

Antibiotic susceptibility profile of bacterial isolates from febrile children under 5 years of age in Nanoro, Burkina Faso

Massa dit Achille Bonko^{1,2} | Marc Christian Tahita¹ | Francois Kiemde^{1,2} |
Palpougouini Lompo¹ | Sibidou Yougbaré¹ | Athanase M. Some¹ | Halidou Tinto¹ |
Petra F. Mens² | Sandra Menting² | Henk D. F. H. Schallig²

¹Institut de Recherche en Science de la Santé – Direction régionale du Centre-Ouest/Unité de Recherche Clinique de Nanoro, Nanoro, Burkina Faso

²Department of Medical Microbiology, Experimental Parasitology Unit, Amsterdam University Medical Centers, Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands

Correspondence

Massa dit Achille Bonko, Institut de Recherche en Science de la Santé – Direction régionale du Centre-Ouest/Unité de Recherche Clinique de Nanoro, Nanoro, Burkina Faso.
Email: bonko.massa@gmail.com

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Abstract

Objectives: Antibiotics efficacy is severely threatened due to emerging resistance worldwide, but there is a paucity of antibiotics efficacy data for the West African region in general. Therefore, this study aimed to determine the antibiotic susceptibility profile of bacterial isolated from febrile children under 5 years of age in Nanoro (Burkina Faso).

Methods: Blood, stool and urine samples were collected from 1099 febrile children attending peripheral health facilities and the referral hospital in Nanoro Health district. Bacterial isolates from these samples were assessed for their susceptibility against commonly used antibiotics by Kirby–Bauer method.

Results: In total, 141 bacterial isolates were recovered from 127 febrile children of which 65 from blood, 65 from stool and 11 from urine. *Salmonella* isolates were most frequently isolated and found to be highly resistant to ampicillin (70%; 56/80) and trimethoprim–sulphamethoxazole (65%; 52/80). *Escherichia coli* isolates showed a high resistance rate to trimethoprim–sulphamethoxazole (100%), ampicillin (100%), ciprofloxacin (71.4%; 10/14), amoxicillin–clavulanate (64.3%; 9/14), ceftriaxone (64.3%; 9/14) and gentamycin (50%; 7/14). Moreover, half of the *E. coli* isolates produced β -lactamase suggesting multi-drug resistance against β -lactam as well as non- β -lactam antibiotics. Multi-drug resistance was observed in 54.6% (59/108) of the isolates, mainly Gram-negative bacteria.

Conclusions: This study showed high resistance rates to common antibiotics used to treat bacterial infections in Nanoro. The work prompts the need to expand antibiotic resistance surveillance studies in Burkina Faso.

KEY WORDS

antibiotic resistance, bacteria, febrile children

Sustainable Development Goals: Good Health and Wellbeing

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INTRODUCTION

Development of antibiotic treatment against bacterial infections has been one of the greatest achievements of modern medicine [1–5]. However, the efficacy of antibiotics is now being jeopardised due to increasing occurrence of antibiotic resistance (ABR). Nowadays, ABR is a severe threat to public health and one of the biggest health challenges mankind faces [6–11]. ABR leads to poorer prognosis, mortality and higher healthcare costs [12–14]. One of the main obstacles to inappropriate febrile disease case management in low- and middle-income countries (LMICs) is the limited availability of practical tools to diagnose the actual cause of febrile infections. This lack of diagnostic tools leads to over-prescription of antibiotics that contributes to increasing ABR [15].

To solve this global threat, WHO has developed a global antimicrobial resistance (AMR) action plan, which encompasses reinforcing AMR knowledge through surveillance and research [12]. A better understanding of local AMR patterns is crucial to guide clinical management of infectious diseases and for the early detection of resistance to first-line antibiotics used in health centres. However, information on the actual extent of ABR in the (sub-Saharan) African region is limited to 6 out of 47 countries where studies on AMR have been performed. The resulting gap in monitoring AMR

weakens decision-making on antibiotic resistance policy and increases the risk of prescription of ineffective drugs [16, 17].

This situation also applies to Burkina Faso, ranked among the poorest countries in the world, where studies have revealed high resistance rates against several commonly prescribed first-line antibiotics in primary healthcare facilities, such as amoxicillin (AMOX), amoxicillin–clavulanic acid (AMC) and ampicillin (AMP) [9, 10, 18–20]. These studies highlight that significant resistance is recorded for several bacterial species, which have spread into hospitals and communities. It has been observed that nurses providing first-line care in primary healthcare facilities use the 10-year old national treatment recommendations [20], but this guideline does not contain up-to-date information about the resistance profiles of different circulating bacterial species in the country. The situation is exacerbated due to the fact that the general public has access to antibiotics without prescription in local shops and markets, where supply and quality of drugs are not appropriately controlled. This practice puts the efficacy of current first-line antibiotic treatments, but also second- and third-line antibiotics, at risk [6, 21].

The first-line antibiotics recommended by the Ministry of Health (MoH) in Burkina Faso to treat various bacterial infections are presented in Table 1. In brief, sepsis/suspected bacterial bloodstream infections (bBSIs) and suspected

TABLE 1 Antibiotic categories and antibiotic agents used for susceptibility testing

Antibiotic categories	Antibiotic agents	Disc content	E-test content
Extended-spectrum cephalosporin; 3rd generation cephalosporin	Ceftriaxone (CRO) ^a	30 µg	0.016–256 mg/L
	Ceftazidime (CAZ)	30 µg	–
Cephameycins	Cefoxitin (FOX)	30 µg	–
Penicillin ^a	Ampicillin (AMP) ^a	10 µg	0.016–256 µg/L
	Penicillin (PEN)	10 µg	–
Penicillin+β-lactamase inhibitor	Amoxicillin-clavulanate (AMC) ^a	20/10 µg	–
Trimethoprim and sulphamide combination (Folate pathway inhibitors)	Trimethoprim-sulphamethoxazole (SXT) ^a	1.25/23.75 µg	–
		–	–
Aminoglycosides	Gentamycin (GEN) ^a	10 µg	–
	Amikacin (AK)	30 µg	–
Quinolone and fluoroquinolones	Ciprofloxacin (CIP) ^a	5 µg	–
	Nalidixic acid (NA)	30 µg	–
	Norfloxacin (NOR)	30 µg	–
Carbapenems	Ertapenem (ETP)	10 µg	–
	Imipenem (IPM)	10 µg	0.02–32 mg/L
Macrolides	Azithromycin (AZI)	15 µg	–
	Erythromycin (ERY) ^a	15 µg	–
Phenicols	Chloramphenicol (CL) ^a	30 µg	–
Lincosamides	Clindamycin (CC)	2 µg	–
Glycopeptides	Vancomycin (VAN)	30 µg	0.016–256 µg/L
Tetracyclines	Tetracycline (TET)	30 µg	–
Nitrofurans	Nitrofurantoin (NI)	30 µg	–

Note: This guideline recommends to treat sepsis (or suspected bacterial bloodstream infections) suspected pneumonia with Ampicillin (AMP) or Gentamycin (GEN). In the case of suspicion of typhoid fever, ciprofloxacin (CIP) is indicated and trimethoprim–sulphamethoxazole (SXT) is used to treat simple pneumonia [18]. For suspected cases of bacterial gastroenteritis, CIP is used and for suspected bacterial urinary tract infection, either SXT or amoxicillin (AMOX) is used [18]. Chloramphenicol (CL) and AMP are mostly used as first-line therapy for bacterial meningitis and ceftriaxone (CRO) as second-line treatment [18].

^aFirst-line treatment proposed by the Ministry of Health of Burkina Faso to treat bacterial infections.

pneumonia are treated with AMP and gentamycin (GEN). When typhoid fever is suspected, ciprofloxacin (CIP) is recommended for treatment. Furthermore, trimethoprim-sulphamethoxazole (SXT) is advised to treat suspected simple pneumonia [20]. For suspected cases of bacterial gastroenteritis (bGE), the first-line antibiotic of choice is also CIP, and for suspected bacterial urinary tract infections (bUTIs), either SXT or AMOX is used [20]. The first-line therapy of meningitis infections is chloramphenicol (CL) and AMP; in case CL appears to be ineffective, ceftriaxone (CRO) is used as second-line treatment [20].

There are currently no structural mechanisms in place in Burkina Faso to monitor antibiotic use and the susceptibility of bacteria to antibiotics. The existing sentinel sites for antibiotic resistance surveillance are mainly in tertiary urban hospitals and often not operational. This results in substandard national guidelines that do not cover the potential variability in antibiotic resistance within the country. In order to provide a more evidence-based advice to the national health policymakers, the present study aims to fill part of the gap in our knowledge on the current effectiveness of antibiotics by presenting the antibiotic susceptibility profile of bacteria isolated from samples of febrile children below 5 years of age attending selected health facilities in Nanoro, Burkina Faso.

METHODS

Patients and clinical samples

The present observational study was conducted in the framework of a larger project investigating the management of febrile children in the Health district of Nanoro, 100 km north of Ouagadougou [22]. The sample collection was conducted from January to December 2015 and from April to October 2016. For the present study, any febrile child (axillary temperature $\geq 37.5^{\circ}\text{C}$; measured at the time of enrolment) under 5 years of age attending one of the four primary healthcare facilities or the referral hospital of the health district of Nanoro was invited to participate in the study. Blood, stool and urine samples were systematically collected at enrolment, and before any prescription or use of antibiotics, for microbiological analyses and antibiotic susceptibility testing (AST), at the laboratory of Microbiology of the Clinical Research Unit of Nanoro (CRUN). If the children could not provide a urine or stool sample at the time of enrolment, sterile containers were provided to the parents/legal guardian to collect these samples at home and return them as soon as possible to the health facility within 48 h after inclusion.

For each child, samples were obtained regardless of the potential cause of the fever. Patient management was done by the health staff of the facility independent of the laboratory outcomes and was done according to the Burkinabe national protocol of diseases management based on the Integrated Management of Childhood Illness (IMCI) [23]. The laboratory results were communicated to the staff of the health facilities to allow them to adjust treatments if needed.

Written informed consent was obtained from parents or legal guardians before data and specimen collection from the children. The study protocol was reviewed and approved by the National Ethical Committee for Health Research, Burkina Faso (Deliberation No. 2014-11-130).

Laboratory procedures

Sample collection and bacterial isolates identification

From each child, 1–3 mL of venous blood was collected into a paediatric blood culture bottle (BD BACTEC Peds Plus™/F culture vials, Becton Dickinson and Company) at enrolment. These bottles were incubated at $35 \pm 2^{\circ}\text{C}$ in an automated incubator BACTEC 9050 (Becton Dickinson and Company) for a maximum of 5 days as recommended by the manufacturer. Positive bottles were Gram stained and further sub-cultured on 5% fresh sheep blood agar (SBA), chocolate agar with PolyViteX (PVX) or IsoVitaleX (IVX), and Gram-negative selective agar (Eosin Methylene Blue (EMB) agar or Mac Conkey agar) and incubated at $35 \pm 2^{\circ}\text{C}$ for 18–24 h. The isolates were identified by standard microbiological methods [24–26]. In addition, the Analytical Profile Index (API; bioMerieux Marcy-L'Etoile, France) 20E system was used for biochemical identification. *Salmonella* isolates were further serotyped using Remel™ agglutinating sera (Thermo Scientific™) [27]. *Staphylococcus aureus* were differentiated from other *Staphylococcus* isolates by their ability to ferment mannitol on mannitol salt agar (MSA), a positive catalase, and to produce coagulase [28, 29]. *Streptococcus pneumoniae* were differentiated from other *Streptococcus* isolates by their ability to induce alpha haemolysis on sheep blood agar, a negative catalase and optochin-sensitive [28, 29].

Fresh stool samples collected in sterile containers were inoculated in *Salmonella* enrichment broth (Sodium Selenite broth), on Hektoen and EMB (only for children under 2 years) agars and incubated at $35 \pm 2^{\circ}\text{C}$ for 18–24 h. After 4–6 h, the sodium selenite broth was sub-cultured on *Salmonella-Shigella* (SS) agar and incubated at $35 \pm 2^{\circ}\text{C}$ for 18–24 h. Suspect colonies sought for were *Salmonella* species, *Shigella* species and enteropathogenic *Escherichia coli* (EPEC) (in children under 2 years). Suspect colonies were further identified according to standard microbiological methods [24–26]. Identified suspected isolates were also serotyped by slide agglutination (Bio-Rad antisera).

Midstream urine samples were collected in sterile containers and screened with a urine dipstick test (Urocolor, Standard Diagnostics Inc). If leucocytes and nitrite were present (indicating a probable urinary infection), the urine samples were plated on appropriate agar (cysteine-lactose-electrolyte-deficient [CLED] and EMB agars) and incubated for 18–24 h at $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$. A pure bacterial growth of $\geq 10^5$ colonies forming units (CFU)/mL was considered as significant bacteriuria according to the Stamm and Kass recommendation [30].

Antimicrobial susceptibility testing

AST of bacterial isolates was done using the Kirby–Bauer and Epsilometer (E-test) methods as per the Clinical and Laboratory Standards Institute (CLSI) guidelines [28, 29]. Antibiotic susceptibility was determined for bacterial isolates recovered in this study and is reported in detail in Table 2. AST of isolated EPEC was not done, as in general gastroenteritis caused by these bacteria is commonly not treated with antibiotics, including in Burkina Faso [20, 31].

A suspension of each bacterial isolate to be tested was prepared at a turbidity of 0.5 McFarland standard according to CLSI guidelines [28, 29] and subsequently plated out on appropriate agars (plate of 100 mm diameter). Next, the inoculated agars with appropriate antibiotic discs or E-tests were incubated for 16–18 h at $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and the results read and interpreted according to CLSI guidelines [28, 29]. The antibiotic discs (BD Seni-Disc™, Becton Dickinson and Company, B.V.) used for AST as well as the minimal inhibition concentration tests (MIC; E-tests; Liofilchem S.r.l., Roseto degli Abruzzi, Italy) are presented in Table 1.

Determination of Extended Spectrum beta-lactamase producers

The extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* was determined by using both ceftazidime (CAZ) (30 µg) and cefotaxime (CTX) (30 µg) discs, alone or in combination with clavulanate (C) (10 µg) discs [28, 29]. An *Enterobacteriaceae* is considered to be an ESBL producing phenotype bacterium if the difference between the inhibition zone diameter for either antibiotic tested in combination (CAZ + C) or (CTX + C) and the inhibition zone diameter of the corresponding antibiotic tested alone (CAZ or CTX) is ≥ 5 mm [28, 29].

Determination of methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus were considered as methicillin-resistant isolate when the inhibition zone diameter of cefoxitin disc (FOX; 30 µg) on Mueller Hinton (MH) agar plate is ≤ 21 mm after 16–18 h of incubation [28, 29].

Quality control

Standard bacteriological procedures were performed following standard operating procedures (SOPs) of the CRUN microbiology department. Monthly internal quality controls are performed and the CRUN laboratory is subjected to external quality control organised by WHO and National Institute for Communicable Diseases (South Africa). American Type Culture Collection (ATCC®) standard reference species were used for the quality control of the antibiotic discs.

Data analysis

The inhibition diameters for each antibiotic tested were recorded using Excel 2016. These data were double entered by two independent technicians and validated by the lab-manager. For the interpretation of the resistant rate of the isolates, the following classification was used for the antibiotics tested: low (resistance rate $<20\%$), moderate (resistance from 20 to 50%), high (resistance rate from 50 to 75%) and alarming (resistance rate from 75 to 100%) [32, 33].

An isolate was considered to be multi-drug resistant (MDR) when it was resistant to at least one antibiotic agent in each of all three antibiotic categories used for therapy or prophylaxis based on Burkina Faso national treatment guidelines.

RESULTS

Study population characteristics

The study population characteristics are presented in Table 3. Overall, 1099 children were included and 55.2% were male. In total, 1099 blood samples (100%), 757 (68.9%) stool samples and 739 (67.2%) urine samples were collected. 127 (11.6%) of the enrolled children had one (or more) confirmed bacterial infection(s). Among them, 141 bacterial isolates were identified of which 65 came from blood, 65 from stool and 11 from urine (Table 4).

In total, 135 Gram-negative bacteria isolates were obtained. *Salmonella* isolates were found in 80/1099 (7.2%) children (51 from blood and 29 from stool), followed by *E. coli* which were isolated from 47/1099 (4.3%) children (33 isolates from stool, 10 from urine and 4 from blood; see Table 4). Gram-positive isolates were cultured from blood; *Streptococcus pneumoniae* from 4/1099 (0.4%) children and *Staphylococcus aureus* from 2 (0.2%) children (Table 4).

Antibiotic susceptibility testing

Antibiotic susceptibility of Gram-negative bacteria

The results of AST are presented in Table 2. Susceptibility patterns analysis of *non-typhoid Salmonella* (NTS) and *E. coli* isolates revealed high resistance rates for several antibiotics tested. In addition, 7 *E. coli* isolates, of which 6 came from urine, produced β -lactamase, suggesting MDR against β -lactam and non- β -lactam antibiotics. Two of four isolates of *typhoidal Salmonella* (TS) showed high resistance to SXT (50%). All *N. meningitidis* isolates (2) tested were resistant to SXT and one was resistant to penicillin (PEN) too. The *H. influenzae* b isolate and the *Klebsiella* isolate were found to be sensitive to most of the antibiotics tested, except for SXT (100% resistant).

The resistance rates to commonly used first-line therapies in Burkina Faso are presented in Table 5. The

TABLE 2 Antibiotic susceptibility profiling of different bacterial isolated from various clinical specimens

Bacteria species, (N)	Infection site												
	Blood						Stool						Urine
	NTS (47)	TS (4)	<i>E. coli</i> (4)	<i>N. m</i> (2)	<i>E. agglomerans</i> (1)	<i>S. p</i> (4)	<i>S. aureus</i> (2)	<i>Hib</i> (1)	NTS (29)	<i>Shigella</i> sp. (3)	<i>E. coli</i> (10)	<i>Klebsiella</i> sp. (1)	
Antibiotics, n (%)													
SXT*	37 (78.7)	2 (50)	4 (100)	2 (100)	0 (0)	2 (50)	0 (0)	1 (100)	13 (44.8)*	1 (33.3)*	10 (100)*	1 (100)*	
AMP*	43 (91.5)*	0 (0)	4 (100)*	0 (0)	0 (0)	0 (0)	-	0 (0)	13 (44.8)	3 (100)	10 (100)*	1 (100)*	
AMC	10 (21.3)*	1 (25)*	2 (50)*	-	0 (0)	-	-	-	7 (24.1)	1 (33.3)	7 (70)*	0 (0)*	
CRO*	0 (0)	0 (0)	2 (50)*	0 (0)*	0 (0)	0 (0)*	-	0 (0)*	0 (0)	0 (0)	7 (70)	0 (0)	
CL	38 (80.8)	2 (50)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	-	11 (37.9)	1 (33.3)	0 (0)	0 (0)	
CIP*	0 (0)	0 (0)	2 (50)	0 (0)	0 (0)	-	0 (0)	0 (0)	2 (6.9)*	0 (0)*	8 (80)	0 (0)	
NA	4 (8.5)	2 (50)	2 (50)	-	0 (0)	-	-	-	2 (6.9)	0 (0)	8 (80)	0 (0)	
GEN*	-	-	2 (50)*	-	0 (0)	-	0 (0)	0 (0)	-	-	5 (50)	0 (0)	
AK	0 (0)	0 (0)	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	0 (0)	1 (10)	0 (0)	
CAZ	0 (0)	0 (0)	2 (50)	-	0 (0)	-	-	-	0 (0)	0 (0)	6 (60)	0 (0)	
IPM	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	-	0 (0)	0 (0)	0 (0)	0 (0)	
ETP	0 (0)	0 (0)	0 (0)	-	0 (0)	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)	
PEN ^a	-	-	-	1 (50)	-	2 (50)	2 (100)	-	-	-	-	-	
ERY	-	-	-	-	-	0 (0)	1 (50)	-	-	-	-	-	
TET	-	-	-	-	-	4 (100)	1 (50)	-	-	-	-	-	
CC	-	-	-	-	-	0 (0)	1 (50)	-	-	-	-	-	
NOR	-	-	-	-	-	-	0 (0)	-	-	-	-	-	
NI	-	-	-	-	-	-	0 (0)	-	-	-	-	-	
VAN	-	-	-	-	-	0 (0)	0 (0)	-	-	-	-	-	
AZI	-	-	-	-	-	0 (0)	-	-	-	-	-	-	

Abbreviations: N (%), the prevalence of resistance phenotypes is presented in percentage; NTS, non-typhoid Salmonella; TS, typhoidal Salmonella; Nm, *Neisseria meningitidis*; Sp, *Streptococcus pneumoniae*; Hib, haemophilus influenzae; CRO, ceftriaxone; AMC, amoxicillin-clavulanate; AMP, ampicillin; GEN, gentamicin; SXT, trimethoprim-sulphamethoxazole; CIP, ciprofloxacin; NA, nalidixic acid; CL, chloramphenicol; ERY, erythromycin; CC, clindamycin; TET, tetracycline; PEN, penicillin; OX, oxacillin; IMP, imipenem; ETP,ertapenem; NOR, norfloxacin; NI, nitrofurantoin; AZI, azithromycin; CAZ, ceftazidim; AK, amikacin; -, not tested; *, first-line treatment proposed by the Ministry of Health of Burkina Faso to treat these infections; sp., species.

^aBased on the breakpoints of non-meningitis for *S. pneumoniae*.

TABLE 3 Basic characteristics of the study population.

Characteristic	Study population N = 1099	Confirmed Bacterial infection		Laboratory confirmed bacterial Infections				Bacterial co-infections			
		Yes		bBSI	bGE	bUTI	bBSI associated to bGE	bBSI associated to bUTI	bGE associated to bUTI	bBSI associated to bGE and bUTI	
Demographic data											
Total, n (%)	1099 (100.0)	127 (11.6)		65 (5.9)	65 (5.9)	11 (1.0)	11 (1.0)	2 (0.2)	3 (0.3)	2 (0.2)	
Male, n (%)	607 (55.2)	59 (9.7)		34 (52.3)	28 (43.1)	5 (45.5)	6 (54.5)	1 (50.0)	2 (66.7)	1 (50)	
Female, n (%)	492 (44.8)	68 (13.8)		31 (47.7)	37 (56.9)	6 (54.5)	5 (45.5)	1 (50.0)	1 (33.3)	1 (50)	
Age ≤12 months (%)	306 (27.8)	33 (10.8)		16 (24.6)	16 (24.6)	5 (45.5)	5 (45.5)	0 (0)	1 (33.3)	0 (0)	
Age >12 months (%)	793 (72.20)	94 (11.8)		49 (75.4)	49 (75.4)	6 (54.5)	6 (54.5)	2 (100)	2 (66.7)	2 (100)	

Abbreviations: bBSI, bacterial gastroenteritis; bGE, bacterial gastroenteritis; bUTI, bacterial urinary tract infection.

resistance rates of *NTS* and *Shigella* isolates causing bGEs were low to moderate. However, in the case of bUTIs, the one *Klebsiella* and 10 *E. coli* isolates were all resistant against SXT (100%). AMP is commonly used to treat invasive bacterial infections, but resistance was found for all isolates from urine samples. In contrast, CRO remained to be effective against *NTS*. Importantly, CRO was shown to be also effective against the two isolates of *N. meningitidis* and *H. influenzae* b, which are often incriminated in meningitis epidemics in Burkina Faso, which is located in Lapeyssonnie's belt.

Antibiotic susceptibility of Gram-positive cocci

The antibiotic susceptibility results of the 6 Gram-positive cocci isolated are presented in Table 2. Of four *Streptococcus pneumoniae*, two isolates were resistant to two of the first-line antibiotics tested (PEN and SXT). The two *Staphylococcus aureus* recovered were both resistant to PEN and one against ERY. In contrast, CRO that is used as the first-line antibiotic to treat bacterial meningitis was effective against *S. pneumoniae*.

Resistance profiling of invasive bacteria isolated from multiple infections

The resistance profiling results of invasive bacteria isolated from multiple infections are presented in Table 6. In total, 11 bacterial isolates (10 *NTS* and 1 *E. coli*) were identified simultaneously in blood and stool. The resistance rate of *NTS* isolates identified from both infection sites against the first-line antibiotics AMP and SXT was of concern. Importantly, two children had three types of different infections. One child had an *E. coli* isolate responsible for bBSI, bGE and bUTI. In another child, two *NTS* isolates were responsible for bBSI and bGE, and one *E. coli* caused bUTI. All these bacteria were fully resistant to AMP and SXT, which are the first-line antibiotics to treat these infections.

Multi-drug resistant (MDR) bacteria

The MDR bacteria results are reported in Table 7. Ten of fourteen (71.4%) *E. coli* isolates revealed resistance to SXT, AMP and CIP. Among *Salmonella* species, 56.3% (45/80) were resistant to SXT, AMP and CL. These antibiotics are recommended by the MoH of Burkina Faso to treat the infections found in this study (Table 5).

DISCUSSION

The present study revealed high resistance rates to many first-line antibiotics commonly prescribed in Burkina Faso to treat bBSIs, bGEs and bUTIs. According to the MoH of

TABLE 4 Distribution of the identified bacterial isolates according to the site of infection

Isolated bacteria	Infection sites			Type of multiple infections					
	Blood (1099); n (%)	Stool (757); n (%)	Urine (739) n (%)	bBSI+bGE (11)		bBSI+bUTI (2)		bGE+bUTI (3)	
				Blood n (%)	Stool n (%)	Blood n (%)	Urine n (%)	Stool n (%)	Urine n (%)
GNB									
<i>NTS</i> (76)	47 (4.3)	29 (3.8)	–	10 (90.9)	10 (90.9)	1 (50)	–	2 (66.7)	–
<i>TS</i> (4)	4 (0.4)	–	–	–	–	–	–	–	–
<i>E. coli</i> (47)	4 (0.4)	33 (4.4)	10 (1.4)	1 (9.9)	1 (9.9)	1 (50)	2 (100)	1 (33.3)	3 (100)
<i>Klebsiella</i> species (1)	–	–	1 (0.1)	–	–	–	–	–	–
<i>N. meningitidis</i> (2)	2 (0.2)	–	–	–	–	–	–	–	–
<i>Shigella</i> species (3)	–	3 (0.4)	–	–	–	–	–	–	–
<i>H. influenzae b</i> (1)	1 (0.1)	–	–	–	–	–	–	–	–
<i>E. agglomerans</i> (1)	1 (0.1)	–	–	–	–	–	–	–	–
GPC									
<i>S. aureus</i> (2)	2 (0.2)	–	–	–	–	–	–	–	–
<i>S. pneumoniae</i> (4)	4 (0.4)	–	–	–	–	–	–	–	–
Total (141)	65 (5.9)	65 (8.6)	11 (1.5)	11 (16.9)	11 (16.9)	2 (0.8)	2 (18.2)	3 (4.6)	3 (27.3)

Abbreviations: The site of infections, that is, blood, gastro-intestinal tract and urinary tract; *NTS*, non-typhoidal Salmonella; *TS*, typhoidal Salmonella; bBSI, bacterial bloodstream infection; bGE, bacterial gastroenteritis; bUTI, bacterial urinary tract infection; –, not found; bBSI+bGE, bacterial bloodstream infection associated with bacterial gastroenteritis; bBSI+bUTI, bacterial bloodstream infection associated with bacterial urinary tract infection; bGE+bUTI, bacterial gastroenteritis associated with bacterial urinary tract infection; GNB, gram-negative bacteria; GPC, gram-positive cocci; *n*, number of bacteria identified per infection site.

TABLE 5 Resistance rates of bacteria isolated to first-line antibiotics used in Burkina Faso^a

Antibiotic, n (%)	Infection type						
	bBSI		bGE			bUTI	
	AMP	GEN	CRO	SXT	CIP	SXT	AMP
Isolated bacteria (N)							
<i>NTS</i> (76)	43 (56.6)	–	0 (0)	13 (17.1)	2 (6.9)	–	–
<i>E. coli</i> (14)	4 (100)	2 (50)	2 (50)	–	–	10 (100)	10 (100)
<i>N. meningitidis</i> (2)	0 (0)	0 (0)	0 (0)	–	–	–	–
<i>Shigella</i> sp. (3)	–	–	–	–	0 (0)	–	–
<i>Klebsiella</i> sp. (1)	–	–	–	–	–	1 (100)	1 (100)
<i>S. pneumoniae</i> (4)	0 (0)	0 (0)	0 (0)	–	–	–	–
<i>S. aureus</i> (2)	–	0 (0)	0 (0)	–	–	–	–

Abbreviations: bBSI, bacterial bloodstream infections (blood stream infections and meningitis); bGE, bacterial gastroenteritis; bUTI, bacterial urinary infection; *NTS*, non-typhoid Salmonella; CRO, ceftriaxone; AMP, ampicillin; GEN, gentamycin; SXT, trimethoprim-sulphamethoxazole; CIP, ciprofloxacin; AMOX, amoxicillin; –, not found.

^aFirst-line treatment proposed by the Ministry of Health of Burkina Faso to treat these infections.

Burkina Faso [20], sepsis/suspected bBSIs caused by *E. coli* or *NTS* are treated with AMP. The high resistance rates we found warrant careful reconsideration of the current treatment guidelines. This observation confirmed other studies from Nanoro [19] and other sub-Saharan African countries that also reported alarming resistance of *E. coli* and *NTS* to first-line antibiotics [34–37].

It is recommended to treat UTIs caused by *E. coli* or *Klebsiella* with SXT or AMOX, but resistance against these antibiotics was also high in this study. Moreover, 85.7% of *E. coli* isolates from urine were β -lactamase enzyme producers. This is worrying, as these isolates

usually show co-resistance to non- β -lactam antibiotics, such as aminoglycosides and fluoroquinolones [38–40]. This explains the high resistance of *E. coli* isolated from urine to antibiotics reported in this study. The observed high resistance of *E. coli* to 3rd generation cephalosporin (CRO) and fluoroquinolones (CIP), which are two essential antibiotics largely used in our study area, is also alarming.

We did not distinguish between bacterial carriage and actual disease and considered all stool samples from which bacterial pathogens could be isolated as cases of bGE. In accordance with SOPs in place at the microbiology laboratory

TABLE 6 Resistance rate to recommended first-line therapy* for the treatment of bacterial multiple infections identified

Isolated bacteria	Infection site	bBSI+bGE (11)					bBSI+bUTI (2)					bGE+UTI (3)					bBSI+bGE+bUTI (2)				
		AMP n (%)	GEN n (%)	CRO n (%)	SXT n (%)	CIP n (%)	AMP n (%)	GEN n (%)	CIP n (%)	SXT n (%)	AMP n (%)	GEN n (%)	CRO n (%)	SXT n (%)	CIP n (%)	SXT n (%)	AMP n (%)	GEN n (%)	CRO n (%)	SXT n (%)	CIP n (%)
<i>NTS</i>	Blood (10)	9 (90)	nAST	0 (0)	8 (80)	5 (50) ^a	1 (100)	nAST	0 (0)	1 (100)	NA	NA	NA	NA	NA	1 (100)	nAST	0 (0)	1 (100)	0 (0)	0 (0)
	Stool (10)	9 (90)	nAST	0 (0)	9 (90)	2 (20) ^b	NA	NA	NA	NA	1 (50)	nAST	NA	nAST	1 (100)	1 (100)	nAST	0 (0)	1 (100)	0 (0)	0 (0)
<i>E. coli</i>	Blood (1)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	NA	NA	NA	NA	NA	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
	Stool (1)	nAST	nAST	nAST	nAST	nAST	NA	NA	NA	NA	nAST	nAST	nAST	nAST	nAST	nAST	nAST	nAST	nAST	nAST	nAST
	Urine (3)	NA	NA	NA	NA	NA	2 (100)	0 (0)	0 (0)	2 (100)	3 (100)	1 (33.3)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)

Abbreviations: bBSI+bGE, bacterial bloodstream infection associated with bacterial gastroenteritis; bBSI+bUTI, bacterial bloodstream infection associated with bacterial gastroenteritis; bBSI+bGE+bUTI, bacterial bloodstream infection associated with bacterial gastroenteritis; bBSI+bUTI, bacterial bloodstream infection associated with bacterial gastroenteritis; bGE+UTI, bacterial gastroenteritis associated with bacterial urinary tract infection; bBSI+bGE+bUTI, bacterial bloodstream infection associated with bacterial gastroenteritis; and bacterial urinary tract infection; NTS, non-typhoid *Salmonella*; CRO, ceftriaxone; AMP, ampicillin; GEN, gentamicin; SXT, trimethoprim-sulphamethoxazole; CIP, ciprofloxacin; NA, not applicable; nAST = no antibiotic susceptibility testing; * = first-line treatment proposed by the Ministry of Health of Burkina Faso to treat these infections; a, b = the antibiotic susceptibility results of NTS isolates are interpreted as Intermediate.

of CRUN, bacterial pathogens considered as causing bGE are *Salmonella* and *Shigella* species and AST was performed on these isolates. Resistance to (first-line) antibiotics to treat bGEs was still acceptable in this study. However, although low resistance of NTS to CIP was found, the efficacy of this antibiotic must be carefully monitored as it is widely used to treat bacillary dysenteries in children under 5 years in West Africa [20, 41].

Despite the rare cases of *N. meningitidis* and *H. influenzae* b reported in the present study, it is relevant to note that these bacteria were fully susceptible to the CL and CRO. This is important as these antibiotics are used to treat meningitis as recommended by MoH of Burkina Faso (located in Lapeyssonnie's belt).

The study further reported a high prevalence of MDR bacteria. This emergence of MDR is a serious public health problem and a threat to the management of bacterial infections. The emergence of specific MDR bacteria is closely linked to the use of broad-spectrum antibiotics for presumptive and definitive therapy. The spread of MDR into the community puts the population further at risk and increases the number of infections caused by MDR bacteria.

Respiratory tract samples were not collected in this study. Suspected respiratory tract infections are often empirically treated in primary health centres with antibiotics, without knowing its actual cause, and this practice can lead to resistance [21, 42]. For example, suspected simple pneumonia (i.e. case where only 1 or 2 clinical signs or symptoms of pneumonia according to IMCI guidelines are seen) should be treated with SXT. This antibiotic was effective against several bacterial infections causing pneumonia in this study. This encourages the use of SXT for the treatment of pneumonia caused by *S. pneumoniae* in children under 5 years of age, but its effectiveness needs to be determined further *in vivo*.

A possible limitation of the study is that in some cases only a few isolates could be tested for susceptibility; for example, only four *S. pneumoniae*, two *S. aureus* and two *N. meningitidis* isolates were tested. According to the CLSI guidelines, analysing the percentage of susceptibility on fewer than 100 isolates should not be done. However, we find it important to present the results of all isolates, as it provides the first insight into possible evolving resistance. The low prevalence of *S. pneumoniae* is likely to be a positive effect of the introduction of the pneumococcal conjugate vaccine in the Burkinabe expanded programme of immunisation (EPI) in October 2013 [43, 44]. However, it remains a concern that the few isolates recovered in the present study showed resistance against the first-line antibiotics recommended in our study area [6, 20].

Our study was restricted to performing a phenotypic assessment on the bacteria isolated from clinical samples collected for investigation. Only disc diffusion technique (Kirby-Bauer method) and to some extent Epsilometer test (E-test) were applied in the context of our laboratory. Other more advanced phenotypic (e.g. automated systems)

TABLE 7 Frequency of multi-drug resistant (MDR) bacterial isolates from various clinical specimens.

Isolated bacteria	Total number of isolates	MDR <i>n</i> (%)
Gram-negative bacteria	102	56 (54.9)
<i>NTS</i>	76	44 (57.9)
<i>TS</i>	4	1 (25)
<i>E. coli</i> ^a	14	10 (71.4)
<i>N. meningitidis</i> Y/W135	2	0
<i>Shigella</i> species	3	1 (33.3)
<i>H. influenza</i> b	1	0
<i>E. agglomerans</i>	1	0
<i>Klebsiella</i> species	1	0
Gram-positive cocci	6	3 (50.0)
<i>S. aureus</i>	2	1 (50.0)
<i>S. pneumoniae</i>	4	2 (50.0)
Total	108	59 (54.6)

Abbreviations: These bacteria were isolated from blood, stool and urine samples collected in children under 5; MDR, Multi-drug resistant; *NTS*, non-typhoidal *Salmonella*; *TS*, typhoidal *Salmonella*.

^aSub-population of *E. coli* isolated from blood and urine.

TABLE 8 Proposed alternative antibiotic treatments to treat common bacterial infections

Infection type	Proposed alternative antibiotic to be used based on the study outcome
Suspicion of a simple bBSI	CRO
Suspicion of a serious bBSI	CRO+GEN
bUTI in a hospitalised patient	GEN
bUTI in a non-hospitalised patient	AMC
bGE	CIP

Abbreviations: bBSI, bacterial bloodstream infections (blood stream infections and meningitis); bGE, bacterial gastroenteritis; bUTI, bacterial urinary infection; CRO, ceftriaxone; GEN, gentamycin; AMC, amoxicillin-clavulanate; CIP, ciprofloxacin.

or genotypic (e.g. polymerase chain reaction) methods to determine antibiotic susceptibility are still out of reach for many laboratories in LMIC [45].

Together our data confirm that the efficacy of many (first-line) antibiotics frequently used in Nanoro to treat common bacterial infections is at high risk. It is likely that this situation is not unique for our study region, but may also apply to Burkina Faso and the whole West Africa region [19, 46]. This will further undermine the precarious health system in place in LMICs if the spread of resistance is not stopped. Actions have to be taken urgently to prevent inappropriate antibiotics use and to contain the spread of resistant bacteria. It is essential that practical tools or simple diagnostic algorithms be developed to correctly diagnose bacterial infections in primary healthcare settings in LMICs, which allow for subsequent appropriate prescription of antimicrobials. Furthermore, the

guidelines for IMCI [23] recommending syndrome-based management and treatment of bacterial infection need to be reconsidered. A possible consequence of the use of the IMCI guidelines is the untargeted, prolonged and repeated exposure of bacteria to essential antibiotics, which may contribute to emerging resistance. Next to this, it is important to have appropriate logistics in place to perform antibiotic susceptibility testing in place in the microbiology laboratory.

Various first-line antibiotics showed reduced *in vitro* effectiveness and may no longer be effective to treat common bacterial infections. It may therefore be necessary to consider alternative treatment options in the Burkina Faso context. Based on the study outcomes, the following alternative treatments can be considered (Table 8): When sepsis or an uncomplicated bBSI is suspected, the treatment could be with a single 3rd generation cephalosporin (CRO). In case of severe sepsis or severe bBSI, the treatment could be a combination of CRO combined with an aminoglycoside, like GEN. In case of a suspected bUTI, we suggest distinguishing between hospitalised and non-hospitalised cases, because the administration route of GEN may have a health safety risk for the outpatient as it needs to be administered intravenously. For a hospitalised patient with bUTI, the proposed treatment would be an aminoglycoside (GEN). However, for a non-hospitalised case, we propose using AMC, which is a combination of AMOX and Clavulanic acid (C) and can be administered orally. For the treatment of bGE, we propose to use fluoroquinolone (CIP), but it is important to monitor resistance to this antibiotic too as it is frequently used even without proper laboratory examinations and/or prescriptions.

CONCLUSION

This study showed high resistance rates to many first-line antibiotics used to treat common bacterial infections in Burkina Faso. The work prompts the need to expand antibiotic resistance surveillance studies in Burkina Faso, and probably the whole region (West Africa).

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DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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