences of high antimicrobial utilization in aquaculture [42]. A 20-year meta-analysis investigating common aquaculture pathogens showed that despite AMR declining in wild-caught seafood, aquaculture isolates maintained antimicrobial susceptibility levels similar to those from two decades prior [42]. Additionally, fish meat on the market often contained antibiotic compounds, such as tetracyclines and fluoroquinolones, in quantities exceeding maximum residue limits [43]. The current meta-analysis supports these findings: isolates from farmed seafood were found to have higher resistance rates than wild-caught seafood against the two most commonly applied antimicrobial classes in aquaculture, tetracyclines and quinolones [44]. International coordination is necessary to compose and execute global policies to regulate antimicrobial usage in aquaculture [41,45].

To reduce wastewater pollutants and bacterial populations, wastewater treatment plants receive much of the multidrug-resistant and pharmaceutical-rich waste drainage from hospital, agricultural, and municipal sources. However, these facilities may accelerate resistance to some antimicrobials [46] and water treatments [47]. Pärnänen et al. correlated European antibiotic consumption with increased ARG prevalence in both influent and treated wastewater effluents [48]. Similar to the current findings, they found that treated effluents exhibited lower resistance levels and lower frequency of ARGs. Although reduced, many ARG-encoding bacteria still survive and are released in effluents [21], where they incorporate into resident microbiomes or disseminate ARGs into the environment [49]. Regulations and AMR monitoring in wastewater are rare, enabling the potential release of hazardous microbes into natural aquatic reservoirs [50]. Even with robust wastewater treatment practices, millions of individuals may still be exposed to AMR bacteria in public waters [51].

Interestingly, wastewater-based epidemiology (WBE) is emerging as a potential tool for monitoring infectious disease transmission and community outbreaks, as seen during the COVID-19 pandemic [52]. With rising clinical AMR levels, observing rates of new genetic variants within wastewater may provide an early indication of clinical patterns. Furthermore, the ease of access, and the ability to adjust for seasonal variability, and to measure influential factors, such as antibiotic consumption or chemical exposure, all provide strong arguments for its use [53]. The current data showed that wastewater AMR profiles were similar to clinical levels, with notable elevations in resistant strains against the fourth-generation cephalosporin, cefepime, as well as the monobactam, aztreonam, a Reserve antibiotic. Although more studies are needed to assess the use of WBE in AMR monitoring before it can be used as a predictive clinical measure, the current data could foreshadow fu-

Table 2
Pooled prevalence and heterogeneity of *Aeromonas* antibiotic susceptibility studies.

	Overall PP (95% CI)	I^2	Clinical studies PP (95% CI)	I^2	Wastewater studies PP (95% CI)	I^2	Surface water PP (95% CI)	I^2 (%)	Drinking water PP (95% CI)	I^2	Seafood studies PP (95% CI)	I^2	Agriculture studies PP (95% CI)	I^2
Aminoglycosides														
Gentamicin-A	9·7 (7·6-12·3)	87·9	10·9 (7·4-15·7)	82·0	9·3 (3·8-21·2)	93·4	3·2 (1·0-9·4)	92·3	1·8 (0·2-15·5)	84·1	10·3 (7·0-14·9)	88·6	12·6 (1·9-52·0)	86·2
Kanamycin-Wa	18·2 (12·2-26·1)	94·1	22·8 (7·3-52·6)	91·7	20·7 (5·6-53·5)	94·7	7·9 (1·7-29·3)	96·5	3·5 (0·3-32·7)	77·9	18·8 (10·5-31·3)	94·2	40·1 (14·6-72·3)	84·6
Streptomycin-Wa	30·4 (24·1-37·4)	92·9	35·5 (20·9-53·4)	81·9	36·8 (14·3-67·2)	94·5	37·4 (20·4-58·2)	96·2	NA	NA	26·0 (18·3-35·4)	92·8	34·6 (14·7-61·8)	84·6
Carbapenems														
Meropenem-Wa	8·7 (5·5-13·6)	85·7	8·5 (4·5-15·5)	61·3	9·1 (3·6-21·3)	88·4	5·8 (0·3-54·7)	93·4	5·3 (2·8-9·9)	0·0	9·3 (2·8-26·4)	85·4	NA	NA
Imipenem-Wa	13·9 (10·2-18·6)	87·7	12·0 (7·7-18·3)	85·1	11·0 (7·2-16·5)	20·6	16·6 (4·7-44·4)	92·6	2·5 (0·6-10·0)	64·4	24·9 (14·5-39·4)	89·8	2·9 (0·7-10·7)	0·0
Cephalosporins														
Cefazolin-A	79·5 (71·4-85·8)	90·0	87 (79·4-92·0)	85·9	NA	NA	90·6 (87·9 – 92·7)	0·0	NA	NA	45·9 (21·6-72·4)	92·8	70·5 (46·9-86·6)	64·9
Cefotaxime-Wa	12·2 (9·3-15·7)	83·0	15·7 (10·8-22·4)	76·0	17·3 (7·3-35·5)	89·2	3·7 (0·7-18·0)	93·7	6·1 (1·3-24·0)	85·4	7·7 (4·3-13·5)	85·5	5·9 (1·7-18·8)	68·9
Ceftriaxone-Wa	12·6 (9·5-16·6)	84·7	17·7 (11·4-26·4)	87·7	29·9 (12·3-56·6)	90·1	3·3 (0·1-51·0)	88·2	8·7 (1·7-35·1)	91·7	6·8 (4·2-10·6)	55·1	13·3 (9·8-17·7)	0·0
Ceftazidime-Wa	8·7 (6·3-11·8)	87·4	9·2 (6·2-13·6)	81·5	10·3 (3·3-28·1)	95·0	2·0 (0·2-15·1)	92·1	2·6 (0·4-16·1)	87·3	7·6 (3·0-17·8)	83·4	21·3 (12·1-34·7)	62·9
Cefepime-Wa	7·7 (4·9-11·9)	84·5	6·0 (3·7-9·7)	74·5	37·5 (14·4-68·2)	93·9	NA	NA	0·6 (0·1-3·9)	0·0	8·2 (5·1-12·7)	44·3	2·3 (0·1-27·7)	0·0
Fluoroquinolones														
Nalidixic acid	33·3 (28·0-38·9)	90·2	31·4 (24·2-39·6)	85·9	67·0 (48·2-81·6)	86·5	15·0 (7·0-29·1)	93·6	26·0 (1·0-92·7)	94·0	43·4 (33·8-53·5)	90·8	14·0 (1·3-66·8)	92·1
Ciprofloxacin-Wa	8·0 (6·3-10·0)	87·5	10·3 (7·6-13·8)	86·7	8·2 (4·3-15·2)	83·5	2·3 (0·8-6·0)	71·2	3·6 (0·1-51·8)	88·2	7·1 (4·6-10·9)	84·8	8·0 (1·4-35·4)	92·5
Norfloxacin-Wa	11·3 (6·8-18·2)	89·2	16·5 (4·7-44·1)	95·4	NA	NA	14·6 (7·6-26·3)	32·7	NA	NA	11·8 (7·0-19·1)	78·8	4·9 (0·1-77·0)	87·5
Ofloxacin-Wa	6·9 (3·7-12·3)	89·5	9·9 (2·7-30·5)	93·5	2·0 (0·1-25·1)	0·0	0·7 (0·1-3·5)	0·0	1·3 (0·1-20·4)	81·8	8·3 (3·9-16·9)	87·0	0·5 (0·0-7·1)	0·0
Macrolides														
Erythromycin-Wa	55·5 (47·6-63·1)	92·4	54·9 (38·1-70·6)	79·2	66·0 (32·3-88·8)	89·9	23·8 (9·7-47·8)	90·8	43·0 (14·9-76·5)	95·3	54·1 (44·4-63·5)	91·0	83·9 (65·2-93·6)	81·2
Monobactams														
Aztreonam-Re	6·9 (4·0-11·6)	86·3	3·8 (1·6-8·4)	59·0	30·5 (13·3-55·6)	91·6	NA	NA	2·8 (0·5-13·6)	86·1	5·0 (1·4-16·4)	82·5	12·9 (2·4-46·8)	81·1
Penicillins/sub-lact														
Piperacillin/tazobactam-Wa	13·7 (9·3-19·6)	84·4	13·7 (9·3-19·6)	84·4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Phenicols														
Chloramphenicol-A	12·2 (9·6-15·4)	89·1	20·7 (14·6-28·4)	84·1	19·5 (6·2-47·3)	93·1	5·4 (1·9-14·0)	94·1	6·2 (0·7-38·4)	91·7	10·1 (6·8-14·7)	87·7	6·2 (2·1-16·8)	79·4
Polypeptides														
Colistin-Re	21·2 (12·6-33·6)	91·9	30·7 (10·9-61·7)	82·0	8·4 (3·1-20·6)	45·2	15·5 (0·1-97·6)	93·3	58·3 (41·9-73·1)	0·0	20·8 (9·5-39·6)	80·5	7·6 (0·2-81·0)	86·4
Sulfonamides														
SXT-A	22·6 (19·1-26·5)	91·4	20·8 (15·9-26·7)	89·1	14·3 (8·3-23·6)	83·1	9·4 (3·4-23·8)	96·9	31·0 (11·2-61·7)	92·7	31·0 (24·5-38·4)	88·3	23·1 (13·5-36·6)	84·1
Tetracyclines														
Tetracycline-A	28·2 (23·8-33·1)	91·7	33·1 (25·5-41·8)	81·0	21·7 (12·1-35·9)	86·6	6·8 (3·1-14·3)	93·9	6·8 (2·4-17·7)	70·3	43·8 (36·2-51·7)	91·9	29·0 (15·6-47·5)	90·0

All clinical papers with only 1 isolate were removed, all other sources required at least 10 isolates to be included. I^2 >50% used mixed-effect; <50% used fixed-effect
A=Access; Wa=Watch; Re=Reserve; CI=confidence interval; NA=not applicable

Table 3
Univariable and multivariable analysis of the correlation of AMR with various sectors, A:Wa index change and EPI in *Aeromonas* populations.

	Univariable analysis									Multivariable analysis								
	Access Drugs			Watch Drugs			All Drugs			Access Drugs			Watch Drugs			All Drugs		
	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value	Odds Ratio	95% CI	*P*-value
Characteristic																		
Source																		
Clinical	1			1			1			1			1			1		
Agriculture	0.97	0.58-1.62	0.915	1.20	0.63-2.28	0.585	1.05	0.71-1.56	0.802	0.62	0.35-1.11	0.107	0.85	0.43-1.68	0.644	0.71	0.4-1.11	0.130
Drinking water	0.64	0.33-1.25	0.192	0.55	0.26-1.14	0.108	0.60	0.37-0.92	0.802	0.73	0.36-1.49	0.386	0.42	0.19-0.91	**0.029**	0.57	0.34-0.97	**0.037**
Seafood	1.38	1.02-1.86	**0.039**	1.03	0.72-1.46	0.878	1.23	0.981.55	0.069	1.38	1.00-1.89	0.050	0.95	0.65-1.40	0.806	1.21	0.95-1.54	0.117
Surface water	0.37	0.23-0.59	**<0.001**	0.55	0.30-1.00	**0.049**	0.42	0.30-0.61	**<0.001**	0.39	0.25-0.63	**<0.001**	0.53	0.29-0.96	**0.037**	0.44	0.30-0.63	**<0.001**
Wastewater	1.14	0.71-1.83	0.585	1.19	0.71-2.00	0.518	1.16	0.82-1.64	0.395	1.28	0.79-2.09	0.317	1.11	0.65-1.91	0.698	1.21	0.85-1.74	0.290
A:Wa change	1.32	1.16-1.50	**<0.001**	1.37	1.18-1.59	**<0.001**	1.34	1.22-1.48	**<0.001**	0.99	0.81-1.19	0.881	1.16	0.93-1.44	0.193	1.05	0.91-1.21	0.538
EPI	0.98	0.97-0.98	**<0.001**	0.98	0.97-0.99	**<0.001**	0.98	0.97-0.98	**<0.001**	0.98	0.96-0.99	**<0.001**	0.98	0.97-1.00	**0.011**	0.98	0.97-0.99	**<0.001**

Analyses were adjusted for 1/N and each antibiotic in its corresponding category; multivariant analysis was adjusted for source, A:Wa change, and EPI. Statistical significance of $P < 0.05$ is in bold

ture rises in cefepime- and aztreonam-resistance among clinical isolates.

Although there are clear benefits of wastewater monitoring, various factors impact the interpretation of findings. For example, it is not easy to account for differences in waste streams. These differences include variable loading of industrial waste or stormwater runoff, the influence on growth/decay from waste travel time and temperature, differences in human population density and associated fecal waste loading, and the presence of a robust microbial wastewater resident community that influences the ecology of microbes and/or genes passing through the systems [28]. The use of WBE in lower-income nations may not be practical due to a lack of adequate infrastructure and/or access to that infrastructure [54]. The current study further identifies the strong correlation between GDP and stronger environmental performance, including waste management and sanitation. Bypasses of wastewater infrastructure are also common, which can result in the discharge of hazardous materials, such as heavy metals, chemicals, and pathogenic bacteria, into waters intended for public use [55,56]. These events would not be captured by traditional WBE efforts. However, metagenomic analysis of wastewater around the world has highlighted the link between countries of lower socioeconomic status and increased prevalence of AMR [57].

Lakes and rivers are common recipients of raw and treated sewage, storm runoff, and industrial waste [58]. Throughout the world, major antibiotics and their metabolic intermediates have been identified in surface water and sediments [59], and elevated downstream from wastewater treatment facilities [60]. The current data identifies surface and drinking water as reservoirs of *Aeromonas* populations that exhibit resistance to nearly all antibiotics tested, indicating that it can transfer resistance in aquatic environments.

Understanding antimicrobial application practices requires an understanding of the ecopolitical landscape in which these compounds are being used. A common strategy to combat AMR includes behavioral interventions to reduce antibiotic prescribing [61]. Although high-income countries have maintained constant levels of antibiotic use between 2000 and 2018, trends of increased consumption predominated among low- to middle-income countries [30]. The United States, France, and Italy lead high-income countries in prescribing, and India, China, and Pakistan lead low-to-middle-income countries [2]. The current data support that from others demonstrating inverse correlations between GDP and AMR, including among top priority pathogens [62,63].

Aeromonas AMR data were also compared against numerous environmental performance indicators to investigate other links. Overall, national environmental performance was inversely correlated with *Aeromonas* AMR rates. Closer examination of the individual aspects, however, identified air quality, sanitation, waste management, pollution emissions, heavy metal exposure, water quality, climate change, and other factors, underscoring the importance of close monitoring and regulatory practices to minimize public health risks. Other studies have also identified poor infrastructure and governance index as correlated with *E. coli* resistance to other antibiotics [63].

Considerable heterogeneity throughout this meta-analysis (Supplemental Figures 18-20) suggests caution when interpreting the findings. Global analysis studies looking at antibiotic resistance are limited in the meta-analysis because many studies focused on multidrug resistance or MAR index and were excluded. This study looked at 21 antibiotics with a focus on the most well-studied antibiotics in major antibiotic categories. Another limitation of the current analysis is the limited number of clinical studies with more than one case. Numerous studies had to be removed from the analysis because they presented data for one isolate. As the majority of studies included small case numbers of *Aeromonas* infections, the criterion for minimum number of isolates per study was changed to two, compared with the ten for environmental and agriculture. Funnel plot analysis of clinical samples reflected lower resistance levels amongst studies with fewer isolates compared with those with larger numbers of isolates. This pattern was evident throughout all source environments (Supplemental Figure 18-20). Another limitation of the study is the absence of *Aeromonas* isolate species identification. Considering most clinical infections are caused by only four *Aeromonas* species (*A. hydrophila, A. veronii, A. caviae,* and *A. dhakensis*) [64], it is difficult to interpret other environmental sources containing more diverse species composition [65–67].

One criterion for inclusion in this study was that articles specify the isolation method used. Variation in methodology alone causes heterogeneity among studies due to the exclusion of some *Aeromonas* species that lack intrinsic resistance to beta-lactams like ampicillin, which is incorporated into many *Aeromonas* selective plates. Another major limitation is the lack of studies from low to middle-high income countries. Additionally, a lack of resistance data from all sources within each country prompts caution when interpreting findings. Despite the numerous uncertainties, a multivariable meta-regression analysis, adjusting for source, antibiotics, and outliers, showed that countries most dedicated to environmental investments and antibiotic stewardship through the reduction of Watch drug consumption provided the most effective means to combat AMR.

5. Conclusions

In this study, *Aeromonas* was identified as an AMR indicator to monitor and expand the understanding of the complexities surrounding AMR from a Global One Health perspective. The interconnectedness of humans and animals with their environment was emphasized in this study, stressing the need for a multidisciplinary approach. Furthermore, the presented data indicate that global antimicrobial stewardship programs must better address socioeconomic and ecopolitical factors. In developing nations, monetary and non-monetary motivators are often perceived to outweigh the long-term benefits of antimicrobial stewardship. The immediate nature of AMR requires aggressive goals; however, the feasibility of these goals depends on high-income nations working closely to aid lower-income nations and provide basic infrastructure supporting clean water, sanitation, and wastewater treatment. International surveillance and enforcement of regulatory standards regarding antimicrobial usage in clinical and agricultural settings may promote sustainable practices to limit the hazard associated with this growing public health crisis. Lastly, to help identify future clinical resistance trends, a greater emphasis on utilizing WBE to provide global surveillance of AMR is suggested.

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Declarations

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Sequence Information: Not applicable

Data sharing

Code, sample information, and ASV taxonomy and abundances are available on GitHub: https://github.com/NewtonLabUWM/Aeromonas_metanalysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106848.

References

[1] Maugeri G, Lychko I, Sobral R, Roque ACA. Identification and antibiotic-susceptibility profiling of infectious bacterial agents: A review of current and future trends. Biotechnol J 2019;14:e1700750.

[2] Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A 2018;115:E3463–70.

[3] Halling-Sorensen B. Inhibition of aerobic growth and nitrification of bacteria in sewage sludge by antibacterial agents. Arch Environ Contam Toxicol 2001;40:451–60.

[4] World Health Organization Sanitation. 2022. https://www.who.int/news-room/fact-sheets/detail/sanitation.

[5] Udikovic-Kolic N, Wichmann F, Broderick NA, Handelsman J. Bloom of resident antibiotic-resistant bacteria in soil following manure fertilization. Proc Natl Acad Sci U S A 2014;111:15202–7.

[6] Pruden A, Larsson DG, Amezquita A, Collignon P, Brandt KK, Graham DW, et al. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ Health Perspect 2013;121:878–85.

[7] Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. Molecules 2018:23.

[8] Bezabih YM, Sabiiti W, Alamneh E, Bezabih A, Peterson GM, Bezabhe WM, et al. The global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* in the community. J Antimicrob Chemother 2021;76:22–9.

[9] Kantele A, Kuenzli E, Dunn SJ, Dance DAB, Newton PN, Davong V, et al. Dynamics of intestinal multidrug-resistant bacteria colonisation contracted by visitors to a high-endemic setting: a prospective, daily, real-time sampling study. Lancet Microbe 2021;2:e151–8.

[10] Vikesland P, Garner E, Gupta S, Kang S, Maile-Moskowitz A, Zhu N. Differential drivers of antimicrobial resistance across the world. Acc Chem Res 2019;52:916–24.

[11] Hernando-Amado S, Coque TM, Baquero F, Martinez JL. Defining and combating antibiotic resistance from One Health and Global Health perspectives. Nat Microbiol 2019;4:1432–42.

[12] Machalaba C, Raufman J, Anyamba A, Berrian AM, Berthe FCJ, Gray GC, et al. Applying a One Health Approach in Global Health and Medicine: Enhancing Involvement of Medical Schools and Global Health Centers. Ann Glob Health 2021;87:30.

[13] World Health Organization. WHO, editor. WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use; 2021. editor https://www.who.int/publications/i/item/2021-aware-classification2021.

[14] World Health Organization. 2022. WHO implementation handbook for national action plans on antimicrobial resistance: guidance for the human health sector.

[15] Lamy B, Baron S, Barraud O. *Aeromonas*: the multifaceted middleman in the One Health world. Curr Opin Microbiol 2022;65:24–32.

[16] Skwor T, Kralova S. *Aeromonas*. In: Doyle M, Diez-Gonzalez F, Hill C, editors. Food Microbiology: Fundamentals and Frontiers. 5th ed 2019. p. 415-36.

[17] Janda JM, Abbott SL. The genus *Aeromonas*: taxonomy, pathogenicity, and infection. Clin Microbiol Rev 2010;23:35–73.

[18] Fernandez-Bravo A, Figueras MJ. An update on the genus *Aeromonas*: Taxonomy, epidemiology, and pathogenicity. Microorganisms 2020;8.

[19] Nhinh DT, Le DV, Van KV, Huong Giang NT, Dang LT, Hoai TD. Prevalence, virulence gene distribution and alarming the multidrug resistance of *Aeromonas hydrophila* associated with disease outbreaks in freshwater aquaculture. Antibiotics 2021;10:532.

[20] Beattie RE, Skwor T, Hristova KR. Survivor microbial populations in post-chlorinated wastewater are strongly associated with untreated hospital sewage and include ceftazidime and meropenem resistant populations. Sci Total Environ 2020;740:140186.

[21] Skwor T, Stringer S, Haggerty J, Johnson J, Duhr S, Johnson M, et al. Prevalence of potentially pathogenic antibiotic-resistant *Aeromonas* spp. in treated urban wastewater effluents versus recipient riverine populations: a 3-year comparative study. Appl Environ Microbiol 2020;86.

[22] McLellan SL, Roguet A. The unexpected habitat in sewer pipes for the propagation of microbial communities and their imprint on urban waters. Curr Opin Biotechnol 2019;57:34–41.
[23] Bello-Lopez JM, Cabrero-Martinez OA, Ibanez-Cervantes G, Hernandez–Cortez C, Pelcastre-Rodriguez LI, Gonzalez-Avila LU, et al. Horizontal gene transfer and its association with antibiotic resistance in the genus *Aeromonas* spp. Microorganisms 2019;7.
[24] Sanz-García F, Gil-Gil T, Laborda P, Ochoa-Sánchez LE, Martínez JL, Hernando-Amado S. Coming from the wild: Multidrug resistant opportunistic pathogens presenting a primary, not human-linked, environmental habitat. Int J Mol Sci 2021;22.
[25] Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
[26] Wickham H. ggplot2 Elegant Graphics for Data Analysis. 2nd ed. Cham: Springer; 2016.
[27] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[28] Anjum MF, Schmitt H, Borjesson S, Berendonk TU, network W. The potential of using *E. coli* as an indicator for the surveillance of antimicrobial resistance (AMR) in the environment. Curr Opin Microbiol 2021;64:152–8.
[29] The World Bank World Development Indicators. 2022. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.
[30] Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health 2021;5:e893–904.
[31] Yale Center for Environmental Law & Policy. 2020 Environmental Performance Index 2020. https://envirocenter.yale.edu/2020-environmental-performance-index.
[32] Diwan AD, Harke SN, Gopalkrishna Panche AN. Aquaculture industry prospective from gut microbiome of fish and shellfish: An overview. J Anim Physiol Anim Nutr (Berl) 2022;106:441–69.
[33] Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw 2010;36:1–48.
[34] Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54:1046–55.
[35] Usui M, Tagaki C, Fukuda A, Okubo T, Boonla C, Suzuki S, et al. Use of *Aeromonas* spp. as general indicators of antimicrobial susceptibility among bacteria in aquatic environments in Thailand. Front Microbiol 2016;7:7.
[36] Costa RA. *Escherichia coli* in seafood: A brief overview. Adv Biosci Biotechnol 2013;04(3):5.
[37] Sakeena MHF, Bennett AA, McLachlan AJ. Non-prescription sales of antimicrobial agents at community pharmacies in developing countries: a systematic review. Int J Antimicrob Ag 2018;52:771–82.
[38] Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health 2018;6:e619–29.
[39] Schar D, Klein EY, Laxminarayan R, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in aquaculture. Sci Rep 2020;10:21878.
[40] FAO The State of World Fisheries and Aquaculture; 2016.
[41] Lulijwa R, Rupia EJ, Alfaro AC. Antibiotic use in aquaculture, policies and regulation, health and environmental risks: a review of the top 15 major producers. Reviews in Aquaculture 2020;12:640–63.
[42] Schar D, Zhao C, Wang Y, Larsson DGJ, Gilbert M, Van Boeckel TP. Twenty-year trends in antimicrobial resistance from aquaculture and fisheries in Asia. Nat Commun 2021;12:5384.
[43] Yipel M, Kurekci C, Tekeli IO, Metli M, Sakin F. Determination of selected antibiotics in farmed fish species using LC-MS/MS. Aquac Res 2017;48:3829–36.
[44] Schar D, Klein EY, Laxminarayan R, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in aquaculture. Sci Rep-UK 2020;10:21878.
[45] Garza M, Mohan CV, Brunton L, Wieland B, Häsler B. Typology of interventions for antimicrobial use and antimicrobial resistance in aquaculture systems in low- and middle-income countries. Int J Antimicrob Ag 2022;59:106495.
[46] An X-L, Su J-Q, Li B, Ouyang W-Y, Zhao Y, Chen Q-L, et al. Tracking antibiotic resistome during wastewater treatment using high throughput quantitative PCR. Environ Int 2018;117:146–53.
[47] Yu D, Ryu K, Zhi S, Otto SJG, Neumann NF. Naturalized *Escherichia coli* in wastewater and the co-evolution of bacterial resistance to water treatment and antibiotics. Front Microbiol 2022;13:810312.
[48] Parnanen KMM, Narciso-da-Rocha C, Kneis D, Berendonk TU, Cacace D, Do TT, et al. Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. Sci Adv 2019;5:eaau9124.
[49] Czekalski N, Gascon Diez E, Burgmann H. Wastewater as a point source of antibiotic-resistance genes in the sediment of a freshwater lake. ISME J 2014;8:1381–90.
[50] Bojar B, Sheridan J, Beattie R, Cahak C, Liedhegner E, Munoz-Price LS, et al. Antibiotic resistance patterns of *Escherichia coli* isolates from the clinic through the wastewater pathway. Int J Hyg Environ Health 2021;238:113863.
[51] Leonard AF, Zhang L, Balfour AJ, Garside R, Gaze WH. Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. Environ Int 2015;82:92–100.
[52] Bivins A, North D, Ahmad A, Ahmed W, Alm E, Been F, et al. Wastewater-based epidemiology: Global collaborative to maximize contributions in the fight against COVID-19. Environ Sci Technol 2020;54:7754–7.
[53] Sims N, Kasprzyk-Hordern B. Future perspectives of wastewater-based epidemiology: Monitoring infectious disease spread and resistance to the community level. Environ Int 2020;139:105689.
[54] Jakariya M, Ahmed F, Islam MA, Al Marzan A, Hasan MN, Hossain M, et al. Wastewater-based epidemiological surveillance to monitor the prevalence of SARS-CoV-2 in developing countries with onsite sanitation facilities. Environ Pollut 2022;311:119679.
[55] Mwanamoki PM, Devarajan N, Niane B, Ngelinkoto P, Thevenon F, Nlandu JW, et al. Trace metal distributions in the sediments from river-reservoir systems: case of the Congo River and Lake Ma Vallee, Kinshasa (Democratic Republic of Congo). Environ Sci Pollut Res Int 2015;22:586–97.
[56] Joseph L, Jun BM, Flora JRV, Park CM, Yoon Y. Removal of heavy metals from water sources in the developing world using low-cost materials: A review. Chemospher 2019;229:142–59.
[57] Hendriksen RS, Munk P, Njage P, van Bunnik B, McNally L, Lukjancenko O, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat Commun 2019;10:1124.
[58] McLellan SL, Fisher JC, Newton RJ. The microbiome of urban waters. Int Microbiol 2015;18:141–9.
[59] Singh R, Singh AP, Kumar S, Giri BS, Kim KH. Antibiotic resistance in major rivers in the world: A systematic review on occurrence, emergence, and management strategies. J Clean Prod 2019;234:1484–505.
[60] Rodriguez-Mozaz S, Chamorro S, Marti E, Huerta B, Gros M, Sanchez-Melsio A, et al. Occurrence of antibiotics and antibiotic resistance genes in hospital and urban wastewaters and their impact on the receiving river. Water Res 2015;69:234–42.
[61] Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: A randomized clinical trial. JAMA 2016;315:562–70.
[62] Savoldi A, Carrara E, Gladstone BP, Azzini AM, Gopel S, Tacconelli E. Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list. J Antimicrob Chemother 2019;74:3619–25.
[63] Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health 2018;2:e398–405.
[64] Pessoa RBG, de Oliveira WF, Correia M, Fontes A, Coelho L. *Aeromonas* and human health disorders: Clinical approaches. Front Microbiol 2022;13:868890.
[65] Miyagi K, Hirai I, Sano K. Distribution of *Aeromonas* species in environmental water used in daily life in Okinawa Prefecture. Japan. Environ Health Prev Med 2016;21:287–94.
[66] Khor WC, Puah SM, Tan JA, Puthucheary SD, Chua KH. Phenotypic and genetic diversity of *Aeromonas* species isolated from fresh water lakes in Malaysia. PLoS One 2015;10:e0145933.
[67] Beaz-Hidalgo R, Figueras MJ. *Aeromonas* spp. whole genomes and virulence factors implicated in fish disease. J Fish Dis 2013;36:371–88.