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Antibiotic resistance in hospital wastewater in West Africa: a systematic review and meta-analysis

Prince Hotor[1*], Fleischer C. N. Kotey[1] and Eric S. Donkor[1*]

Abstract

Background The occurrence of antibiotic-resistant bacteria (ARB) has become a global menace and therefore increases morbidity, mortality and healthcare costs. Globally, hospital wastewater (HWW) has been identified as a significant source of antibiotic-resistant elements.

Objectives This review aims to systematically review and to perform meta-analyses from evidence on antibiotic resistance studies in HWW in West Africa.

Methods The review was conducted in compliance with PRISMA and included studies published between 1990 and 2024 in West Africa from the Scopus, PubMed, and Web of Science databases. Eligible studies that characterized resistant bacteria, genes, or antibiotic residues in HWW were included. Meta-analyses for resistant bacteria and genes as well risk of bias using the Newcastle–Ottawa scale were conducted.

Results Out of 23 studies reviewed, resistant bacteria were reported in 39% (*E. coli*), 26% (*K. pneumoniae*), and 17% (*P. aeruginosa*), while 17 studies reported ARGs, with *blaTEM* (29%), *blaOXA- 48* (18%), *blaSHV* (18%), and *mecA* (18%) being the most common. Only 4% and 9% of studies focused on toxin genes and antibiotic residues, respectively. Meta-analysis showed pooled prevalence rates for resistant bacteria: *E. coli* 42.6% (95% CI: 26.7%–60.3%) and *K. pneumoniae* 32.1% (95% CI: 28.8%- 36.5%), and ARGs: *blaTEM* 76.0% (95% CI = 64.6%–84.6%) and *blaSHV* 59.3% (95% CI = 19.5%–89.8%).

Conclusion This systematic review highlights significant findings of high levels of ARGs and ARBs of public health concern in HWW in West Africa. This highlights the need to improve upon the monitoring of antibiotic resistance and treatment of HWW in West Africa.

Keywords Antibiotic resistance, Hospital wastewater, Antibiotic-resistant bacteria, Antibiotic resistance genes, Antibiotic residues, West Africa, Wastewater treatment, Horizontal gene transfer

Introduction

The rapid global rise in antibiotic resistance (AR) is significantly diminishing the effectiveness of many antibiotics, leading to higher mortality and morbidity rates, prolonged hospitalizations, and escalating healthcare costs [1]. According to Global Research on Antimicrobial Resistance (GRAM), one million people die each year from 1990 to 2021, attributed to AR [2]. It has been estimated that the burden of deaths by antibiotic resistance

*Correspondence:
Prince Hotor
photor001@st.ug.edu.gh
Eric S. Donkor
esampane-donkor@ug.edu.gh
[1] Department of Medical Microbiology, University of Ghana Medical School, 00233 Accra, Ghana

may increase to 10 million each year by 2050, if action is not taken now [3]. The available evidence indicates that the attributable cost of resistant infection ranges from -US$2,371.4 to +US$29,289.1 (adjusted for 2020 price) per patient episode; the mean excess length of stay (LoS) is 7.4 days (95% CI: 3.4–11.4), the odds ratios of mortality for resistant infection is 1.844 (95% CI: 1.187–2.865) and readmission is 1.492 (95% CI: 1.231–1.807) [4]. According to the systematic review and meta-analyses [4], the baseline for estimation of these cost were between resistant and their non-resistant counterpart. For example, in some studies, the cost of treating methicillin-resistant *Staphylococcus aureus* (MRSA) related illness is higher than non-resistant methicillin-susceptible *Staphylococcus aureus* (MSSA). Additionally, the early mortality of a some resistant-related illnesses in hospitals also accounts for low cost in treatment as compared to susceptible ones. Finally, the method of treatment and hospital facilities used in the treatment process varies from different health facility and could also affect the cost variation between susceptible and resistant-related illnesses [5]. In low- and middle-income regions such as West Africa, an estimated 1.85 million deaths in 2019 were associated (deaths where infection was a contributing factor) with infections, 524,000 were associated (resistance complicated treatment but may not have been the primary cause of death) with antibiotic resistance, and 125,000 were directly attributable (antibiotic resistance was the direct cause of death) to resistant infections [6]. Several factors have been implicated as contributory factors to the phenomenon, some of which include inappropriate use of antibiotics in human health and agriculture, genetic mutations, poor infection control in healthcare facilities, poor hygiene, and lapses in antimicrobial stewardship such as inconsistent implementation and enforcement [7–9]. Additionally, gaps in antibiotic resistance research, including limited surveillance data and insufficient development of novel antibiotics, further exacerbate the issue. Thus, addressing antibiotic-resistance from the "One Health" perspective, which considers the spread of antibiotic-resistant bacteria (ARB), antibiotic resistance genes (ARGs), and antibiotic residues (ARe) between and within humans, animals, and the environment, has been touted as an efficient approach to resolving the antibiotic resistance crisis [10]. In the environment, wastewater from municipalities, hospitals, treatment plants, and aquatic environments serve as reservoirs for large amounts of ARGs (including transposons), ARB, and ARes, as well as other chemical agents [11, 12]. These ecosystem components, along with physiochemical parameters such as temperature, pH, and redox conditions, create environments that facilitate the spread of antibiotic resistance. Factors such as horizontal gene transfer (HGT), selective pressure from microbial competition, and prolonged exposure to antibiotic residues further drive this process [13].

Globally, the hospital environment, where nosocomial infections are rife, is a hotspot for the transfer of antibiotic resistance properties between bacteria species [14]. Notably, hospital wastewater (HWW) across the globe is reported to contain ARGs, ARes, and a combination of ARB and non-ARB. This provides an environment for exchanging resistance genes and selectively pressuring bacteria, exacerbating the occurrence of resistant species [15]. Even though wastewater effluents from various hospital units are treated [16], most of these treatments are either ineffective or inefficient, leading to the transfer of these antibiotic-resistant components to aquatic ecosystems, such as rivers, streams and drainage systems, potentially endangering public health [17]. In West Africa, where the antibiotic resistance crisis is at its highest [18], HWW is a major source of antibiotic resistance transfer or infection in most West African countries [19]; thus, management should take care to prevent the spread of antibiotic resistant and antibiotic-resistant-related infections [20]. Additionally, research into hospital waste-related antibiotic-resistant, especially in the context of ARGs, ARB, antibiotic resistant elements, and ARes, is limited [21]. Similarly, appraisals of the effectiveness of HWW treatments in reducing the potential for infection and antibiotic resistance transfer from HWW are sparse [21].

Existing systematic reviews on antibiotic resistance (AR) in hospital wastewater (HWW) primarily focus on global or Africa-wide data, often limited to bacteria and/or resistance genes [21, 22]. Additionally, reviews on antibiotic residues are either systematic review protocols [23] or scoping reviews that explore their effects on adjacent water bodies (e.g., rivers, streams) [24]. However, AR in HWW results from complex interactions among antibiotic-resistant bacteria (ARBs), antibiotic resistance genes (ARGs), antibiotic residues (ARes), and physiochemical parameters. In West Africa, there is a lack of systematic reviews and meta-analyses that comprehensively examine AR in HWW, including ARBs, ARGs, and ARes—critical data needed to assess the state of AR research in HWW. This review aims to bridge this gap by providing a systematic overview and meta-analysis of antibiotic resistance in West African HWW. It will offer insights into the prevalence of AR in the region, evaluate the effectiveness of HWW treatment strategies, and highlight the need for expanded research. Ultimately, the findings will help inform policies and strategies for the effective treatment and management of HWW in West Africa.

Materials and methods

Search strategy

A systematic review without meta-analysis was conducted using the PRISMA guideline for reporting systematic reviews [25]. Individual studies spanning 1990–2024 were resourced from three databases (Scopus, PubMed, and Web of Science) on the 25 th of July 2024 and re-searched again on the 30 th of August 2024. The search queries together with the connectors used were "Antibiotic resistance bacteria" OR "Antibiotic resistance genes", OR "Antibiotic residues" AND "Hospital wastewater", AND West Africa countries ('Benin', OR 'Burkina Faso', OR 'Cape Verde', OR 'Côte d'Ivoire', OR 'Gambia', OR 'Ghana', OR 'Guinea', OR 'Guinea-Bissau', OR 'Liberia', OR 'Mali', OR 'Niger', OR 'Nigeria', OR 'Senegal', OR 'Sierra Leone', OR 'Togo'. The comprehensive details of the search strategy is provided in Table S31.

Study selection

To ensure that all the studies and records collected met the criteria essential for this systematic review, several inclusion and exclusion criteria were followed. For the inclusions, all original research work that was conducted in West Africa, with studies on either ARGs, ARB, or ARes in HWW, were selected. Additionally, studies whose full texts were accessible were the only ones used. Conversely, systematic and literature reviews, studies outside West Africa, studies that did not include HWW, and studies with no access to full-length articles were excluded. Additionally, studies that were not published in the English language were also excluded.

Quality assessment

This study was based on previously published research articles with observational evidence. To maintain the quality of the review, all duplicate articles were meticulously identified and removed. The abstracts of the selected articles were carefully examined and verified prior to analysis to ensure that only relevant and high-quality information was included. The quality assessment of the chosen articles was independently conducted by the authors.

Data extraction and analysis

Data was extracted from individual studies via a customized form, and a database was created specifically for this review in Microsoft Excel 2016. Additionally, the map was designed via the Python language. The form captured details such as the authors'names; study title; year of publication; country of study; hospital and unit where samples were collected; keywords; sampling methods; identified ARGs, ARB, and ARes; and identification methods used. For studies reporting findings in percentages, these were converted to whole numbers to ensure consistency across the data. To calculate pooled prevalence rates and the corresponding 95% confidence intervals (CIs), meta-analysis was done using Comprehensive meta-analysis software Version 3.3.070. Utilizing statistical techniques including the tau-squared test and I-squared statistic, the heterogeneity of the included papers was evaluated. A random-effects model was employed for the meta-analysis if significant heterogeneity was seen; otherwise, a fixed-effects model was utilized. Publication bias was assessed visually using funnel plots to detect asymmetry that could arise from non-publication of small or non-significant studies. This assessment of bias was only conducted for factors with three or more studies.

Evaluation of bias

Possible biases in individual studies were assessed by means of the Newcastle Ottawa Scale, which is used to assess non-randomized studies [26]. For cross-sectional studies, the NOS assesses selection, comparability, and outcome criteria. Each study was rated out of four stars for the choice of study populations, two stars for comparability of groups, and three stars for the verification of the chosen outcome of interest. The samples with six stars or above were classified as having low-risk biases, those with four to five stars as having moderate-risk bias, and those with below four stars as having high-risk biases. In using NOS, two individuals (P.H and ESD) independently assessed the individual studies, and disagreement in the assigned number of stars was discussed and reviewed. Details of quality assessment are shown in Supplementary Table S4.

Results

Search results

The total number of articles (4,016) from the various databases (Scopus, PubMed, and Web of Science) collected from using all the search queries were thoroughly screened via Mendeley (Version 1.19.8) by Elsevier to adequately identify and remove duplicates (2,606 articles removed), after which the remaining records were transferred to the free version of the Rayyan website (a systematic review and meta-analysis online website) [25]. The Rayyan system was used to further identify and resolve duplicates (347 articles) that were not picked up by Mendeley via a comparison percentage (89–100%) interval. After this, the remaining 1,063 articles were screened via Rayyan, and systematic reviews and other reviews (91 articles) were excluded. Additionally, 942 articles that were not conducted in West Africa were excluded. Four of the remaining 30 articles were subsequently removed because the full articles could not be assessed (after

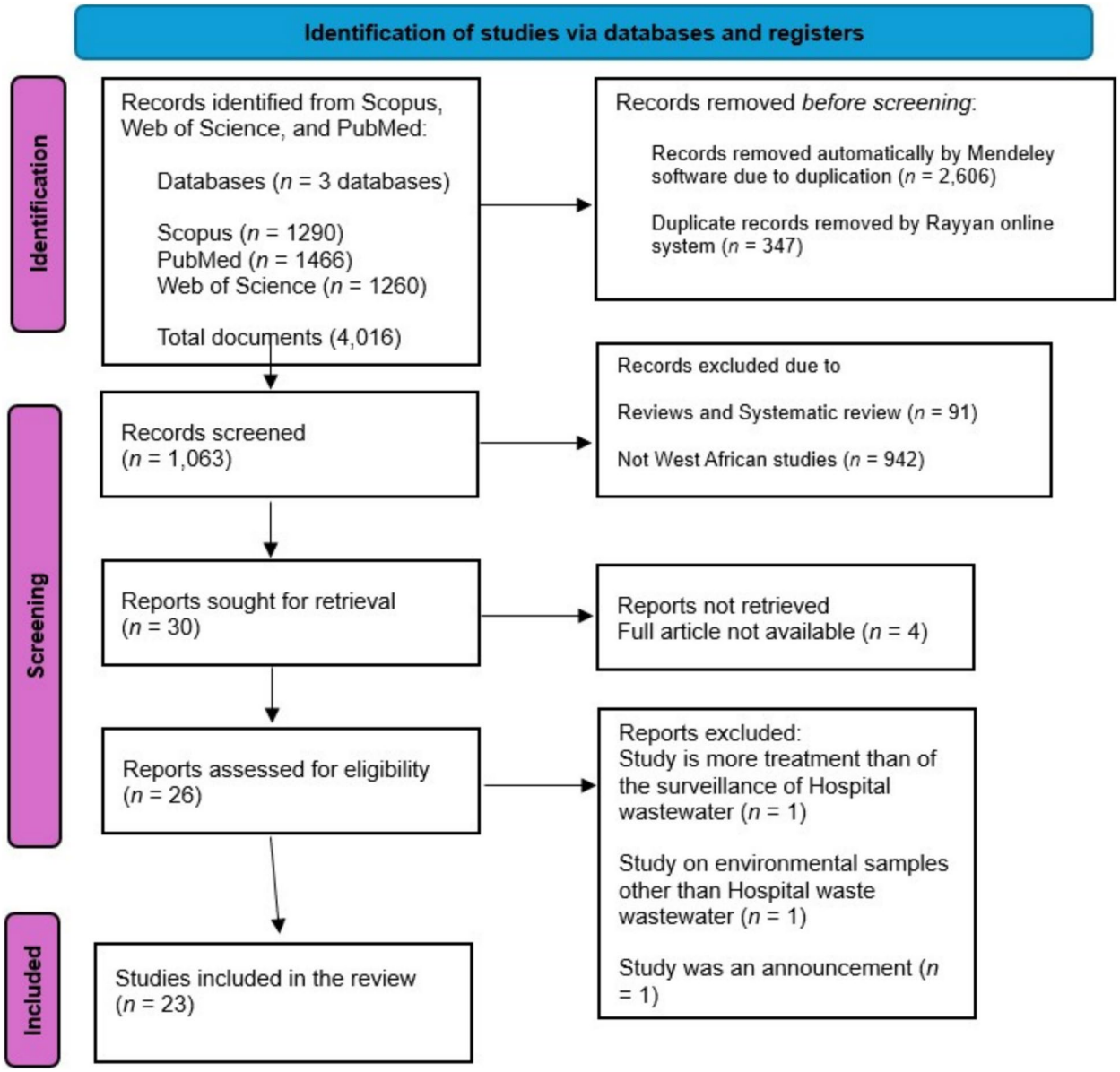

Fig. 1 Schematic representation of the search strategy for records and articles using the PRISMA criteria

searching through alternative websites such as ResearchGate). The titles and abstracts of the remaining 26 articles were further screened to ensure that they met the inclusion and exclusion criteria. One article was removed because it focused more on the treatment of HWW to remove microorganisms than on the identification of resistance in HWW. Finally, out of the 25 articles, one was on hospital-unrelated wastewater, and one study was an announcement. The remaining 23 articles were used for the systematic review. A schematic diagram of the study selection process is shown in Fig. 1.

Study characteristics

Figure 2 displays the West African map showing the number of studies conducted in the individual West African countries. Among the 23 studies used in this review, 13 were conducted in Nigeria [27–40], followed by Ghana (n = 4) [39, 41–44], Burkina Faso (n = 5) [45–49], and Benin (n = 1) [45], and within 2008–2024, a timeframe of 16 years. Among the 58 hospitals in West Africa where antimicrobial resistance in HWW was conducted, 17 are medical and health centres [32-34, 37, 47,-50], eight are university hospitals [27, 28, 31, 38, 46, 47], and five are teaching hospitals [34, 39, 41, 43, 44, 48].

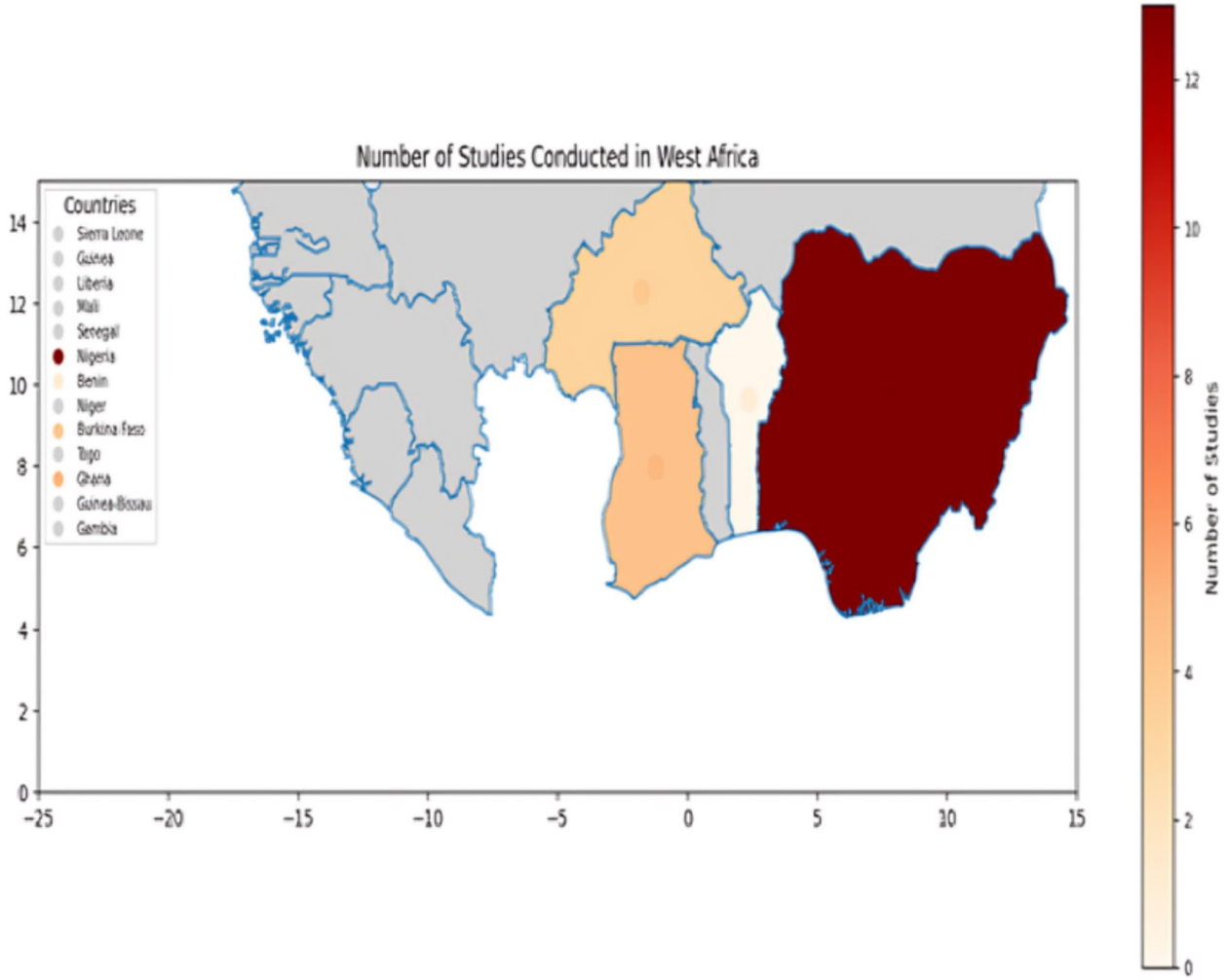

Fig. 2 West African countries that have several studies on antimicrobial resistance in HWW

About 26% (6/23) of the studies were conducted in teaching hospitals [34, 37, 39, 41, 43, 48], 35% (8/23) in university hospitals and university medical centres [27, 28, 30, 34, 46, 47], and 13% (3/23) in regional hospitals [33, 42, 48]. In 30% of the studies (7/23), the units from where samples were taken were not specified. In contrast, 9% (2/23) were from HWW collection units [32, 38], 13% (3/23) from HWWTP [27, 35, 39], 13% (3/23) from sewers and septic tanks [42, 45, 48], and the remaining units were laboratories [30, 34, 37, 47], sick bay [38], diagnostic centres [33], hospital washrooms [37], and maternity and child health units [43].

In terms of sampling approach, 26% (6/23) of the studies sampled biweekly [34, 38], and weekly [32, 37, 40], and [35], while in one (representing 4% of the studies) [38], sampling was done monthly. For some (3/23, 13%), the sampling was done daily, with some being consecutive days [28] while others selected days (Mondays and Thursdays) [43], and another twice daily [31]. On the other hand, there were some studies (3/23) (13%) in which samples were collected seasonally [27, 45], and [41]. In some studies (2/23) (9%), sampling was done at intervals of minutes [33] and [43] while about 35% of the remaining studies did not indicate sampling times. Details of the sampling technique and time is in Table S2.

In terms of sampling style, (2/23) 9% of the studies sampled randomly [47], while the remaining studies did not indicate their sampling style. Additionally, all studies with samples $\leq$50 HWW (6/23) were about 26% [31, 36, 41, 49], while about (5/23) 22% of the studies recorded to have taken over 50 samples [32, 43, 45, 47, 48].

Only (1/23, 4%) of the studies assessed the physicochemical properties of HWW. The measured parameters included pH, dissolved oxygen (DO), chemical oxygen demand (COD), and biological oxygen demand (BOD). pH ranged from 5.31 ± 0.62 (postnatal ward) to 8.93 ± 0.74 (children's ward). DO levels varied from 2.01 ± 0.02 mg/L (UNIMED Laundry) to 8.31 ± 0.11 mg/L (UNIMED

Water Source). COD values were between 5.11 ± 0.05 mg/L (UNIMED Water Source) and 931.44 ± 5.06 mg/L (UNIMED Laundry), while BOD ranged from 3.68 ± 0.07 mg/L (FUTA Water Source) to 11.73 ± 0.93 mg/L (UNIMED Laundry). In some cases, the BOD/COD ratio was below 0.03, suggesting low biodegradability of organic matter.

In order to identify bacteria and discover antibiotic resistance genes (ARGs), the included research used a combination of culture-based, phenotypic, and molecular approaches. Every study (23/23, 100%) isolated bacterium using culture-based methods, however the culture media and incubation conditions varied. In 9 out of 23 research, MacConkey Agar was the most commonly utilised medium. It was incubated for 18 to 24 h at 35 ± 2 °C. For the primary purpose of isolating Staphylococcus species, mannitol salt agar was placed on 7/23, 30%, and incubated for 24 h at 37 °C. In (3/23, 13%) of the investigations, chromogenic coliform agar was used, which is normally incubated for 24 h at 37 °C.

Additionally, specific culture media were used, such as Clostridium welchii agar supplemented with kanamycin in (1/23, 4%), which was incubated anaerobically for three days at 37 °C. For coliform differentiation, Eosin Methylene Blue (EMB) agar was utilised in (6/23, 26%) and incubated for 24 h at 37 °C. To identify haemolytic bacteria, blood agar was used in (5/23, 22%) and incubated at 37 °C for 24 h under 5% CO_2 conditions. Additional culture conditions included the use of Plate Count Agar for general bacterial enumeration in (1/23, 4%), incubated at 37 °C for 24 h, and CHROMagar for multidrug-resistant strains in (2/23, 9%), incubated at 37 °C for 24 to 48 h.

Bacterial identification was conducted using various biochemical and molecular techniques. Biochemical testing was performed in (5/23, 22%) of studies using API 20E and API 20 NE kits for Enterobacteriaceae and non-fermenting Gram-negative bacteria, respectively. MALDI-TOF–MS was used in (4/23, 17%), while Gram staining and biochemical tests were performed in (6/23, 26%) for preliminary bacterial characterization. Some studies further confirmed bacterial species using the API 20E identification system (3/23, 13%) and the API 20 NE system (2/23, 9%). The VITEK 2 automated system was used in (1/23, 4%) for rapid bacterial identification. Molecular methods were also employed for bacterial identification in (11/23, 48%) of studies. Conventional PCR targeting the 16S rRNA gene was conducted in (5/11, 45%), while Sanger sequencing was used in (3/11, 27%) for confirming bacterial species. Whole Genome Sequencing (WGS) was applied in (3/11, 27%) for complete bacterial genome characterization, enabling species-level identification and resistance gene detection.

In most studies antibiotic susceptibility testing (AST) was carried out and the Kirby-Bauer disk diffusion method was used by (16/23, 70%). Among these (14/16, 87%) followed CLSI guidelines while (2/16, 13%) was in accordance with EUCAST protocols. AST was performed on (11/16, 69%) of studies at 35 ± 2 °C for 18–24 h and (5/16, 31%) at 37 °C for 18–24 h. Minimum inhibitory concentration (MIC) values were determined by the Broth Microdilution (BMD) method in (2/23, 9%) of the studies. Moreover, the Double Disc Synergy Test (DDST) was used in (4/23, 17%) to eye for Extended Spectrum Beta-Lactamase (ESBL) producers of bacteria.

Studies were widely using molecular techniques to confirm ARGs positivity; in (18/23, 78%) studies, the positivity was confirmed by the use of PCR methods. Both conventional PCR and multiplex PCR were similarly used, in (9/18, 50%) of cases. In (13/23, 57%) of the studies, gel electrophoresis was used to visualize the gene. In (5/23, 22%), Sanger sequencing was used and in (3/23, 13%) WGS was applied. For high precision gene quantification, high precision gene quantification was done by quantitative PCR (2/23, 9%) and droplet digital PCR (ddPCR, 1/23, 4%). Table 1 provides a detailed information on the various culturing, gene and bacterial identification, and AST methods.

Risk of bias

The risk of bias was assessed to ascertain the quality of the studies used for the review. All the 23 studies were used for this risk of bias. The assessment was modified as done by Hassoun-Kheir et al. [52]. The overall assessment can be judged as good. Out of the 23 studies, 19 (82.6%) was judged to have low-risk, and 4 (17%) a moderate risk. When it comes to the area of selection, only (2/3) studies had (3-star rating) [45, 53], this due to the comparison made through samples taken from different countries. In the area of comparability none of the studies had a mark, because no confounding variables was controlled. Finally, in the area of outcome, (22/23) of studies got (3-star) except [28] that had (2/3), due non-assessment of bacteria/gene and co-factors.

Antibiotic susceptibility result

Out of the 23 studies included in this review, 25 antibiotics (for AST analyses) appearing in three or more papers were analyzed. The prevalence for these antibiotics were 52.17% each for ciprofloxacin and gentamicin, 47.83% for ceftazidime, 30.43% each for cefotaxime and imipenem, 26.09% each for tetracycline, ampicillin, cefepime, and ceftriaxone, 21.74% each for ertapenem, amoxicillin-clavulanate, amikacin, and erythromycin, 17.39% each for meropenem, cefoxitin, azithromycin, and cefuroxime, and 13.04% each for vancomycin, cefpodoxime,

Table 1 Summary of culturing, gene and bacterial identification, and AST methods

Summary of culture-based technique	Gene identification technique	Bacteria identification	AST method	Reference
thioglycolate medium at 37 °C for 3 days. Clostridium welchii agar plates + kanamycin at. 37 °C under anaerobic conditions and sheep blood agar	Multiplex PCR of genes	16S rRNA Sanger sequencing	EUCAST 2021 guidelines using the Kirby Buer disk diffusion, on Fastidious Anaerobe Agar plates containing 5% horse blood	[42]
Mannitol Salt agar	PCR amplification of genes and gel electrophoresis	Biochemical test	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[50]
MacConckey agar + Cefotaxime, at 35 ± 3 °C for 24 h	PCR amplification of genes and gel electrophoresis	API 20E (BioMerieux SA, Lyon, France) system	Using recommendations from CA-SFM 2019 with the Kirby Buer disk diffusion method on Mueller Hinton Agar	[46]
(eosin methylene blue (EMB), centrimide, MacConkey, salmonella-shigella, and nutritional agar),	PCR amplification of gene and gel electrophoresis	N/A	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[32]
nutrient agar medium + sulfadiazine, a sulfonamide, 35 ± 2 °C for 24 h	PCR amplification of genes and gel electrophoresis	Gram staining and biochemical test	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[36]
Chromocult® Coliform Agar, Plate count Agar Tri-phenyl Tetrazolium Chloride (TTC) agar supplemented with ceftriaxone, 37 ºC for 24 h.Confromation with Eosin Methylene Blue (EMB) agar,	Multiplex PCR of genes and sequencing	MALDI-TOF–MS and API 20E gallery (bioMerieux, Marcy-l'Etoile France)	Using recommendations from CA-SFM 2021 and EUCAST 2021 guidelines using the Kirby Buer disk diffusion	[47]
enriched within Bacto tryptic soy broth, Mannitol salt agar for 33ºC for 24 h. MRSA CHROMagar base at 37 ºC for 48 h	PCR amplification of genes and gel electrophoresis	16SrRNA PCR and sanger sequencing	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 37ºC 18–24 h	[40]
thiosulphate citrate bile salts sucrose (TCBS) at 37ºC for 48 h	N/A	PCR and sanger sequencing	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 37ºC 18–24 h	[29]
Mannitol Salt Agar (MSA) for isolating Staphylococcus aureus, Eosin Methylene Blue (EMB) for Escherichia coli, and MacConkey agar as a selective agent for Enterobacteriaceae at 37ºC for 24 h	Conventional PCR of the beta-lactamase gene and sequencing	Gram staining and biochemical test. 16SrRNA PCR and sanger sequencing	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 37ºC 18–24 h	[51]
Mesophilic aerobic flora (FAMT) was carried out using ISO 7218 (2007) standard procedures. Total	N/A	API 20 NE kit (bioMeéreux®, France) for Pseudomonas and API 20E kit (bioMeéreux®, France)	Using recommendations from CA-SFM 2019	[49]
N/A	N/A	N/A	N/A	[28]
N/A	Metagenomics and bioinformatic analysis	Metagenomics and bioinformatic analysis	N/A	[45]
MacConkey agar 35 ± 2 ºC for 18–24 h. double disc synergy test (DDST) for detecting ESBL and	Real Time PCR (Multiplex PCR)	API 20E identification kit (API System, France)	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[37]
MacConkey and blood agar for *Enterobacteriaceae* and *Streptococcus*, respectively for 37 °C for 24–48 h	N/A	Gram staining and biochemical test	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[33]

Table 1 (continued)

Summary of culture-based technique	Gene identification technique	Bacteria identification	AST method	Reference
MacConkey agar plates, with and without gentamicin, imipenem, amikacin,	Commercial PCR of RTmase and carbapenems genes, and whole genome sequencing	MALDI-TOF–MS	EUCAST and CLSI guidelines, Broth Microdilution (BMD) method	[44]
CHROMagar E. coli (CHROMagar, France) amended with cefotaxime, 35 ± 2 °C overnight. Confirmation of ESBL using double disc synergy test (DDST)	qPCR	API 20E (bioMérieux, Inc., Durham, NC) and Enterotube II (Becton, Dickinson, and Company) identification systems	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 35 ± 2 °C for 18–24 h	[35]
CHROMagar Acinetobacter media with CHROMagar MDR Supplement CR102 (CHROMagar, 37 °C for 24 h. after which was supplemented with cefotaxime for resistant *A. baumanii*	Whole genome sequencing and bioinformatic analysis	VITEK two automated system	VITEK two automated system using the CLSI guidelines using the AMR testing N281 cards	[27]
ESBL selective ChromAgar at 35°C for 24 h. for positive control Cystine Lactose Electrolyte Deficient (CLED) agar was used. Purification on Eosin Methylene blue. Confirmation test using double disc synergy test (DDST) using Mueller Hinton agar. AmpC-lactamase production using Mueller Hinton agar. immuno- nonchromatographic test for testing carbapenems	N/A	API20E system (Biomérieux, Marcy-l'Etoile, France)	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 37°C 18–24 h	[48]
Direct streaking samples on 5% sheep blood and chocolate agar at 37 °C for 24 h. under 5% CO_2. Also, Mannitol salt agar and MacConkey agar for 24 h. at 37°C. Confirmation using double-disk synergy test (DDST) for ESBL using Mueller Hinton agar	N/A	Gram stain, biochemical test, and MALDI-TOF–MS	CLSI, Kirby Buer disk diffusion Methods on Mueller Hinton agar, 37°C 18–24 h	[43]
Standard culturing on Chromogenic coliform agar at 37°C for 24 h, after subsequent culturing on eosin methylene blue for confirmation. Further confirmation using double-disc synergy test (DDST) for ESBL using Mueller Hinton agar	Whole genome sequencing and bioinformatic analysis	Gram stain and MALDI-TOF–MS	Using CLSI Kirby Buer disk diffusion method on Muellar Hinton agar, 37°C 18–24 h	[41]
N/A	droplet digital polymerase chain reaction (ddPCR) of TB resistant gene from water	N/A	N/A	[39]
Membrane filtration method on nutrient agar, and selective media (Salmonella Shigella agar, Eosin Methylene Blue agar, MacConkey agar and Mannitol Salt agar) at 37°C for 24 h	Conventional PCR of *mecA* from DNA and visualizing using gel	Sequencing of 16SrNA gene	Using CLSI guidelines, the Kirby Buer disk diffusion method, with Muller Hinton agar, 37°C 18–24 h	[31]

chloramphenicol, oxacillin, nalidixic acid, norfloxacin, Fosfomycin, and trimethoprim-sulfamethoxazole. Out of studies reviewed, the resistance rate of isolates to ciprofloxacin was in a range between (5.6–100.0%), gentamicin (8.0–100.0%), ceftazidime (12.5–100.0%), cefotaxime (10.0–100.0%), imipenem (4.0–100.0%), tetracycline (25.0–100.0%), ampicillin (63.2–100%), cefepime (12.5–100%), ceftriaxone (14.0–100.0%), ertapenem (3.4–100.0%), amoxicillin-clavulanate (20.0–100.0%), amikacin (2.25–21.10%), erythromycin (12.5–91.3%), meropenem (8.19–100.0%), cefoxitin (12.36–100.00%), azithromycin (32.00–68.69%), and cefuroxime (5.6–100.0%) (Table S2).

Antibiotic resistance bacteria, genes, and residues

Out of the 23 reviewed papers, (9/23) 39% reported the isolation or identification of *E. coli* followed by *K. pneumoniae* (6/23) 26%, and *P. aeruginosa* (4/23) 17%. *Enterobacter cloacae* were identified in (3/23) 13% reviewed, with (2/3) 9% of papers indicating the identification of *S. epidermis, S. aureus, Citrobacter spp*., and *Bacillus cereus*. The remainder (1/23) 4% includes *Shigella spp., Serratia spp., Salmonella spp., Proteus spp*., and *R. rettgeri*.

Similarly, (6/23) 26% of the reviewed papers did not record the isolation or identification of ARGs. From the remainder (17/23), (11/17) 65% were beta-lactamase genes, (3/17) 17% each were methicillin resistance and aminoglycoside resistance genes, and (2/17) 12% each were tetracycline resistance and sulphonamide resistance genes. Other classes of ARGs reported (1/17) 6% each includes, colistin, macrolide, trimethoprim, mycobacterial, quinolone, chloramphenicol, disinfectant, and others (Unknown classifications) (Table S3). Of these, only (1/23) 4% reported the identification of ARGs directly from the HWW [45].

From these reported ARGs, three of them: *blaTEM* (5/17) 29%, *blaOXA- 48* (3/17) 18%, *blaSHV* (3/17) 18%, and *mecA* (3/17) 18% were reported by ≥3 reviewed papers. The others reported by two reviewed papers include *blaCMY- 1*, *blaCTX-M- 1*, *blaCTX-M- 15*, *blaCTX-M- 25*, *blaCTX-M- 8*, *blaCTX-M- 9*, *blaDIM- 1*, *blaIMP*, *blaNDM*, *blaOXA- 1*, *blaOXA- 58*, *blaVIM*, *su1*, *tetA*, and *tetB* (Table S3). Additionally, only one study [42] reported on the isolation and identification of toxin genes: *plc*, *cpe*, *becA/B—Beta2*, *cpb*, *etx*, and *itx*. In terms of genes present in bacteris isolated, 19 of the entire *E.coli* isolated possessed *blaTEM* gene, while 14 isolates possessed *blaCTX- 25, blaCTX-M8,* and *blaCTX-M2* as reported by [38]. Similarly, 8 of the EBSL isolates, harbored *blaTEM, blaCTX-M- 2, blaCTX-M- 8 blaCTX-M-25, All had blaCTX-M- 1 and blaCTX-M- 9* [35].

Altogether, only (2/23) 9% studies reported the detection and identification of antibiotic residues directly from HWW [28, 49], these residues include, amoxicillin, chloramphenicol ceftriaxone, azithromycin, ciprofloxacin, clarithromycin, erythromycin, norfloxacin, ofloxacin, oxytetracycline, sulfamethazine, sulfadoxine, sulfamethazine, sulfamethoxazole, tetracycline, thiamphenicol, trimethoprimria.

Meta-analyses of resistant bacteria and resistance genes

Meta-analysis on the resistant bacteria was conducted for bacteria reported by two or more papers. These resistant bacteria were *E. coli, K. pneumoniae*, *P. aeruginosa, Enterobacter cloacae*, *S. epidermis*, *S. aureus,* and *B. cereus* (Table S5–S11). Even though (9/23) 39.1% of studies reported the isolation and detection of *E. coli,* only 44.4% were eligible for the meta-analysis. The ineligible studies [32, 35, 41, 54], and [38] were not included because for some, the total isolates were not provided in both the paper and supplementary materials, while for others, the total number of isolates was the same as the number of *E. coli* (Table S5).

Similarly, (6/23) 26.1% of studies reported the identification of *K. pneumoniae.* However, only (4/6) 66.7% were eligible for the meta-analysis [43, 46, 48] and [47]. Ineligible studies [54] and [32], were excluded because the total number of isolates was not provided (Table S6).

Altogether, 50% (2/4) of studies that reported resistant *P. aeruginosa* were included in the meta-analysis [36] and [33], while the remaining studies [54] and [32] were excluded because full data on the total number of *P. aeruginosa* and number of *P. aeruginosa* was not included (Table S7). Studies included in the meta-analysis, reporting on *Enterobacter cloacae* (2/3) 66.7% [43] and [37], *S. epidermis* (2/2) 100% [30] and [40], *S. aureus* (2/2) 100% [33] and [40], and *Bacillus cereus* (2/2) 100% [33] and [55]. One of the studies on *Enterobacter cloacae* [32] was excluded because number of *cloacae* was not indicated (Table S8–S11).

The pooled prevalence of *E. coli* in the ($n = 4$) studies was 42.6% (95% CI: 26.7%–60.3%) (Figure S2), *K. pneumoniae* ($n = 4$) 32.1% (95% Cl: 28.8%–36.5%) (Figure S4), *P. aeruginosa* ($n = 2$) 23.7% (95% CI = 8.0%–52.8%) (Figure S5), *Enterobacter cloacae* ($n = 2$) 2.9% (95% CI = 0.6%–12.4%) (Figure S6), *S. epidermis* ($n = 2$) 19.1% (95% CI = 2.3%–70.6%) (Figure S7), *S. aureus* ($n = 2$) 19.5% (95% CI = 0.8%–88.2%) (Figure S8), and *B. cereus* ($n = 2$) 18.2% (95% CI = 6.9%–39.8%) (Figure S9).Table 2 summarizes the pool prevalence of the resistant bacteria isolated from HWW among the studies.

Like the resistant bacteria, ARGs reported in two or more reviewed studies were used for the meta-analyses. These 19 ARGs met the criteria for inclusion: *blaTEM*, *blaOXA- 48*, *blaSHV*, *mecA*, *blaCMY- 1*, *blaCTX-M- 1*, *blaCTX-M- 15*, *blaCTX-M- 25*, *blaCTX-M- 8*, *blaCTX-M- 9*, *blaDIM- 1*, *blaIMP*, *blaNDM*, *blaOXA- 1*,

Table 2 Summary of the pool prevalence of isolated resistant bacteria from HWW included in the meta-analysis

Resistant bacteria	No. of papers	No. of bacteria isolated	Pooled prevalence (%)	I^2 (%)	*p*-value
E. coli	4	308	42.6	94.37	< 0.001
K. pneumoniae	4	250	32.1	96.49	< 0.001
P. aeruginosa	2	10	23.7	67.72	0.078
Enterobacter cloacae	2	6	2.9	52.97	0.145
S. epidermis	2	29	19.1	94.87	< 0.001
S. aureus	2	45	19.5	95.33	< 0.001
B. cereus	2	12	18.2	68.86	0.073

NB: The *p*-value associated with the pooled prevalence indicates whether the estimated prevalence is significantly different from zero at the 95% confidence level

A *p*-value ≤ 0.05 suggests that the pooled prevalence is statistically significant

blaOXA- 58, *blaVIM*, *Sul- 1*, *TetA*, *and TetB* (Table S11–S29). However, due to incompleteness of data regarding total number of isolates and number of isolates harbouring a particular gene in some studies, some were further excluded (i.e. *blaCTX-M- 15*, *blaDIM- 1*, *blaIMP*, *blaNDM*, *blaOXA- 58*, and *blaVIM).*

Out of the 13 ARGs eligible for meta-analysis, some studies were excluded. Only (2/3) of studies reporting the presence of *blaOXA- 48* were used for the meta-analysis [47] and [46]. Similarly, another gene with only (2/3) studies used for meta-analysis was *mecA* [30] and [31]. The exclusion of these studies is due to unavailability of either complete data on total isolates or number of isolates harboring such genes.

The pooled prevalences of the ARGs were *blaTEM* (n= 5) 76.0% (95% CI =64.6%–84.6%) (Figure S11), *blaOXA- 48* (n= 2) 12.0% (95% CI =5.8%–23.1%) (Figure S12), *blaSHV* (n= 3) 59.3% (95% CI =19.5%–89.8%) (Figure S14), *mecA* (n= 2) 32.1% (95% CI =14.2%–57.4%) (Figure S15), *blaCMY- 1* (n= 2) 17.7% (95% CI =8.1%–34.4%) (Figure S16), *blaCTX-M- 1* (n= 2) 97.2% (95% CI =82.8%–99.6%) (Figure S17), *blaCTX-M- 25* (n= 2) 61.0% (95% CI =44.4%–75.4%) (Figure S18), *blaCTX-M- 8* (n= 2) 97.2% (95% CI =82.8%–99.6%) (Figure S19), *blaCTX-M- 9* (n= 2) 97.2% (95% CI =82.8%–99%) (Figure S20), *blaOXA- 1* (n= 2) 45.7% (95% CI =7.4%–89.9%) (Figure S21), *sul- 1* (n= 2) 12.8% (95% CI =3.2%–39.5%) (Figure S22), *Tet A* (n= 2) 69.1% (95% CI =7.6%–98.4%) (Figure S23), and *Tet B* (n= 2) 30.8% (95% CI =12.0%–59.2%) (Figure S24). Table 3 summarises the ARG pooled prevalences.

Table 3 Summary of the pooled prevalence of ARGs included in the meta-analysis

ARGs	No. of papers	No. of isolates	Pooled prevalence (%)	I^2 (%)	p-value
blaTEM	5	98	76.0	33.65	0.197
blaOXA- 48	2	7	12.0	0	0.496
blaSHV	3	43	89.6	89.65	< 0.001
mecA	2	13	32.1	57.49	0.125
blaCMY- 1	2	6	17.7	0	0.359
blaCTX-M- 1	2	36	97.2	0	0.740
blaCTX-M- 25	2	22	61.0	0	0.629
blaCTX-M- 8	2	36	97.2	0	0.740
blaCTX-M- 9	2	36	97.2	0	0.740
blaOXA- 1	2	24	45.7	77.48	0.035
sul- 1	2	2	12.8	0	0.699
Tet A	2	9	69.1	75.07	0.045
Tet B	2	4	30.8	0	0.853

NB: The *p*-value associated with the pooled prevalence indicates whether the estimated prevalence is significantly different from zero at the 95% confidence level

A *p*-value ≤ 0.05 suggests that the pooled prevalence is statistically significant

Discussion

The objective of this systematic review and meta-analysis was to describe the status of antibacterial resistance comprehensively in HWW in West Africa, regarding the presence of resistant bacteria, resistance genes, and detection of antibiotic residues. Although the antibiotic resistance crisis is at its highest in the region [56], fundamental work on antibacterial resistance prevalence in HWW remains scarce, with only 23 eligible articles published between 1990 and 2024. This demonstrates a research gap, which encompasses a larger problem of poor monitoring and lack of proper structures of mitigating ABR threats in HWW. The few studies [4] that were excluded were due inability to get the full articles. This represents approximately 13.3% of the total studies reviewed, which may introduce a limitation by potentially excluding relevant findings. The missing data could impact the comprehensiveness of our analysis, particularly if these studies contained unique insights or region-specific trends. However, the remaining articles provide a broad and representative overview of the topic. Additionally, most of the eligible studies emanated from Nigeria,

while just a few were from Ghana, Benin, and Burkina Faso may either suggest presence of available funding or a high interest in HWW-related antibiotic resistance in that country. Additionally, that most of the sampling conducted in HWWTPs at medical centres and teaching hospitals is very laudable as most of these centres are hotspots for serious health related cases.

In the included studies, culture-dependent techniques, PCR, and metagenomic analysis were used in detection and analysis. The culture-based methods, including use of selective media, biochemical tests, and antibiotic susceptibility tests, were most frequently used, despite their drawbacks, such as inability to isolate non-culturable bacteria and detect new resistance genes. Bacterial PCR and whole-genome sequencing made the detection of resistance genes such as *blaTEM, blaCTX-M*, and *blaSHV* more effective. However, metagenomics, which is a more comprehensive approach to identifying the bacteria and the low-density resistance genes, was used in only two of the 23 studies reviewed. This underscores the need to increase the application of metagenomics in West Africa to better understand the looming antibiotic resistance profiles and the resistome of HWW in the region.

The high prevalence of *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* in HWW is a public health threat due to their potential to harbour and disseminate antibiotic resistance genes, increasing the risk of treatment failures in clinical settings. These pathogens can persist in the environment, contaminate water sources, and facilitate the spread of multidrug-resistant infections, posing serious challenges to infection control and public health management. These bacteria can cause a range of nosocomial infections including bloodstream, pneumonia and urinary tract infections and most of these infections are often resistant to multiple drugs. For example, *E. coli* is associated with severe diseases including septicaemia and urinary tract infections and produces just a low virulence [21] while *K. pneumoniae* is related to a high infection density acquired in hospitals with appreciable rates of morbidity and mortality [57]. Along the same line, *P. aeruginosa* is the common cause of bacteraemia and sepsis in the hospital setting, especially in immunocompromised patients, and is innately resistant to multiple antibiotics making treatment challenging [58]. The pooled prevalence of *E. coli* in HWW 42.6% (95% CI: 26.7%–60.3%) is quite high compared to a HWW in Switzerland (34.1%) [59], but lower than a study conducted in Algeria in a HWW (89.6%) [60]. In terms of different reservoirs, the prevalence is higher compared to that in Ethiopian animal food 15% (95% CI =13%–17%) [61], and lower in a swimming pool in Bangladesh (33.3%) [62]. This varying prevalence of *E. coli* across different regions and reservoirs sterns from conditions or source of such reservoirs, methods used in detection, as well as the level of treatments of HWW in the hospitals.

Research has found unequal amounts of microbial contamination in drinking water sources in Ghana. According to [63], 13.3% packaged drinking water samples were contaminated with *Escherichia coli* which denoted the faecal contamination and health risks. Like so, [64] found E. coli and *Pseudomonas aeruginosa* in sachet packaged drinking water with microbial loads well beyond recommended safety levels. The study went on to identify *Enterobacter aerogenes, Klebsiella spp*. and *Proteus vulgaris*, in addition to poor water quality management.

Untreated or inadequately treated HWW discharge is a major contributor to the contamination from ARes, ARGs, and ARBs. As discussed by [65], the risk of pathogenic bacteria, ARes, or multidrug resistant organism contaminating drinking water supplies in the presence of HWW is high. These results underscore the importance of developing better discharge from HWW services and monitoring drinking water sources routinely for microbial contamination to protect public health.

The prevalence of *blaTEM*, *blaOXA- 48*, *blaSHV*, and *mecA* were 29%, 18%, 18%, and 18%, respectively. The presence of *blaTEM* gene in pathogen or HWW, depicts the high possibility or presence of beta-lactamase enzymes conferring resistance to penicillin [66]. Similarly, *blaOXA- 48* gene found in several reservoirs including HWW codes for carbapenemase enzymes that render carbapenems ineffective, important drugs used in fighting multidrug-resistant infections [67]. The *blaSHV* gene encodes for beta-lactamase that display resistance to several beta-lactam antibiotics including penicillin and cephalosporins [68]. Finally, the *mecA* gene detected is responsible for methicillin resistant in *S. aureus*, thus increasing the spread of MRSA infection [69]. The pooled prevalence of *blaTEM* 76.0% (95% CI =64.6%– 84.6%) in HWW is higher than that of an urban wastewater effluent in South Africa (56.4%) [70], global wastewater 49.88% (95% CI, 35.01%–64.76%) [71], and Indonesia HWW (0.4%). The higher prevalence of *blaTEM* compared to the above countries and region, shows that, West African HWW is highly polluted with pathogens harbouring the gene or they are highly concentrated in the HWW and thus, requires an efficient and effective treatment regimen for public health safety and to prevent further gene transfer in the HWW.

The few studies (about 9%) that worked on antibiotic residue shows great limitations in the studies conducted in West Africa. This could be from lack of facilities or equipment such as HPLC, LC–MS which are useful in elucidating the presence and concentrations of antibiotic residues in HWW [72–74]. According to literature,

a better understanding of resistance transfer in wastewater comes about from the knowledge in the presence of antibiotic residue, antibiotic ARGs, and the presence of antibiotic resistant and non-resistant bacteria [75, 76]. By this logic, conducting ABR in HWW considering all these three main components will generate a comprehensive data to elucidate the mechanisms or nature of resistance transfer.

The high prevalence of resistant bacteria such as *E. coli* and *P. aeruginosa* in HWW and within drinking water sources throughout most of West Africa establishes a clear need for effective measures to preventing pathogen exposure. This is one important strategy to adopt, which is that staff handling HWW (and its treatment) should do so while wearing the appropriate personal protective equipment. Moreover, HWW should be properly and effectively treated prior to discharge into the nearby water bodies to reduce the risks of contamination.

Moreover, HWW treatment and patient facilities should be physically separated to minimize risk of transmission. In addition, hospital management should impose strict control on quality assurance policies to see to it that the levels of resistant genes, antibiotic residues and bacteria before and after treatment remain at safe standard. If not observed, it might lead to biotic contamination of the water bodies under use for mankind for domestic, agricultural and industrial purposes, thereby raising the risk of human exposure to antibiotic resistant pathogens.

One major strength of this systematic review is that it is the first to be conducted on ARGs, ARB, and antibiotic residues in HWW systems in West Africa, providing robust insights on antimicrobial resistance in an understudied antibiotic-resistance hotspot in the region. However, only the existing data were analysed for the purposes of this research. For example, some articles could not be incorporated because their full texts were not accessible. Also, some of the cross-sectional studies were omitted from the meta-analysis component of the study, owing to missing data, which might have impacted the overall prevalence. The disparities in the methods of detection and identification of the ARB and ARGs, along with the heterogeneity of sampling strategies, may have introduced variations in the type of bacteria and genes detected in the outcome underlying the quantification. Another drawback is the scarcity of information about antibiotic residues in HWW, which inhibit proper evaluation of transmission patterns. As a result, meta-analysis could not be done on the available antibiotic residues data.

Challenges in hospital wastewater management and antibiotic resistance in West Africa

In West Africa, the presence of antibiotic-resistant bacteria like *Escherichia coli* and *Pseudomonas aeruginosa* in HWW raises important public health and environmental issues. The inadequate treatment of hospital effluents in the region is one of the major challenges because resistant bacteria and ARes get into other sources of water such as reservoirs used for irrigation purposes [77]. For instance, many healthcare facilities lack adequate wastewater treatment infrastructure causing effluents, which are either untreated or partially treated to be discharged to rivers and groundwater [78]. In addition, overuse and misuse of antibiotics in hospitals feeds the buildup of resistant strains in the wastewater, complicating efforts to control the rise of antimicrobial resistance (AMR).

Another challenge is that there is no regular monitoring and surveillance of HWW [79]. In many hospitals, there are no protocols in place to test microbial loads and resistance patterns before wastewater is discharged [79]. By not monitoring this gap, the resistant pathogens continue to spread into the environment without intervention. Additionally, the persistence of bacterial contamination in hospital water systems is influenced by inconsistent disinfection practices. However, in some facilities, water disinfection is not performed routinely, which exposes them to nosocomial infection and the contamination of seemingly nearby water sources. There is also a further concern around the limited awareness that healthcare workers have regarding the risk of HWW contamination [80]. Often, doctors and hospital staff do not get routinely informed about the levels of microbial contamination so they cannot take preventative measures to limit exposure.

Recommendations for improving hospital wastewater surveillance and treatment

To tackle the problem of HWW contamination, improved surveillance and wastewater treatment strategies need to be practised. All hospitals should develop standardized testing protocols to detect the levels of bacterial contamination, antibiotic residues and resistance genes in wastewater before and immediately following the treatment. In addition, the advanced wastewater treatment technologies such as membrane filtration, ozonation, or electrochemical disinfection could reduce very substantially the loads of microorganisms before effluents are discharged to the water bodies.

HWW treatment is also important to stop the increase of resistant bacteria caused by patients returning to hospitals if they have a drug treatment. Enforcing strict guidelines for antibiotic prescription, promoting the use of antibiotics only for necessary situations, and promotion of alternative antibiotics that are not broad spectrum are ways by which this can be done. Further efforts to AMR control will include training health care professionals of rational use antibiotic and risk of HWW contamination.

Additionally, hospital water systems in the hospital ought to be regularly disinfected to prevent persistent or spread of bacteria. Establishment of a standardized schedule of disinfection in facilities and physical separation of patient care areas from HWW treatment plants is recommended to reduce exposure risk. In addition, governments must also enforce the strict environmental regulations to compel hospitals to follow the wastewater treatment criteria before the discharging of effluent.

Conclusions

The study highlights a desire to continue closely tracking HWW in West Africa to safeguard the health of patients and others in and around hospitals. *E. coli, K. pneumoniae, and P. aeruginosa* as well as the resistance genes *blaTEM, blaOXA- 48, blaSHV,* and *mecA* were identified to point to heightened public health concerns concerning the discharge of the resistant organisms into the nearby water bodies. Hence, the treatment procedures require reconsideration and enhancement of the HWW treatment plans to eliminate resistant bacteria, genes, and antibiotics. In turn, it is necessary to expand the surveillance efforts concerning antibiotic residue if there is a desire to build a vast set of data that would allow managing antibiotic residue levels and the corresponding effects on orientations for management practices and the formation of public health policies.

Abbreviations

AR	Antibiotic Resistance
ABR	Antimicrobial Resistance
ARB	Antibiotic-Resistant Bacteria
ARGs	Antibiotic Resistance Genes
ARes	Antibiotic Residues
HGT	Horizontal Gene Transfer
HWW	Hospital Wastewater
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle Ottawa Scale
HWWTP	Hospital Wastewater Treatment Plant
CI	Confidence Interval

Supplementary Information

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Supplementary Material 1

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Authors' contributions

P.H and E.S.D. conceptualize the idea, P.H and E.S.D. designed the methodology of the review, while software usage was done by P.H and E.S.D., All authors were involved in the validation process. Formal analysis was performed by P.H and E.S.D. Data curation was done by P.H and E.S.D., writing—original draft preparation was by P.H., writing—review and editing was performed by P.H, E.S.D, and F.C.N.K., visualization was P.H., funding acquisition was by E.S.D. All authors have read and agreed to the published version of the manuscript."

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Data availability

Not applicable, however supplementary data is available.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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