



Review

Antimicrobial resistance in West Africa: a systematic review and meta-analysis



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ABSTRACT

Growing data suggest that antimicrobial-resistant bacterial infections are common in low- and middle-income countries. This review summarises the microbiology of key bacterial syndromes encountered in West Africa and estimates the prevalence of antimicrobial resistance (AMR) that could compromise first-line empirical treatment. We systematically searched for studies reporting on the epidemiology of bacterial infection and prevalence of AMR in West Africa within key clinical syndromes. Within each syndrome, the pooled proportion and 95% confidence interval were calculated for each pathogen–antibiotic pair using random-effects models. Among 281 full-text articles reviewed, 120 met the eligibility criteria. The majority of studies originated from Nigeria (70; 58.3%), Ghana (15; 12.5%) and Senegal (15; 12.5%). Overall, 43 studies (35.8%) focused on urinary tract infections (UTI), 38 (31.7%) on bloodstream infections (BSI), 27 (22.5%) on meningitis, 7 (5.8%) on diarrhoea and 5 (4.2%) on pneumonia. Children comprised the majority of subjects. Studies of UTI reported moderate to high rates of AMR to commonly used antibiotics including evidence of the emergence of cephalosporin resistance. We found moderate rates of AMR among common bloodstream pathogens to typical first-line antibiotics including ampicillin, cotrimoxazole, gentamicin and amoxicillin/clavulanate. Among *S. pneumoniae* strains isolated in patients with meningitis, levels of penicillin resistance were low to moderate with no significant resistance noted to ceftriaxone or cefotaxime. AMR was common in this region, particularly in hospitalized patients with BSI and both outpatient and hospitalized patients with UTI. This raises concern given the limited diagnostic capability and second-line treatment options in the public sector in West Africa.

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1. Introduction

Antimicrobial resistance (AMR) has become a significant threat to the prevention and treatment of bacterial infections globally [1]. Importantly, in low- and middle-income countries, the potential for AMR to lead to increased morbidity and mortality may be greater given the higher burden of bacterial illness in low-income countries, delayed presentation, weaker access to diagnostics (particularly microbiology) and the reduced availability of second-line antibiotics [2].

One critical aspect to the global response to AMR is surveillance. However, according to a 2014 report by the World Health

Organization (WHO), the WHO Africa region has one of the largest gaps in data on the prevalence of AMR [2] as a consequence of limited laboratory capacity and surveillance networks. An external quality assessment reported several deficits in antimicrobial susceptibility testing in many African countries [3]. With limited information available on AMR, health departments and humanitarian actors providing health care in this region lack practical information on how AMR may compromise first-line empirical treatments of common bacterial infections.

Recent efforts to define the map of AMR in sub-Saharan Africa are not easily translatable into action. For example, a 2014 WHO report compiled existing data on AMR focusing on certain bacteria–antimicrobial drug combinations thought to be of public health importance [2]. However, physicians and other prescribers, particularly in the absence of microbiology, recognise and manage clinical syndromes rather than specific bacteria. Therefore, the current analysis aims to evaluate AMR in the West Africa region by clinical syndrome. For the treatment of syndromes, a better

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understanding of the epidemiology of the most prevalent bacterial infections of public health importance may allow improved decision-making on empirical (first-line) antibiotic strategies. Thus, a systematic review was performed to describe the aetiology and AMR patterns within key bacterial syndromes encountered in this region. The five bacterial diseases focused on were pneumonia, meningitis, urinary tract infection (UTI), bloodstream infection (BSI) and diarrhoea. These are common and serious bacterial infections of high public health importance in West Africa.

2. Methods

The systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [4]. Based on the United Nations geoscheme, the region of West Africa includes the countries of Benin, Burkina Faso, Cape Verde, Ivory Coast, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Senegal, Sierra Leone and Togo [5]. Relevant literature was identified from EMBASE and PubMed databases using specific search terms of key bacterial pathogens and common serious clinical syndromes combined with the 17 countries in West Africa (Fig. 1).

2.1. Inclusion criteria and exclusions

A systematic review was undertaken to identify studies carried out in West Africa published between 1 January 1990 and 31 December 2012 that describe bacterial causes of infection and associated AMR. English and French language studies were included. Publications were reviewed by one author and were discussed with at least two authors to determine eligibility. Only published literature that provided original data on AMR in adult and paediatric populations were included. Studies focusing on five syndromes (pneumonia, meningitis, UTI, BSI and diarrhoea) were included. Studies on burn infections, sexually transmitted infections, tuberculosis, non-bacterial pathogens and outbreak investigations were not included. To minimise bias, studies that

reported data for <10 patients or that used convenience sampling were excluded. Based on National Committee for Clinical Laboratory Standards (NCCLS) [currently the Clinical and Laboratory Standards Institute (CLSI)] recommendations, studies reporting on <10 isolates of a particular pathogen were excluded [6]. Studies reporting aggregated data were also excluded. For example, studies with the methodology of aggregating resistance rates in a large category such as ‘Gram-negative organisms’ were excluded. Also, if clinical presentations were aggregated (e.g. combining patients with urinary or gastrointestinal symptoms) or if studies reported on a mixture of specimen types (e.g. urine and blood specimens aggregated), these studies were excluded. Studies reporting on specimens outside the scope of the review (e.g. rectal swabs) and studies on healthy patient populations with no symptoms were also excluded.

A standardised tool was developed to collect information from investigations, including study characteristics, bacteria isolated and AMR rates. Retrospective studies emerging from microbiology laboratories reporting results of culture and sensitivity testing for patients with syndromes of interest were categorised as laboratory studies. Prospective or retrospective studies from hospitals or clinics that included patients who fit a particular syndrome (e.g. meningitis) were considered clinical studies (including case-series studies of >10 patients). Surveillance studies were studies focused on a particular pathogen carried out by reference laboratories or a network of sentinel laboratories [7].

For each of the five common syndromes included in this review, the analysis focused on specific pathogens [7]: (i) UTI, *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* from urine; (ii) BSIs, *E. coli*, *Haemophilus influenzae*, *Klebsiella* spp., non-typhoidal *Salmonella* (NTS), *Salmonella enterica* serovar Typhi, *Staphylococcus aureus* and *Streptococcus pneumoniae* from blood; (iii) pneumonia, *H. influenzae*, *S. aureus* and *S. pneumoniae* from cerebrospinal fluid (CSF), blood, lung aspirates, sputum, bronchoalveolar liquid or pleural fluid; (iv) meningitis, *H. influenzae*, *Neisseria meningitidis* and *S. pneumoniae* from blood or CSF; and (v) diarrhoea, *E. coli*, *Shigella dysenteriae* and *Vibrio cholerae* from faeces. For each of the key

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(extended-spectrum beta-lactamase OR beta-lactamase OR ESBL OR antimicrobial resistance* OR antibiotic resistance* OR multiresistant OR multidrug-resistant OR drug resistance OR antibacterial OR antibiotic OR antimicrobial OR bacterial resistance OR Enterobacteriaceae OR gram-negative OR gram-positive) AND (*Escherichia coli* OR *E. coli* OR *Klebsiella* OR *Salmonella* OR typhoid OR Enterobacter OR *Staphylococcus aureus* OR methicillin-resistant *Staphylococcus aureus* OR *Streptococcus pneumoniae* OR *Pseudomonas* OR *Pneumococcus* OR *Shigella* OR *cholerae* OR *cholera* OR *Haemophilus* OR *N. meningitidis* OR *Neisseria*) AND (urinary tract infection OR UTI OR bloodstream infection OR bacteremia OR bacteraemia OR sepsis OR septicemia OR septicaemia OR diarrhea OR diarrhoea OR acute gastrointestinal infection OR meningitis OR cerebrospinal meningitis OR CSF OR pneumonia OR acute respiratory infection) AND (Individual Country or Western Africa)

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'extended-spectrum beta-lactamase' OR 'beta-lactamase' OR 'esbl enterobacteriaceae' OR 'antibiotic resistance' OR 'Multidrug resistance' OR 'drug resistance' OR 'antiinfective agent' OR 'antibiotic agent' OR Enterobacteriaceae OR 'gram-negative bacterium' OR 'gram-positive bacterium' AND '*Escherichia coli*' OR *Klebsiella* OR *Salmonella* OR '*Salmonella typhi*' OR Enterobacter OR '*Staphylococcus aureus*' OR '*methicillin-resistant Staphylococcus aureus*' OR '*Streptococcus pneumoniae*' OR '*Pseudomonas aeruginosa*' OR *Shigella* OR '*Shigella dysenteriae*' OR *cholera* OR *Haemophilus* OR '*Neisseria meningitidis*' OR *Neisseria* AND 'urinary tract infection' OR 'bloodstream infection' OR bacteremia OR sepsis OR septicemia OR diarrhea OR 'acute gastroenteritis' OR meningitis OR 'cerebrospinal meningitis' OR 'cerebrospinal fluid' OR pneumonia OR 'respiratory tract infection' AND (Individual Country or Western Africa)

Fig. 1. Search terms used to identify relevant literature from the EMBASE and PubMed databases.

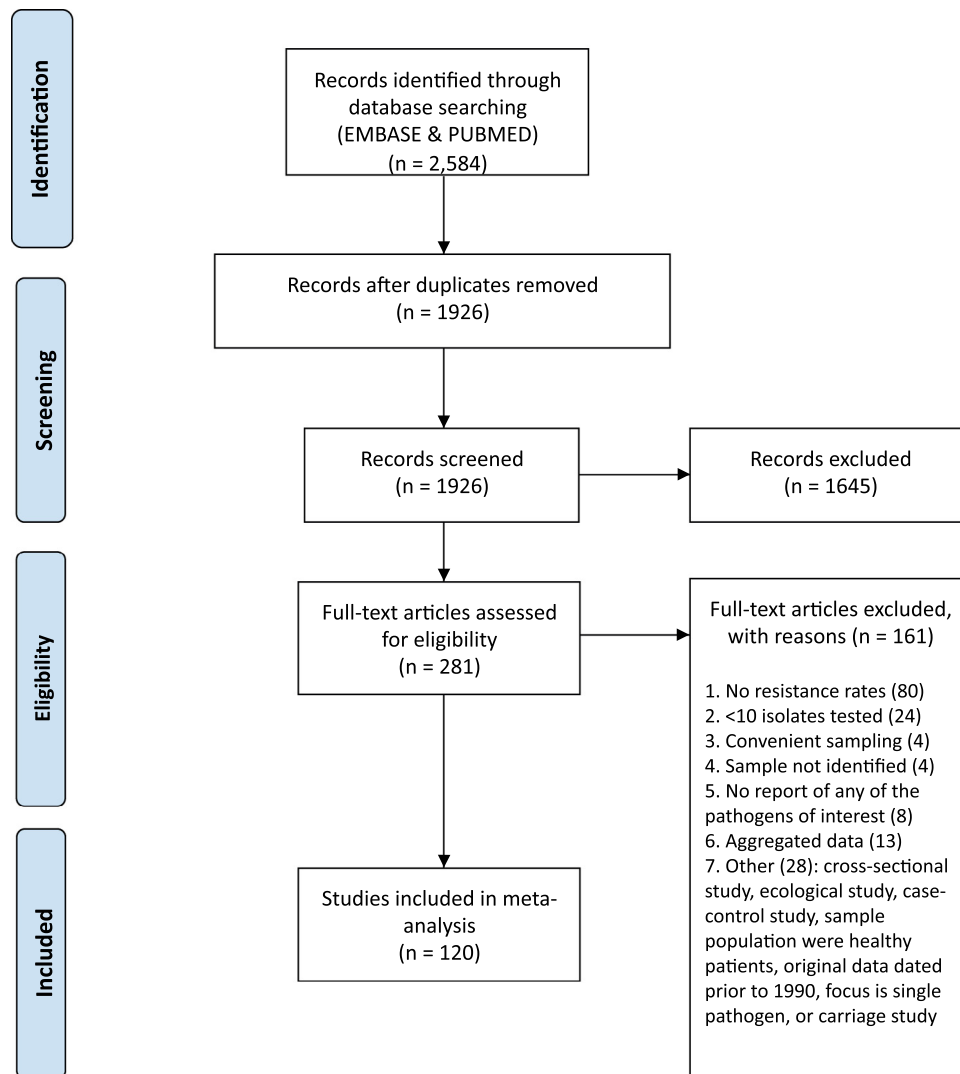


Fig. 2. Selection process of studies.

pathogens, resistance to a limited number of antibiotics was described based on common first-line drugs used in West Africa.

2.2. Data analysis

For each syndrome, the point prevalence and 95% confidence interval (CI) were calculated for each pathogen–antimicrobial pair. Random-effects meta-analysis was used to calculate an overall proportion for each syndrome [8]. Data analysis was performed using StatsDirect Statistical Analysis Software v.3.0.187 (<http://www.statsdirect.com/>; accessed 1 December 2016). Proportions were transformed via the Freeman–Tukey double arcsine method [9,10] and then an inverse-variance weighted random-effects meta-analysis was performed by conventional methods [11]. In addition, for studies reporting intermediate resistance rates, intermediate-resistant strains were grouped with resistant strains.

3. Results

3.1. Overview of study characteristics

Among 2584 initial records screened, 281 articles were reviewed in full and 120 met the eligibility criteria and were included

in this review (Fig. 2). The largest number of studies originated from three countries, namely Nigeria (70; 58.3%), Ghana (15; 12.5%) and Senegal (15; 12.5%) (Fig. 3). Overall, 43 studies (35.8%) focused on UTIs, 38 (31.7%) on BSIs, 27 (22.5%) on meningitis, 7 (5.8%) on diarrhoea and 5 (4.2%) on pneumonia. Among 99 studies that described age, 65 (66%) focused on paediatric populations. For studies reporting participation by sex, females comprised 45% (interquartile range 41–59%) of subjects.

The majority of studies were conducted in urban settings (100/114; 87.7%) and the majority of patients received care in hospitals (95/115; 82.6%). The predominant study designs were retrospective clinical studies (48/120; 40.0%) and prospective clinical studies (43/120; 35.8%); the remainder were laboratory-based studies (24/120; 20.0%) and surveillance studies (5/120; 4.2%). Among studies that reported the type of microbiology laboratory used, 68% (65/95) involved a teaching hospital with an associated laboratory. The remainder of studies involved routine clinical laboratories (22/95; 23%), ‘research’ laboratories (5/95; 5%) and reference laboratories (3/95; 3%). Studies predominantly made use of disk diffusion tests (101/107; 94.4%) as the methodology of antibiotic susceptibility testing, followed by dilution test (4/107; 3.7%) and Etest (2/107; 1.9%). Studies reported a variety of microbiological standards as references; the sources were the French Society of Microbiology

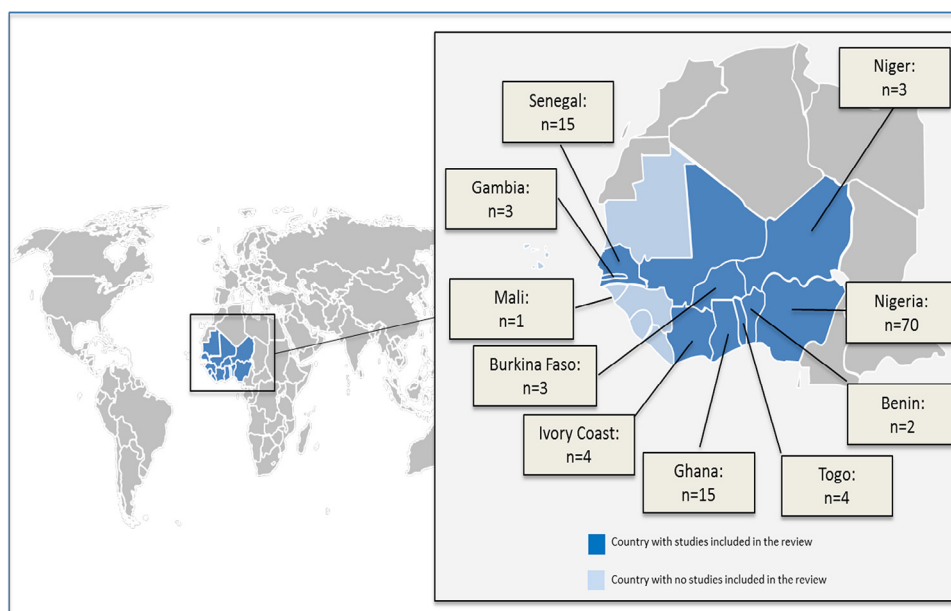


Fig. 3. Map of the West African region, with number of studies in the review by country.

(20/50; 40%), the NCCLS (19/50; 38%), the CLSI (7/50, 14%) and the British Society for Antimicrobial Chemotherapy (BSAC) (4/50, 8%).

3.2. Resistance rates for bacterial pathogens

3.2.1. Urinary tract infections (Table 1) [12–54]

Studies of UTI originated from Nigeria ($n = 31$), Senegal ($n = 4$), Ghana ($n = 4$), Benin ($n = 2$), Burkina Faso ($n = 1$) and Ivory Coast ($n = 1$). Among these studies, 53% focused on adult populations and 86% were conducted in urban settings. Resistance rates in inpatient and outpatient settings were examined separately (Table 1). In outpatient settings, among *E. coli* and *Klebsiella* spp. isolates, resistance to ampicillin was reported in 75.4% (95% CI 70.3–78.6%) and 97.0% (95% CI 89.3–100%) of strains, respectively. Trimethoprim/sulfamethoxazole (SXT) resistance was noted in 60.4% (95% CI 52.5–68.0%) of *E. coli* isolates and in 58.4% (95% CI 22.6–89.8%) of *Klebsiella* spp. isolates. Approximately one-third of urinary *E. coli* and *Klebsiella* isolates were resistant to amoxicillin/clavulanate (AMC), including 38.8% (95% CI 22.3–56.8%) of *E. coli* and 30.3% (95% CI 19.0–42.9%) of *Klebsiella* spp.

Among isolates from inpatients, levels of AMR were generally higher, including moderate to high rates of resistance to third-generation cephalosporins and aminoglycosides. Compared with other commonly used agents, the levels of resistance in inpatients to ciprofloxacin were lower in isolates of *E. coli* (24.0%, 95% CI 10.6–40.8%), *Klebsiella* spp. (22.0%, 95% CI 10.3–36.8%) and *P. aeruginosa* (22.2%, 95% CI 4.8–47.3%). SXT and ampicillin appeared to be poorly active for inpatient treatment of UTI.

3.2.2. Bloodstream infections (Table 2) [55–92]

Studies on BSIs originated from Nigeria ($n = 21$), Senegal ($n = 7$), Ghana ($n = 5$), The Gambia ($n = 2$), Burkina Faso ($n = 1$), Niger ($n = 1$) and Togo ($n = 1$). Among these studies, 84% reported results from paediatric populations and 87% were conducted in urban settings. The following overall rates of AMR were observed for antimicrobials among Gram-negative pathogens in blood: ampicillin, 68.4% (1257/1838); chloramphenicol, 52.4% (288/550); SXT, 54.7% (1077/1968); AMC, 41.5% (414/998); and gentamicin, 37.2% (572/1537). The most active antibiotics for Gram-negative BSIs were third-generation cephalosporins for which resistance was observed in 17.7%

(156/879) of isolates, and fluoroquinolones for which resistance was observed in 12.1% (568/4701). In most studies, sensitivity to carbapenems (e.g. imipenem/cilastatin) was not tested.

Overall, 30.6% (95% CI 11.3–54.0%) of *S. aureus* bloodstream isolates were resistant to cloxacillin, 19.6% (95% CI 10.1–31.2%) were resistant to erythromycin and 44.7% (95% CI 29.5–60.3%) were reported resistant to SXT. For bloodstream isolates of salmonellae (both NTS and *Salmonella* Typhi), there was no reported resistance to ceftriaxone or ciprofloxacin, whilst moderate rates of resistance to SXT, ampicillin and chloramphenicol were reported.

Among *E. coli* and *Klebsiella* spp. isolates, a high rate of resistance to ampicillin and SXT was observed. Third-generation cephalosporins were active among *E. coli* and *Klebsiella* isolates associated with BSIs. However, some data to the contrary were observed. For example, a study of Nigerian children reported that 90% (9/10) of *E. coli* bloodstream isolates were resistant to ceftazidime [70]. A study from Nigeria reported an 82% (81/99) rate of ceftriaxone resistance among *Klebsiella* isolated from blood [69]. Another Nigerian study from 1996 reported that 82% (14/17) of *Klebsiella* were resistant to ceftazidime and 71% (12/17) to ceftriaxone [78].

3.2.3. Meningitis (Table 3) [93–119]

A total of 27 studies on meningitis were included in this review. Meningitis studies originated from Nigeria ($n = 10$), Ghana ($n = 5$), Senegal ($n = 4$), Ivory Coast ($n = 3$), Togo ($n = 3$), Mali ($n = 1$) and Niger ($n = 1$). Among these studies, 70% focused on paediatric populations and 93% were carried out in urban settings.

The following meningitis pathogens were included in this review: *S. pneumoniae*, *N. meningitidis* and *H. influenzae*. The overall rate of reported resistance to penicillin among *S. pneumoniae* and *N. meningitidis* was 13%. Resistance to penicillin was noted among 17.9% (95% CI 7.6–30.9%) of meningococcal isolates and 12.3% (95% CI 6.3–19.8%) of *S. pneumoniae* isolates. Ampicillin resistance was observed in 16.2% (95% CI 8.3–26.0%) of *H. influenzae* strains. Penicillin resistance was not routinely reported as intermediate or high-level. Cephalosporin resistance among *S. pneumoniae* was rarely reported [$< 1\%$ (3/365), ceftriaxone]. In contrast, the global resistance rate among *S. pneumoniae*, *N. meningitidis* and *H. influenzae* for chloramphenicol was 9.9% (300/3024). Moreover, 14.3% (95% CI

Table 1

Urinary tract infections: antimicrobial resistance rates of *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* stratified by outpatient and inpatient.

Antimicrobial agent	<i>E. coli</i>		<i>Klebsiella</i> spp.		<i>P. aeruginosa</i>	
	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)
Ampicillin						
Inpatient	81.0 (63.4–93.8)	18 (2376)	90.2 (80.9–96.6)	11 (1041)	–	–
Outpatient	74.5 (70.3–78.6)	6 (1905)	97.0 (89.3–100)	4 (380)	–	–
Amoxicillin/clavulanic acid (AMC)						
Inpatient	52.5 (24.7–79.5)	11 (431)	77.5 (62.6–89.4)	5 (108)	–	–
Outpatient	38.8 (22.3–56.8)	6 (2723)	30.3 (19.0–42.9)	4 (390)	–	–
Ceftriaxone						
Inpatient	18.4 (9.9–28.4)	9 (641)	30.7 (15.1–48.7)	6 (238)	–	–
Outpatient	–	–	–	–	–	–
Ceftazidime						
Inpatient	47.7 (26.3–69.7)	9 (220)	44.5 (25.4–64.5)	7 (196)	25.0 ^a	2 (44)
Outpatient	26.0 (0–79.4)	3 (1491)	12.6 ^a	2 (278)	7.0	1 (43)
Gentamicin						
Inpatient	37.7 (25.7–50.5)	24 (2983)	42.1 (28.7–56.1)	13 (1016)	–	–
Outpatient	9.3 (4.2–16.1)	6 (2682)	13.5 (1.6–34.3)	4 (490)	–	–
Ciprofloxacin						
Inpatient	24.0 (10.6–40.8)	9 (2648)	22.1 (10.3–36.8)	5 (194)	22.2 (4.8–47.3)	3 (161)
Outpatient	11.7 (9.0–14.8)	5 (2666)	5.1 (0.5–14.0)	4 (608)	0.9	1 (219)
Trimethoprim/sulfamethoxazole (SXT)						
Inpatient	80.1 (67.0–90.6)	23 (2290)	85.3 (72.0–94.8)	13 (943)	–	–
Outpatient	60.4 (52.5–68.0)	7 (2915)	58.4 (22.6–89.8)	5 (524)	–	–

CI, confidence interval.

^a When combining just two studies, the biostatistical analysis was limited. Therefore, mean resistance without the 95% CI was reported.

<20% resistance
20–39% resistance
40–59% resistance
60–79% resistance
80–100% resistance

9.7–19.5%) of pneumococcal isolates were resistant to chloramphenicol, and resistance to chloramphenicol was noted in 4.6% (95% CI 1.3–9.2%) of meningococcal isolates. Among *H. influenzae* strains, 9.7% (95% CI 5.5–14.9%) were resistant to chloramphenicol.

3.2.4. Diarrhoea (Table 4) [120–126]

Seven studies on diarrhoea were included from Nigeria ($n = 5$), Ghana ($n = 1$) and Niger ($n = 1$). Among these studies, 57% were performed among paediatric populations and more than one-half were

Table 2

Bloodstream infections: antimicrobial resistance rates of *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella* spp., non-typhoidal *Salmonella* (NTS), *Salmonella enterica* serotype Typhi, *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Antimicrobial agent	<i>E. coli</i>		<i>K. pneumoniae/Klebsiella</i> spp.		NTS		<i>Salmonella</i> Typhi		<i>S. pneumoniae</i>		<i>S. aureus</i>	
	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)
Ampicillin	74.5 (61.9–85.4)	11 (754)	92.5 (80.5–99.5)	11 (586)	75.1 (54.2–91.3)	3 (308)	40.1 (6.5–79.8)	4 (190)	–	–	–	–
Penicillin	–	–	–	–	–	–	–	–	19.8 (0.3–53.2)	3 (71)	82.7 (66.9–94.5)	9 (251)
Oxacillin	–	–	–	–	–	–	–	–	–	–	56.9 ^a	1 (130)
Cloxacillin											30.6 (11.3–54.0)	13 (757)
Amoxicillin-clavulanic acid	56.2 (23.3–86.5)	5 (430)	66.1 (37.5–90.0)	6 (170)	56.7 (24.0–86.5)	3 (289)	14.3 ^b	2 (109)	–	–	–	–
Ceftriaxone	11.9 (4.3–22.0)	11 (720)	24.2 (8.1–44.8)	11 (476)	0	3 (278)	0	4 (198)	2.5 (0–17.2)	3 (41)	–	–
Ceftazidime	12.0 (4.1–22.6)	8 (645)	32.0 (21.3–43.7)	11 (554)	–	–	–	–	–	–	–	–
Gentamicin	21.6 (10.5–34.9)	12 (306)	54.7 (45.0–64.2)	15 (686)	–	–	–	–	–	–	–	–
Ciprofloxacin	13.2 (4.8–24.3)	7 (637)	11.8 (3.8–22.8)	5 (311)	0	3 (316)	0	4 (198)	–	–	23.0 (4.7–49.1)	6 (614)
Nalidixic acid	–	–	–	–	1.6	1 (125)	0.8 (0–5.6)	3 (69)	–	–	–	–
SXT	73.8 (56.5–88.1)	10 (555)	81.5 (70.3–90.8)	9 (322)	59.0 (24.6–89.0)	3 (258)	31.1 (10.5–56.1)	5 (211)	92.9 (78.4–100.0)	4 (86)	44.7 (29.5–60.3)	12 (536)
Chloramphenicol	–	–	–	–	65.1 (31.8–91.8)	3 (316)	38.3 (19.4–59.0)	4 (145)	15.3 (2.0–35.3)	4 (89)	–	–
Erythromycin	–	–	–	–	–	–	–	–	–	–	19.6 (10.1–31.2)	17 (1470)

CI, confidence interval; SXT, trimethoprim/sulfamethoxazole.

^a Insufficient number of isolates to make an estimate regarding resistance.

^b When combining just two studies, the biostatistical analysis was limited. Therefore, mean resistance without the 95% CI was reported.

<20% resistance
20–39% resistance
40–59% resistance
60–79% resistance
80–100% resistance

Table 3Meningitis: antimicrobial resistance rates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*.

Antimicrobial agent	<i>S. pneumoniae</i>		<i>H. influenzae</i>		<i>N. meningitidis</i>	
	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)
Ampicillin	–	–	16.2 (8.3–26.0)	9 (735)	–	–
AMC	–	–	4.6	1 (175)	–	–
Penicillin	12.3 (6.3–19.8)	17 (2016)	–	–	17.9 (7.6–30.9)	11 (677)
Ceftriaxone	0.2 (0–1.4)	7 (365)	–	–	–	–
Cefotaxime	1.3 (0–6.8)	5 (782)	–	–	–	–
SXT	56.4 (37.0–74.8)	8 (974)	50.4 (19.1–81.5)	3 (240)	50.1 (32.2–68.0)	5 (213)
Chloramphenicol	14.3 (9.7–19.5)	18 (1550)	9.7 (5.5–14.9)	9 (684)	4.6 (1.3–9.2)	11 (790)

CI, confidence interval; SXT, trimethoprim/sulfamethoxazole.

<20% resistance
20–39% resistance
40–59% resistance
60–79% resistance
80–100% resistance

conducted in rural settings. The following rates of AMR were observed among *E. coli* isolates: SXT, 66.5% (95% CI 37.6–90.0%); ampicillin, 71.2% (95% CI 46.8–90.4%); and gentamicin, 20.8% (95% CI 4.7–43.8%). Only 3.4% (95% CI 0–15.7%) of *E. coli* isolates were resistant to ciprofloxacin. *Shigella* spp. were commonly resistant to nalidixic acid (19.3%, 95% CI 2.1–45.9%) and SXT (86.9%, 95% CI 71.1–97.4%). Only one study reported AMR data on *V. cholerae* ($n = 30$ isolates), which did not allow for inclusion in the table).

4. Discussion

We found that in the West Africa region, particularly in patients with BSI and UTI, a moderate level of AMR is present and is likely to undermine typical empirical antibiotic strategies. This observation raises particular concern given the limited diagnostic capability and second-line treatment options in the public sector in West Africa. Existing antibiotic recommendations for syndrome-based management of bacterial infections may need to be reconsidered in this region given the growing prevalence of AMR. Another important finding is that there is a need for more standardised methodology in studies of bacterial illness in West Africa. We found a paucity of studies that made use of a prospective design that can provide the least biased information on the prevalence of key pathogens and AMR.

Previous studies have found that BSIs are frequently encountered in children admitted to hospital with fever in sub-Saharan Africa, particularly in those with risk factors including sickle cell anaemia, malnutrition and human immunodeficiency virus (HIV) infection [67,127–129]. We found that in the West Africa region among common bloodstream pathogens, including *Klebsiella* spp., *E. coli*, *Salmonella* Typhi and NTS, moderate rates of AMR to commonly used antibiotics, including ampicillin, SXT, gentamicin and AMC, were present.

Current guidelines, including the WHO's 'Pocket book of hospital care for children', recommend ampicillin and gentamicin as empirical treatment for sepsis [130]. These data, combined with the potential growth of methicillin-resistant *S. aureus* (MRSA) in the region, give reason to be concerned that ampicillin and gentamicin may no longer be optimal therapy in this region for sepsis/suspected BSIs. Ideally, empirical treatment should be driven by prospective clinical trials with epidemiological data, such as the data presented here, informing recommendations in the interim until such trials can be conducted.

We found that urinary tract pathogens in this region were associated with a moderate to high level of resistance to commonly used antibiotics. Studies from West Africa revealed moderate to high rates of AMR among *E. coli* and *Klebsiella* spp. to ampicillin, AMC and SXT both among inpatients and outpatients. In addition, AMR was unexpectedly observed among inpatients with UTIs to third-generation cephalosporins, suggesting that extended-spectrum β -lactamase (ESBL)-producing organisms may be important pathogens in this clinical context. Of note, current recommendations for the treatment of hospitalised children in the WHO's 'Pocket book of hospital care for children' include SXT, ampicillin or amoxicillin [130]. Antibiotic resistance was lower in UTI isolates to fluoroquinolones; ciprofloxacin was moderately active among inpatients and was highly active in outpatients with UTI caused by *E. coli*, *Klebsiella* spp. and *P. aeruginosa*, suggesting that fluoroquinolones might be a better choice for UTI, especially in higher risk scenarios with symptoms or signs of upper tract infection or sepsis. Other potentially important antibiotics such as nitrofurantoin and fosfomycin were not tested but should be part of future studies. Prospective studies or, minimally, regular analysis of existing microbiology data are also needed to inform optimal treatment of UTI in West Africa.

Bacterial meningitis remains an important disease in West Africa, with the key pathogens known to be *S. pneumoniae*, *N. meningitidis*

Table 4Diarrhoea: antimicrobial resistance rates of *Escherichia coli* and *Shigella* spp.

Antimicrobial agent	<i>E. coli</i>		<i>Shigella dysenteriae/Shigella</i> spp.	
	Pooled proportion (95% CI)	No. of studies (no. of isolates)	Pooled proportion (95% CI)	No. of studies (no. of isolates)
Ampicillin	71.2 (46.8–90.4)	5 (837)	81.7 ^a	2 (196)
AMC	59.8 ^a	2 (531)	–	–
Gentamicin	20.8 (4.7–43.8)	7 (1368)	–	–
Ciprofloxacin	3.4 (0–15.7)	3 (537)	100.0 ^b	1 (16)
Nalidixic acid	–	–	19.3 (2.1–45.9)	5 (379)
SXT	66.5 (37.6–90.0)	5 (1284)	86.9 (71.1–97.4)	4 (367)
Chloramphenicol	–	–	66.1 ^a	2 (196)
Tetracycline	–	–	–	–

CI, confidence interval; AMC, amoxicillin/clavulanic acid; SXT, trimethoprim/sulfamethoxazole.

^a When combining just two studies, the biostatistical analysis was limited. Therefore, mean resistance without the 95% CI was reported.^b Insufficient number of isolates to make an estimate regarding resistance to ciprofloxacin.

<20% resistance
20–39% resistance
40–59% resistance
60–79% resistance
80–100% resistance

and *H. influenzae*. Overall levels of penicillin resistance were low among *S. pneumoniae* (12.3%) and no significant resistance was noted to ceftriaxone or cefotaxime. For meningococcal isolates, the overall reported rate of penicillin resistance across studies was slightly higher (16.2%). Chloramphenicol resistance rates were low for *S. pneumoniae*, *N. meningitidis* and *H. influenzae*, suggesting that this antibiotic remains an alternative when first-line agents, safer are not available. Ampicillin resistance was noted in 16.2% of *H. influenzae*, which is consistent with the 28% reported in a recent meta-analysis [131]. Third-generation cephalosporins remain highly active against strains of *S. pneumoniae* causing meningitis in this region; they have historically been effective against *N. meningitidis* in the region and remain an excellent empirical choice for bacterial meningitis in West Africa when available.

There were few studies on the epidemiology of pneumonia and AMR associated with pneumonia in West Africa. As a result, we did not include these data in our analysis [132–136]. The epidemiology of pneumonia will change with the broader use of effective vaccines for *S. pneumoniae* and *H. influenzae*. Large, prospective clinical trials, including studies in progress, will help to meet this gap [137]. Studies of diarrhoea from West Africa were also limited. *Escherichia coli* and *Shigella* spp. were common isolates in patients with diarrhoea syndromes in the region. The overall level of resistance to SXT and ampicillin was high for both pathogens. For hospitalised children with dysentery, WHO guidelines recommend fluoroquinolones and recommend against SXT and ampicillin/

amoxicillin, which appears consistent with our data. For *Shigella* spp. specifically, there was insufficient data to draw definitive conclusions regarding sensitivity to ciprofloxacin, but the majority of studies suggest that as empirical therapy for suspected bacterial diarrhoeal syndromes in this region, a fluoroquinolone is justified.

There are several limitations to this study. First, there were too few studies of patients with pneumonia or bacterial diarrhoea to make robust estimates about the prevalence of resistance in pulmonary and diarrhoea-associated bacterial pathogens in West Africa. A second limitation was that publications from certain countries were exceedingly scarce. These countries, including Niger, Mali, Sierra Leone and Burkina Faso, are some of the very poorest countries in the region. The net effect is that the analysis oversamples from certain countries (particularly Nigeria and Senegal) whilst undersampling others, such that conclusions drawn may not be valid for all countries in the region. Even within individual countries, AMR rates are unlikely to be homogenous and are likely to differ, particularly between urban and rural contexts. A greater number of studies from a diversity of contexts within individual countries are also needed to construct the most accurate estimates of antibiotic resistance.

A third limitation was that studies of bacterial infections in this region had a heterogeneous methodology. Many studies could not be included because of convenience sampling (study design), inappropriate results reporting (e.g. combining all Gram-negatives in a single category) or vague methodology. A particular challenge was the absence of a standardised panel of antibiotics against which

Gram-positive and Gram-negative organisms were tested, which can make it difficult to combine results across studies. Last, we may be overestimating rates of AMR because microbiology in Africa, when available, tends to be a diagnostic tool within referral hospitals where there is likely to be more antibiotic pressure and a greater proportion of patients presenting with treatment failure and/or after empirical antibiotics elsewhere. More rigorous research is needed, particularly prospective trials in community settings, to avoid this potential source of bias. Strengths include the use of a planned systematic approach, a broad search strategy spanning 20 years of published research, and inclusion criteria based on common clinical syndromes rather than pathogens (given that most clinicians in the region work without microbiology support) as well as the involvement of authors with expertise both in microbiology and clinical infectious diseases.

The current review, by combining multiple studies, provides an initial estimate of the level of AMR in the West Africa region and illustrates where large knowledge gaps exist both by disease and by geography. At this point, the emergence of AMR in bacterial syndromes is not yet reflected in key treatment guidelines. Optimal empirical antibiotic treatment of common invasive bacterial infections in this region should, in the long-run, be informed by prospective clinical trials; there are currently very few high-quality studies of this type. Considering how little is known about the actual clinical impact of AMR and the disadvantages of reflexively escalating to strategies based on empirical use of broader-spectrum agents such as cephalosporins, rigorous therapeutic studies are needed. Ignoring the emergence of AMR in West Africa is not an option. The negative impact of resistance on patient outcomes in BSI is beginning to be documented in sub-Saharan Africa [138]. Quantifying and responding to AMR will be premised on greater funding, investments in laboratory capacity which remains inadequate in the region, development of affordable novel antimicrobial agents, and support for high-quality patient-oriented research that can produce more rigorous prospective studies to guide more effective use of empirical antibiotics in this most underserved area of the world.

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