Current status of resistance to antibiotics in the Democratic Republic of the Congo: A review

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Abstract

An overview of the literature was conducted to assess prevalence and mechanisms of antibiotic resistance to date, mainly to β-lactam antibiotics, cephalosporins, carbapenems, colistin and tigecycline in DR Congo. English and French publications were listed and analysed using PubMed/Medline, Google Scholar and African Journals database between January 1st, 1990 and December 31, 2019. For the 30 published articles found: i) Bacterial resistance to antibiotics concerned both Gram-negative and Gram-positive bacteria; ii) Multidrug resistance prevalence was the same in half of *Streptococcus pneumoniae* isolates; iii) A worrying prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was noted, associated with co-resistance to several other antibiotics; iv) Resistance to 3rd generation cephalosporins was very high in *Enterobacteriaceae,* mainly due to $bla_{\text{CTX-M-1}}$ group and bla_{SHV} genes. Data on carbapenem and colistin resistance were not available until now. Further work is required to set up a surveillance system for antibiotic resistance in this country.

Introduction

There is a growing concern on antimicrobial resistance (AMR) worldwide [1]. Resistance against antimicrobial agents s in clinically relevant bacteria is one of the most imminent threats to public health and especially to our most vulnerable patient populations [2,3]. The treatment of bacterial infections in Africa is largely empirical and, in most instances, there are no laboratory results to guide therapy [4,5]. The spread of AMR bacteria is problematic for the medical community as a whole as it compromises empirical treatment regimens by delaying the administration of appropriate antibiotic therapy and reducing appropriate treatment options [6,7]. AMR remains a real challenge in resource-limited countries due to a lack of available antibiotics with multidrug-resistant isolates being labelled on the basis of a small number of antibiotics tested, with economic consequences and yet the use of the old molecules is very effective. The consequences of AMR are not limited to patients with infections, but to a whole system including the environmental and agro-pastoral sector that hemming enough resistance genes. Hence, there is a need for action to significantly reduce the expansion of the phenomenon, whose distribution varies considerably from one country to another [8,9]. To combat the global threat of AMR, improved surveillance to detect emerging and long-term resistance trends is vital, several global initiatives, such as the Fleming Fund, have been recently established to improve laboratory capacity in low- and middle-income countries [10].

As recently reported, there is a link between antibiotic resistance genes found in human pathogens and those found in non-pathogenic, commensal and environmental organisms, prompting further studies of natural and human-associated reservoirs of resistance genes [11]. Many hypotheses can be evoked, even though the relationship between antibiotic use and antibiotic resistance remains complex [12]. Resistance selection pressure continues as

antimicrobials are released into the environment, largely while remaining in their active forms. These drugs frequently found in wastewater for example contributed greatly to the environmental selection of antibiotic-resistant bacteria [13-17]. As reported by many health care settings, *Enterobacteriaceae*, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii* have been identified as emerging organisms of concern for multidrug resistance, and have encouraged researches in this area [18,19]. Resistance to antibiotics is the result of either by reducing its affinity, lowering its concentration, or destroying it in order to effectively reduce or cancel the interaction with its target [20]. Therefore, depending on the involved mechanism, the resistance level can vary considerably [21].

Over the past decade, the increase in multidrug resistance of Gram-negative rods and in particular the spread of resistance to carbapenems in *Enterobacteriaceae*, *Pseudomonas* spp. and *Acinetobacter* spp., has prompted the return of colistin (or polymyxin E) as a treatment of last resort. Extended-spectrum β-lactamase (ESBL)-producing pathogens and methicillin resistant *Staphylococcus aureus* (MRSA) are endemic in many hospitals worldwide and are also increasingly detected in the community [22-25]. Carbapenem-resistant enterobacterial infections (CRE) are being increasingly observed, mainly in health care facilities, but also in the community; they are associated with management difficulties due to the lack of alternative active molecules and cause outbreaks difficult to control in health care facilities in low-income countries where hygiene is poor and the population is overcrowded, in addition to an epidemic context of ESBL that was still not effectively controlled [26].

Challenge of humanitarian disaster, infectious diseases and AMR spread in war context

In Democratic Republic of Congo (DRC), data on AMR are scarce; some bacteria are being included in surveillance cross sectional study, such as *Salmonella* spp. and *S. aureus,* but there are unknown prospects focused on other bacteria and in many parts of the country [27,28]. The DRC is a vast country (2.3 million km of area) divided into 26 provinces. Each province is divided into health districts, which in turn are divided into health zones (called "zones de santé"). A health zone in the DRC corresponds to what is internationally referred to as a health district [29]. The conflict in DRC has resulted in a health-system collapse and created a humanitarian disaster. An estimated 5.4 million excess deaths occurred from 1997 to 2004, with fewer than 10% attributable to violence and the rest to preventable and treatable medical conditions, such as malaria, diarrhea, pneumonia, and malnutrition [30]. Armed conflicts and other disastrous natural phenomena can lead to major population displacements. An emergency unsustainable infrastructure is temporarily built, and often with overcrowding, insufficient if not insufficient drinking water and sanitation, which gives its populations a risk of exposure to communicable diseases, especially those with epidemic potential [31]. The country had been the site of two wars involving multiple African nations and armed conflict between rebels and soldiers for the past 16 years, characterized by extreme violence, massive population displacements from east to west, and the collapse of all existing infrastructure [32,33]. Massive population movements are at the root of most risk factors, people are displaced to regions and areas where resources and services are insufficient and where contact with other naïve populations with new vectors of infectious diseases is potentially more frequent. This leads to large numbers of people going to camps, often associated with overcrowding, inadequate housing and poor water conditions, resulting in the spread of pathogenic microorganisms, as reported by UNHCR in January 2018 in Eastern Congo (**Fig. 1**) [34,35].

The deterioration of health services is probably one of the main risk factors for communicable diseases in this type of humanitarian disaster, both for individuals and populations. Access to health care in such conditions is impossible, which is a key risk factor for the serious progression of most communicable diseases in the individual. As the spread and detection of cases becomes a major challenge, emergency measures to be implemented remain unavailable, including public health services, vaccination, communicable disease prevention and control measures and surveillance, making epidemics more likely, more difficult to detect and more difficult to control [35,36].

Review methods

For this review, we searched PubMed/Medline, Google Scholar and African Journals for articles written in French and in English on bacterial resistance to antibiotics in DR Congo. We used the search terms “bacterial resistance”, “antibiotic and resistance”, “antimicrobial resistance”, “microbial resistance”, “susceptibility”, “resistance” combined with the name of Democratic Republic of Congo. We screened the search results for relevant, methodologically rigorous studies and conducted a forward search of the references of many of the relevant results to identify additional studies. Articles were reviewed and publications using original data on antibiotics resistance in humans and environment samples were included. The studies site, study period, organism isolated, the resistance phenotype observed, the molecular methodology used as well as the antimicrobial resistance genes found were appraised and analysed. This review on antibacterial resistance in DRC focuses on available published literature on the subject dating from 1990 to December 31st, 2019.

Resistance pattern among Gram-negative and Gram-positive bacteria

Enterobacteriaceae:

For *Enterobacteriaceae*, the emergence and spread of CTX-M type ESBLs are global, with the highest prevalence observed in low-income countries, particularly in the community with an estimated carrying prevalence of 70%, 35% and 15% respectively in Asia, the Eastern Mediterranean Basin and Africa [24].

Salmonella

Salmonella spp. is the most studied bacterial genus in DRC as a result of the research set up and is still ongoing since 2008 on bacteremia. Indeed, since the first publications on bacteremia, the prevalence of resistance to ampicillin, chloramphenicol and cotrimoxazole are particularly high (90 – 100%) [37,38]. The most frequently isolated species are *Salmonella enteritidis, Salmonella typhimurium* and *Salmonella* Typhi. The level of resistance is as high for *S.* Typhi as it is for non-Typhi *Salmonella* (NTS). Ampicillin, chloramphenicol and cotrimoxazole are no longer susceptible in more than 70% of isolates [38,39,40]. For Muyembe et al. in 2009, all isolates (11 isolates) of *S.* Typhi were resistant to ampicillin and cotrimoxazole [41]. Finally, a decreased susceptibility to ciprofloxacin was also observed between 59 to 65% [42,43,44]. Several resistance genes were detected in *Salmonella* spp. strains isolated from DRC including, $bla_{\text{TEM-1b}}$ and $bla_{\text{SHV-2a}}$ genes [27,37,43]. Moreover, *S.* Typhi harboring $bla_{\text{CTX-M}}$ genes has been described in blood cultures in a bacteremic patient in 2018 [45]. Resistance to chloramphenicol, aminoglycosides, quinolones and sulfonamides is correlated to the presence of *catA1*, *strA/B*, *sul1*, *dfrA1* genes and the *aac(6')-1aa* gene [37,40]. Some mutations on *gyrA* gene, as well as the presence of *qnrB1* and *aac(6')-Ib-cr* genes were found in strains resistant to fluoroquinolones (Table 1 and Table 2). Puyvelde et

al., in 2019, analysed the entire genome of 81 strains of *S. typhimurium* by high-throughput sequencing. They reported that 67% of the isolates (54/81) were ESBL-producers and 63% were multidrug resistant (MDR), according to the definition used for *Salmonella* spp., i.e. resistant to both ampicillin, chloramphenicol and cotrimoxazole. Several resistances genes were found, including *catA, bla*$_{\text{TEM-1}}$*, bla*$_{\text{SHV-2A}}$, *dfrA, dfrA1, dfrA14, mphA* and a mutation in the *gyrA* gene (S83Y) [46]. Bieke et al., in 2019, analysed 295 *S.* Typhi, 93 of which were sequenced (WGS): 38.4% (114/295) were resistant to ampicillin, chloramphenicol and cotrimoxazole; 24.5% (73/295) had decreased sensitivity to ciprofloxacin, mainly due to mutations detected in the *gyrA* (S83E, S83Y, D87Y, D87G, A119E) and *gyrB* (E466D, S464Y) genes [47].

Escherichia coli

E. coli is one of the most isolated microorganisms in bacteriology laboratories. A single emerging clonal group of *E. coli*, designated sequence type 131 (ST131) by multilocus sequence typing, has been identified as a factor in the AMR epidemic in *E. coli*, especially for first-line agents such as fluoroquinolones and extended-spectrum cephalosporins. *E. coli* contains a wide array of genetic diversity, most notably among genes that confer virulence and resistance [48,49]. In DRC, five studies carried out in 2001, 2014 and 2015 showed that the resistance rates of *E. coli* varied from 65 to 90% to penicillin [42,50,51], from 6 to 15% to ceftriaxone and 15.4% to 31.5% to ciprofloxacin [52,53]. For studies in which resistance genes were sought, the *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{SHV-18}}$ genes were reported (Table 1) [53,54]. In Bukavu, a recent study conducted in 2019 by Irenge et al. using whole genome sequencing of 21 *E. coli* strains showed that 33% of the strains (7 out of the 21 *E. coli*) belonged to ST131 and exhibited more virulence genes as compared to compared to the same clone in the NCBI database. The majority of ESBL genes included *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{SHV-12}}$ in all the isolates.

Several other AMR genes have been found including *bla*$_{\text{OXA-1}}$, *bla*$_{\text{TEM-1}}$, as well as genes encoding resistance to aminoglycosides, quinolones, chloramphenicol, rifampicin, tetracyclines and sulfonamides. As a matter of fact, *bla*$_{\text{CTX-M-15}}$ gene is the most frequently found ESBL gene among African hospital strains [55,56].

Klebsiella pneumoniae

K. pneumoniae is a frequent cause of nosocomial infections and has also emerged as an agent of severe community-acquired infections, including pyogenic liver abscess, pneumonia, and meningitis. *K. pneumoniae* clinical isolates are evolving toward increasing levels of antimicrobial drug resistance, placing this species among the infectious bacterial pathogens that are most challenging to control [57]. In a study on urinary tract infection aetiologies in Bukavu, Leonid et al. found that *K. pneumoniae* was the second most frequently identified microorganism after *E. coli* [53]. Its resistance profile in studies published in the DRC in 2012 and 2015 showed a resistance rate of less than 35% for both amoxicillin/clavulanate acid (14%-19%), ceftriaxone (14% -19%) and ciprofloxacin (12%-33%). One out of the 21 strains of *K. pneumoniae* was phenotypically resistant to imipenem. No further studies were performed to screen for the carbapenemase genes. Studies have shown that the use of carbapenems promotes the emergence of carbapenemase-producing isolates. In Bukavu, the use of these molecules is increasingly becoming part of the therapeutic arsenal of clinicians [58]. The resistance genes described for *K. pneumoniae* in DRC are the *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{SHV-18}}$ genes, as previously reported for *E. coli* [52,54,59].

Others Gram-negative bacteria (including non-fermenting rods)

The available data do not allow the resistance profile of these other bacteria to be established, given the small number of isolates tested (Table 2). Those microorganisms are *Citrobacter freundii, Enterobacter* spp*., and Proteus* spp*. Enterobacter cloacae* is an

opportunistic pathogen that can cause several types of infections in the lower respiratory tract, surgical sites, urinary tract and central nervous system. Moreover, this species is frequently associated with nosocomial infections during outbreaks, emphasizing the need for rapid detection and typing of such pathogens. *C. freundii* is considered a commensal of the intestinal tract of humans and other animals. However, this species can also cause diarrhea and other infections in humans [60,61]. De Boeck et al. in Kinshasa reported the presence of $bla_{\text{CTX-M-15}}$, $bla_{\text{SHV-18}}$ and $bla_{\text{SHV-2-like}}$ genes in *C. freundii* and *E. cloacae* strains, demonstrating that the two ESBL genes are widely disseminated in *Enterobacteriaceae* [54,59]. In a recent study conducted by Leonid et al., out of the 78 analysed strains of *Vibrio cholerae*, all were resistant to cotrimoxazole and nalidixic acid, 12% (9/78) had reduced susceptibility to ciprofloxacin and 14% (11/78) were resistant to ampicillin. They were still sensitive to chloramphenicol and tetracyclines. Many AMR genes were detected (Tab. 1) [62]. Finally, there are no data available on the occurrence and resistance profile of non-fermenting Gram-negative bacilli in RDC.

Resistance pattern among Gram-positive bacteria

Staphylococcus aureus

S. aureus is one of major human pathogens, associated with wide spectrum of localized or systemic infections including wound infections, osteomyelitis, food poisoning, endocarditis, as well as more serious illnesses, such as pneumonia and bacteremia [63,64]. In RDC, the prevalence of bacterial infections caused by methicillin-resistant *S. aureus* (MRSA) varied from 16 to 64% [28,44,65,66,67], which is similar to the prevalence reported in other African countries [68]. The reported prevalences of antibiotics resistance are as follows: 33 to 72 % against to tetracyclines, 5 to 54 % against cotrimoxazole, 31 % against gentamicin, 26 to 69% against erythromycin and 20 to 59% against ciprofloxacin [28,44,66].

Streptococcus pneumoniae

S. pneumoniae is the leading cause of pneumonia and bacterial meningitis. It is commonly encountered in children and in immunocompromised and elderly populations and it has considerable implications for healthcare systems worldwide [69]. To date, multidrug-resistant *S. pneumoniae* (MDR-SP) have been isolated from both adults and children around the world. These isolates are resistant to penicillin, clindamycin, cotrimoxazole and erythromycin [70]. In DRC, a study performed on 23 *S. pneumoniae* isolates, showed that the prevalence of penicillin resistance was 34%, 21% to cotrimoxazole and 13% to cefuroxime (Table 2) [71]. Serotyping had not been completed, yet it would give us valuable information on circulating strains depending on the vaccine used. A recent study of 163 nasal carriage isolates of *S. pneumoniae* in children under 60 months of age reported 62% (n=101) of resistance to penicillin G, 42% (n=68) to ampicillin, and 37% (n=61) to ceftriaxone. Almost all strains were resistant to cotrimoxazole (94%) and 43% (n=70) were resistant to more than three classes of antibiotics [72].

Perspectives

Surrounded by nine neighboring countries, the DRC faces many security and health challenges, including population movement, high mortality rates and recurrent endemic diseases, which make it impossible for the health system to make antibiotic resistance a priority. With an annual budget of about US$6 billion, 1.2% of which is allocated to the health sector, for a population estimated at 85 million [73]. Despite the existence of 39 officially recognized medical schools, most of which are located in urban areas, the training of clinical microbiologists remains a real problem because entirely self-financed, so that the number of microbiologists is very low in relation to actual needs [29]. The DRC is almost last with its human development index (168/169), public spending on health is among the lowest

with two dollars per capita. In this context of advanced poverty, investment in laboratory materials and other diagnostic equipments for infectious diseases is therefore impossible. The WHO recommends a minimum of $35 per capita to safeguard a country's population [74]. Out of the 424 hospitals in the country, very few have organized a microbiology service due to lack of electricity, infrastructure and especially qualified personnel, as the only university in the country that trains them markets 2 to 4 clinical microbiologists per year [75]. The serious threat of antibiotic resistance in the DRC is the ineffectiveness of the antibacterial molecules available on the market, which means that the use of old molecules which prove to be more active with multidrug resistant isolates elsewhere should quickly orient the regulatory authorities to change procurement policies.

In light of these challenges, there is an urgent need to create collaborative networks with all microbiology laboratories across the country, which will then be linked to external laboratories to effectively address the AMR problem.

Conclusion

This review summarizes the current state of our knowledge regarding antimicrobial susceptibility of the common organisms causing serious community and hospital-acquired infections in DRC. Many studies focused on *Salmonella* spp.*, S. aureus* and *V. cholerae*. Bacterial resistance to antibiotics concerns both Gram negative and Gram-positive bacteria. Multidrug resistance prevalence is almost common in half of *S. pneumoniae* isolates. More disturbing, we can note a worrying prevalence of MRSA with co-resistance to several other antibiotics, and of ESBL-producers in *Enterobacteriaceae* with the diffusion of $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-18}}$ genes. Data on non-fermenting Gram negative bacilli, as well as carbapenem and colistin resistance, are not available.

Ethical issues

There are no ethical concerns with this paper and ethical review board approval was not required as no human subjects were involved.

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Transparency declaration:

The authors declare no conflict of interest.

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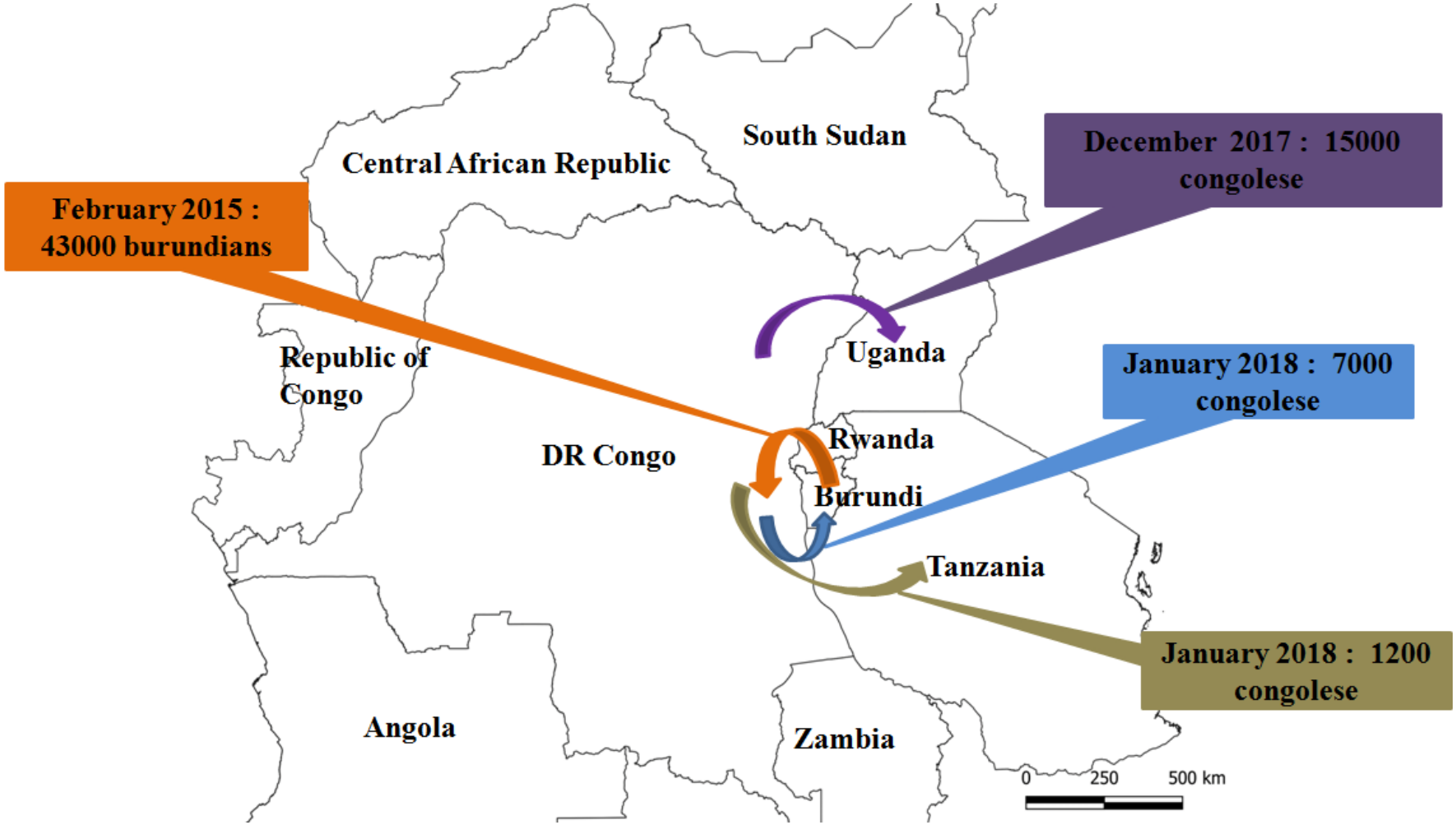
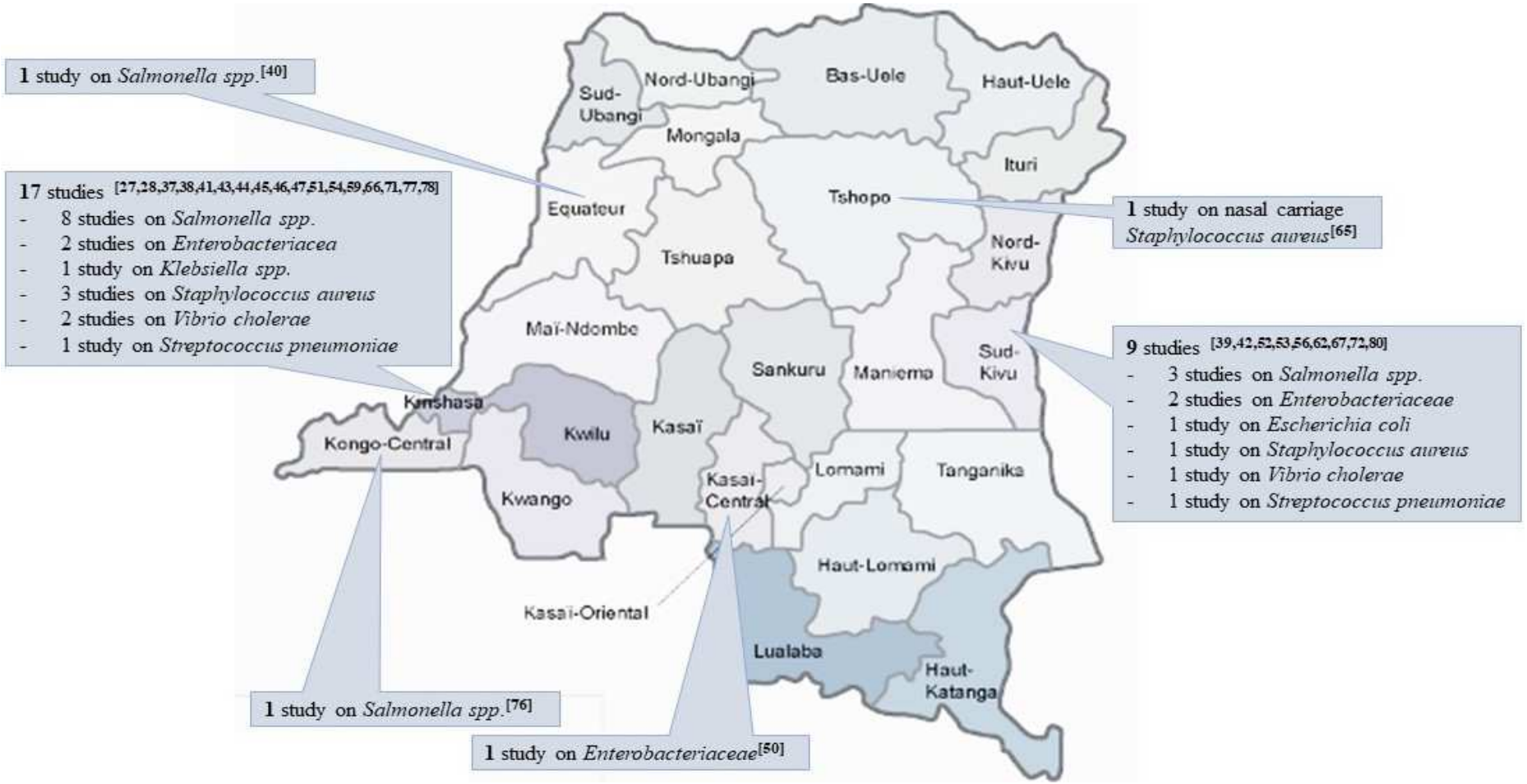


Figure 1: Movement of population in the context of armed conflict in Eastern part of Democratic Republic of Congo.



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537 **Figure 2**: Localization of published data on antimicrobial resistance in Democratic Republic of the Congo.

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539 **Table 1**: Main antimicrobial resistance genes found in Democratic Republic of Congo

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Species	Methods	N° of strains	Antibiotic resistance genes	References
Salmonella spp.	PCR, gene sequencing, whole genome sequencing	453	*bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{SHV-2a}}$, *mph(A), gyrA* mutation, *qnrB1, aac(6')-Ib-cr, bla*$_{\text{TEM-1}}$, *bla*$_{\text{TEM-1b}}$, *catA1, strA/B, sul1, dfrA1, aac(6')-1aa*	[27,37, 38, 40, 43,45,47,77]
E. coli	PCR, Whole genome sequencing	21	*bla*$_{\text{CTX-M-1}}$, *bla*$_{\text{TEM}}$, *bla*$_{\text{CMY}}$, *bla*$_{\text{OXA}}$, *aac3, ant2'', ant3'', aph3'', aph6, pbp2, aac6', qnrB, mphA, cat, catA, catB, arr, folp, sulI, sulII, tetA, tetB, tetD, dhfr*	[53,56]
Klebsiella spp.	PCR	3	*bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{SHV}}$ variants	[59]
S. aureus	PCR, Whole genome sequencing	148	*aac(6')-aph(2'')*, *tetK, emrC, mecA* gene found, mutation in *femA* gene found, *dfrG*, *rpoB*, *emrC*	[28,44]
Vibrio cholerae	Whole genome sequencing	78	*cardB, intSXT, sxt/R391, sulII, sulI, qnrVC, aph3-dprime, aph6, drfA, dhfr, flor, gyrA* (S83I)*, parC* (S85L)	[46]

Table 2. Prevalence of resistance among bacteria isolated in Democratic Republic of Congo

Study period	Microorganism isolated (year of isolation)	Prevalence of resistance % (N)	Gene identified	References
1993	*Salmonella* spp.(1986)	90% (n=90) of resistance to ampicillin, chloramphenicol, streptomycin and tetracycline	ND[a]	[76]
2001	*Salmonella* spp. and *E. coli* (1990)	100% of resistance to ampicillin and chloramphenicol for *S. enteridis*, 65% (n=46) of resistance to ampicillin and chloramphenicol for *E. coli* (n=19)	ND	[42]
2009	*Salmonella* Typhi (2005)	All the strains (n=11) exhibited resistance to ampicillin (>256 mg/L) and cotrimoxazole (>32 mg/L)	ND	[41]
2010	*Salmonella spp.*(2006)	For *S. typhimurium*, high proportion of isolates were resistant to ampicillin (85.7%), chloramphenicol (92.5%), and cotrimoxazole (94.7%), 6.1% of *S. enteritidis* tested were resistant to nalidixic acid and ciprofloxacin, 10.2% of *S. enteritidis* isolates were resistant to gentamicin. 89.7% of *S.* Typhi isolates presented a similar antimicrobial resistant profile as the one observed among NTS[b]	Two isolates displayed resistance to cefoxitin (32mg/L); the presence of the genes $bla_{\text{CMY-1}}$, $bla_{\text{CMY-2}}$, bla_{ACC}, $bla_{\text{CTX-M}}$, and bla_{TEM} was negative	[39]
2013	*Salmonella typhimirium* (2006)	100% (n=11) of resistance to ampicillin, cotrimoxazole, and chloramphenicol	$bla_{\text{TEM-1b}}$, *catA1, strA/B, sul1, dfrA1, aac(6')-1aa*	[37]
2014	*Salmonella* spp. (2011)	96% (n=180) of resistance to ampicillin; chloramphenicol and cotrimoxazole,	$bla_{\text{SHV-2a}}$, *mph(A)*	[38]
2014	*Salmonella* spp. (2012)	72.2% (n=18) of *S.* Typhi isolates showed co-resistance to ampicillin and cotrimoxazole, 33.3% showed additional resistance to chloramphenicol and hence were MDR[c]. 97.6% (n=85) of NTS isolates were MDR; 1.0 % *S. typhimurium* isolate had additional DCS[d]	*gyrA* gene mutation found	[40]
2015	*Salmonella* spp. (2014)	*S.* Typhi isolates (n=164), MDR and DCS rates were 37.8%	*gyrA* mutation found, *qnrB1*, *aac(6')*-	[27]

		and 37.2%, respectively. MDR were 90.2% and 79.7%, respectively for *S. typhimurium* (386) and *S. enteritidis* (390). ESBL production was observed in 12.7% of *S. typhimurium* isolates	*Ib-cr, bla*$_{\text{TEM-1}}$	
2017	*Salmonella* Typhi (2015)	Production of ESBL[e] was confirmed by PCR, the first time in DR Congo on *S.* Typhi. The isolate further showed decreased ciprofloxacin to pefloxacin and nalidixic acid with resistance	*bla*$_{\text{CTX-M-15}}$	[43]
2018	*Salmonella* Typhi (2017)	ESBL-producing *S.* Typhi isolate with a decreased ciprofloxacin susceptibility	*bla*$_{\text{CTX-M-15}}$	[45]
2018	*Salmonella* spp. (2014)	27% (n=60) of resistance to cefuroxime, 20% to ceftriaxone and norfloxacin	ND	[80]
2019	*Salmonella typhimurium* (2016)	67% (54/81) were ESBL producers and 63% were MDR (resistance both to ampicillin, chloramphenicol and cotrimoxazole).	*catA, bla*$_{\text{TEM-1}}$*, dfrA, dfrA1, dfrA14, bla*$_{\text{SHV-2A}}$*, mphA, gyr A* mutation (S83Y)	[46]
2019	*Salmonella* Typhi (2017)	38.4% (114/295) were resistant to ampicillin, chloramphenicol and cotrimoxazole; 24.5% (73/295) had decreased sensitivity to ciprofloxacin	*gyrA* (S83E, S83Y, D87Y, D87G, A119E), *gyrB* (E466D, S464Y)	[47]
2012	*Enterobacteriaceae* (2011)	7.4% (n=190) ESBL-producing *Enterobacteriaceae*	*bla*$_{\text{CTX-M-1}}$ group	[59]
2014	*Enterobacteriaceae* and Non fermenting Gram-negative rods (2013)	16.3% (n=643) of isolates displayed a MDR phenotype; 80% (n=25) of isolates were ESBL-producers	*bla*$_{\text{CTX-M-1}}$ group	[53]
2014	*Enterobacteriaceae* (2013)	100% (n=79) of resistance to tetracycline, over 90% of resistance to ampicillin, cotrimoxazole and chloramphenicol and over 65% of resistance to norfloxacin	ND	[51]

2015	*Enterobacteriaceae* (2014)	100% (n=112) of resistance to cotrimoxazole, 67-100% of resistance to ampicillin and > 50% of them were ESBL producers	ND	[52]
2015	*Enterobacteriaceae* and Gram-positive cocci (2015)	98% (n=38) of *E. coli* and 65% (n=22) of *S. aureus* resisted to penicillin, and 92% of *E. coli* and 73% of *S. aureus* resisted to cefotaxime	ND	[50]
2012	*Klebsiella* spp. and *E. aerogenes* (2010)	5.3% (150) of ESBL producers (8 isolates).	5 $bla_{\text{CTX-M}}$ genes and 3 bla_{SHV} variants	[54]
2019	*Escherichia coli* (2014)	All isolates were MDR corresponding to ESBL producers (n=21). Twenty-one (21/21) and 19/21 strains were susceptible to imipenem and amikacin, respectively	$bla_{\text{CTX-M-1}}$, bla_{TEM}, bla_{CMY}, bla_{OXA}, *aac3, ant2'', ant3'', aph3'', aph6, pbp2, aac6', qnrB, mphA, cat, catA, catB, arr, folP, sulI, sulII, tetA, tetB, tetD, dhfr*	[56]
2014	*Staphylococcus* spp.(2013)	63.5% (n=74) of *S. aureus* and 90% (n=15) of CNS[f] were MRSA[g] and MR-CNS, respectively	ND	[66]
2015	*Staphylococcus aureus*(2011)	16% (n=63) of MRSA	ND	[65]
2016	*Staphylococcus aureus* (2014)	33% (n=100) were MRSA, 72% of resistance to cyclins and 54% of resistance to cotrimoxazole	*mecA*, mutation in *femA* gene found, *dfrG*, *rpoB*, *emrC*	[28]
2017	*Staphylococcus aureus* (2016)	36% (n=45) of isolates were MRSA	ND	[67]
2017	*Staphylococcus aureus* (2013)	25% (n=108) were MRSA, 31% were resistant to aminoglycosides, 26 % to macrolides and 20 % to ciprofloxacin	*aac(6')-aph(2'')*, *tetK*, *emrC*	[44]
2015	*Vibrio cholerae* (2013)	98% (n=36) of resistance to cotrimoxazole, 71% to nitrofurantoin and 18% to nalidixic acid.	ND	[77]
2015	*Vibrio cholerae* (2012)	Although sensitivity to fluoroquinolones seemed to be preserved, strain resistance patterns continued to evolve with	MLVA genotyping, no resistance genes searched	[78]

		the circulation of isolates resistant to tetracyclines and ampicillin from 2007 to 2010, and displayed a single antimicrobial drug susceptibility profile: resistance to most antimicrobial drugs (chloramphenicol, erythromycin, cotrimoxazole) except cyclines and fluoroquinolones.		
2019	*Vibrio cholerae* (2017)	100% (n=78) of resistance and nalidixic acid, 12% and 14% of resistance to ciprofloxacin and ampicillin, respectively	*cardB, IntSXT, sxt/R391, sulII, sulI, qnrVC, aph3-dprime, aph6, drfA, dhfr, flor, gyr*A (S83I), *parC* (S85L),	[62]
2016	*Streptococcus pneumoniae and Haemophilus influenzae* (2014)	83% (n=23) of *S. pneumoniae* isolates were resistant to penicillin, 28% (n=23) of *H. influenzae* were resistant to amoxicillin/clavulanate acid	ND	[71]
2018	*Streptococcus pneumoniae* (2015)	70 out of the 163 isolates (43%) of the pneumococci were MDR (non-susceptible to ≥3 classes of antimicrobial agents, including the β-lactams).	ND (PCR done for serotyping only)	[72]

[a] ND, not determined; [b] NTS: Non Typhi *Salmonella;* [c] MDR: multidrug resistant; [d] DCS: Decreased Ciprofloxacin Susceptibility; [e] ESBL: extended spectrum β-lactamase; [f] CNS: coagulase negative *Staphylococcus;* [g] MRSA: methicillin resistant *S. aureus.*