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ß-Lactams and Quinolones Genetic Resistance in West Africa from 2009 -2018 - A Meta-Analysis

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ABSTRACT

The increased resistance of bacteria to antibiotics due to their misuse is a major public health concern. The present study aims to assess the prevalence of ß-lactam and/or quinolone resistance and bla_{BLSE} and *Qnr* genes in West Africa over a ten-year period (2009-2018). PubMed, Google Scholar and African Journal Online have been systematically consulted. Eighty-two publications were included in the study after analysis of inclusion criteria. Burkina Faso (19.5%, 16/82) and Nigeria (39%, 32/82) had more publication included. The majority of studies (78.05%, 64/82) focused on bacterial strains of medical origin. Strains of *Escherichia coli, Klebsiella pneumoniae, Salmonella spp., Pseudomonas aeruginosa* and *Enterobacteriaceae* are strains that have been studied for resistance to β-lactams and/or quinolones. The average prevalence of overall resistance of β-lactam-resistant pathogens and quinolones in West Africa is respectively 42.62% and 42.10%. The average prevalence of ß-lactam and/or quinolone resistance by bacterial strain was 44.75% and 49.3%, respectively, in *Klebsiella Pneumoniae* strains. In *E. coli* strains, it was 46.81% and 43%. The prevalence of *Bla* and *Qnr* genes was 43.77% and 55.70%, respectively. The gene *CTX-M* (53.57%) and *qnrS* (57.72%) are the genes bla_{BLSE} and *Qnr* with the highest prevalence in West Africa. This study shows a high prevalence of ß-lactam and quinolone resistance in West Africa over the last ten years. The use of β-lactams and quinolones in humans and animals should be urgently limited.

INTRODUCTION

ß-lactams and quinolones are major families of antibiotics widely used in clinical practice. ß-lactams act by inhibiting the synthesis of the bacterial wall by binding to penicillin-binding proteins (PLP), enzymes involved in the synthesis of peptidoglycan (1). However, quinolones work by inhibiting DNA gyrase in Gram-negative bacteria and by blocking topoisomerase IV in Gram-positive bacteria (2, 3). In Gram-negative bacilli (BGN), there are several types of mechanisms of resistance to ß-lactams and quinolones. These include mutations in antibiotic targets, membrane impermeability, active efflux mechanism, and in particular enzymatic inactivation by β-lactamases and quinolone acetylation (enzymatic), inactivation (AAC (6 ') - enzyme Ib-cr) (4, 5). The first β-lactamase (TEM-1/2, SHV-1) and quinolone (qnrA) plasmid was first described in the 1960s and 1970s respectively in Enterobacteriaceae and quickly spread to other families of bacteria (6). Before the emergence of these enzymes, new stable β-lactams (in particular the broad-spectrum cephalosporins) and new quinolones were described in the years 1970-1980 and 2004 respectively (7-9). However, their intensive clinical use was followed by the early onset of resistance. In 2005, a second mechanism of plasmid resistance contributing independently to the resistance of quinolones by modification of the molecule was described. This determinant (aac (6') - 1b-cr) (7, 10) is a 6' variant of acetyltransferase whose acetylation spectrum, generally limited to aminoglycosides, is extended to ciprofloxacin and Norfloxacin (5, 11). Infections caused by ESBL-producing strains are associated with high morbidity and mortality, prolonged hospital stay, and increased hospital costs (12, 13). Until the 2000s, the spread of ESBL-producing enterobacteria mainly concerned the hospital environment; numerous hospital epidemics in intensive care or long-term hospitalization have been described (14, 15). However, today the widespread dissemination of this type of resistance within the community is a major public health problem (12, 16). This emergence of resistance is observed in several countries. Currently, the prevalence of beta-lactam and quinolone resistance varies between countries and hospitals, but in all cases, CTX-M (Cefotaxime) is considered to be the most common type of ESBL in the world (17). The genes coding for resistance to ß-lactams and quinolones are of chromosomal or plasmid origin (18-20). These genes have also been detected on transposons and integrons facilitating the horizontal transfer of the latter to the phylogenetically distant species. The plasmid, easily transmissible by the in vitro conjugation of enterobacteria, is the essential element in the emergence of resistance to beta-lactams and quinolones (21, 22). This property explains the easy release of enzymes such as CTX-M, qnrB1 and aac (6') - 1b-cr,

which are gaining importance compared to other types of enzymes resistant to beta-lactams and quinolones (23). In Africa, in patients treated in hospitals or in communities, it has been shown that the prevalence of resistance to β-lactams and quinolones varies from country to country and from the type of sample studied. The most common type of gene involved in the production of hospital and community type ESBL in Africa is class A ESBL (4, 23). CTX-M-15 is the most common gene in a high proportion of the samples, regardless of country. It is generally associated with other types of CTX-M, TEM and SHV genes (4, 6, 24). The majority of studies are carried out in North or Southern Africa (25, 26). Thus, to solve the problem of bacteria resistant to β-lactams and quinolones in West Africa, the acquisition of data is necessary for better treatment of the infections caused by these bacterial strains and develop a strategy to control the antimicrobial resistance.

METHODS

Protocol

A systematic review of the published literature was undertaken, in accordance with the preferred reporting elements for systemic reviews. Our initial objective was to carry out systematic analysis and a meta-analysis to identify and quantify the relevant articles reporting a genetic resistance to ß-lactams and fluoroquinolones in West African countries. However, evaluation of the published studies showed that only one study was appropriate for the meta-analysis.

Data sources and research strategy

We have developed search strategies for three electronic databases: PubMed, Google Scholar and African Journal Online. The language of the publications examined was produced in French and/or English. Terms used included the terminology of antimicrobial resistance (e.g. quinolones or fluoroquinolones, extended spectrum β-lactamases [ESBL]), West African countries, and molecular characterization of the resistance of ESBL and quinolones genes.

Item selection criteria

Research related to the issue of our study was included. We did not apply any exclusion or limitation criteria based on the methodology used for the detection of resistance to ß-lactams or quinolones. Studies that looked only at the antimicrobial phenotype and did not answer the

research question were excluded (Figure 1). Endnote version X8 (Thomson Reuters) was used to create a bibliography, to collect and manage the articles selected and cited.

Data extraction

The authors independently reviewed all abstracts identified by the search strategy. The authors selected abstracts of articles according to the inclusion criteria. The selected full length of articles were downloaded into the appropriate databases and the data was saved in the MS Excel file under the titles of the samples analyzed, organisms isolated prevalence of ESBL production, prevalence of resistance to quinolones, ESBL and quinolone resistance genes detected.

Sampling plans and methods used in the studies

The studies reviewed included a variety of sampling points. The most common sampling points were for community infections. Variations in terms of sample size, sampling frame (criteria for sampling, inclusion and exclusion of samples to be studied), and isolation protocols between studies, even for the same microorganism. There was no uniformity among studies with regards to the isolation and identification protocol.

All studies have used conventional microbiological methods for the isolation and identification of bacteria. Phenotypic detection was performed by antibiotic disc synergy methods for phenotypic detection of ESBL and Antibiotic methods for detection of quinolone resistance. Eighteen publications (15.5%) combined conventional microbiology with molecular methods.

Data analysis

The extracted data were used for descriptive statistical analyzes. Further analysis was carried out in several stages. The Meta-analyzes and plotting of the graphs of the main pathogenic bacteria and the prevalence of antibiotic resistance as well as the estimation of the effect of the country were carried out using SPSS version 21 software.

RESULTS

Among the 210 publications gathered from the PubMed, Google Scholar and AJOL databases, eighty two (82) publications which dealt specifically with resistance to ß-lactams

and/or quinolones were considered to be eligible for inclusion in this review. The flow diagram of the documentary research and the selection of the studies is presented in Fig. 1.

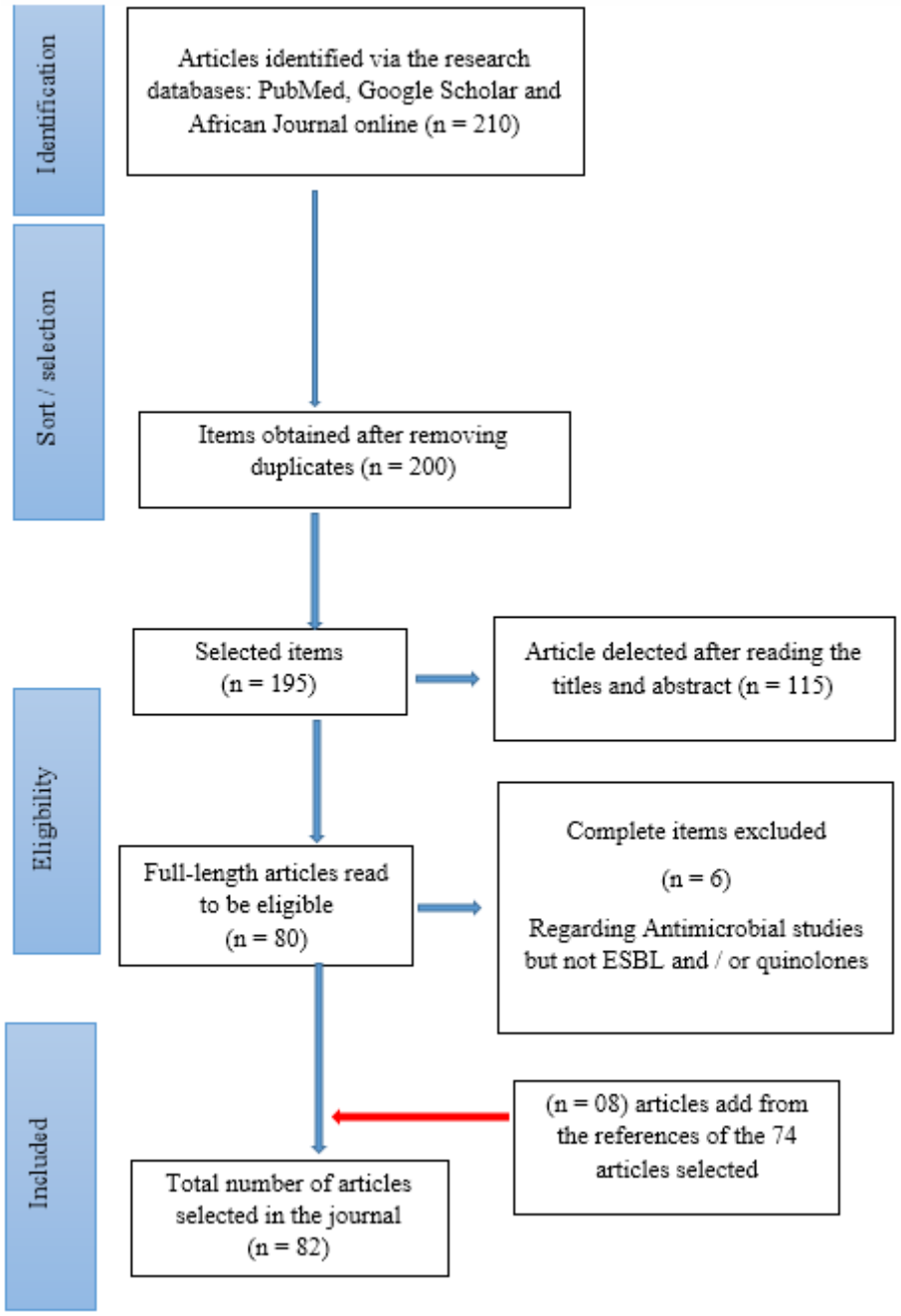

Figure No. 1: Diagram detailing study selection. Abbreviation: ESBL: Extended Spectrum Beta Lactamases

Documents included in the analysis by country and types of products examined

Table 1 shows the number of publications from each country that were included in this review. Burkina Faso (19.5%, 16/82) and Nigeria (39%, 32/82) had more articles included

than the other countries. Niger (6.1%, 5/82), Ghana (07.3%, 6/82) and Senegal (8.5%, 7/82) (n = 5 to 7) were followed in terms of publication in the study period. The other countries of West Africa: Mauritania, Sierra Leone, Guinea Bissau, Benin, Mali, Côte d'Ivoire, and Togo with one to four publications.

Table No. 1: Number of articles by country

Countries	Manuscript number, n (%)	References
Benin	2 (2.4)	1, 2
Burkina Faso	16 (19.5)	3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18
Ghana	6 (7.3)	19, 20, 21, 22, 23,24
Guinee Bissau	1 (1.2)	25
Ivory Coast	4 (3.7)	26, 27, 28,29
Mali	3 (3.9)	30, 31,32
Mauritania	1 (1.2)	33
Niger	5 (6.1)	34, 35, 36, 37,38
Nigeria	32 (39.0)	39,40,41,42,43,44,45,46,47,48,49,50,51, 52,53,54,55,56,57,58,59,60,61,62,63,64, 65,66,67,68,69,70
Senegal	7 (8.5)	71, 72, 73, 74, 75, 76,77
Sierra Leon	1 (1.22)	78
Togo	4 (4.87)	79, 80, 81,82
Total	82 (100)	

Resistance to ß-lactams and/or quinolones varied in terms of origin or type of sample. For analyzes, we have grouped these elements into a wider range of origin, as indicated in Table 2. The majority of studies (78.05%, 64/82) focused on bacterial strains isolated from hospital or community infection. Only 13.41% (11/82) of the publications studied resistance to ß-lactams and/or quinolones on bacterial strains isolated from the environment. The remaining 8.54% (7/82) were food-related publications such as vegetables, fruit, juice, meat, ready-made meals.

Table No. 2: Field of study covered in publications.

Field	Nature of the sample	Number of items
Hospital and community infection	Faeces, urine, blood, vaginal swabs ...	64
Environmental	Water, animal faeces, effluent, surface.	11
Food	Vegetable, fruit, juice, meat, cooked or uncooked dish …	7
Total		82

Isolated microorganisms by domain

Table 3 shows the strains of *Escherichiacoli*, *Klebsiella sp*, *Salmonella*, *Pseudomonas* and *Enterobacteriaceae* other than the strains of *Escherichia coli* and *Klebsiella sp*, which have been the subject of studies on resistance to ß-lactams and/or to quinolones in different fields. Most of them are isolated in community or hospital infections. In addition, certain publications have been carried out on several bacterial strains in one field or either on the same bacterial species in several fields. This led to the obtaining of the total number of bacterial strains (n = 126) higher than the total number of publications (n = 82). This should not be seen as a difference. The other microorganisms mentioned in these publications are *Campylobacter*, *Yersinia*, *Serratia* and *Vibrio*, most of them have only been identified the genus.

Table No. 3: Number of articles having carried out their study on the production of ESBL and/or the resistance of quinolones in frequently isolated species according to the field of study

	Medical	**Food**	**Environment**	**Total (%)**
Escherichia coli	26	16	4	46 (36)
Klebsiella pneumoniae	22	10	5	37 (29)
Enterobacteriaceae[*]	5	5	2	12 (10)
Salmonella	10	3	1	14 (11)
Pseudomonas aeruginoas	4	3	1	8 (06)
Autre[**]	2	5	1	9 (07)
Total			126	

[*]*Enterobacteriaceae* except *Escherichia coli* and *Klebsiella pneumoniae;* **other: Gram-negative bacteria included *Campylobacter Yersinia, Serratia* and *Vibrio.*

Percentage of publication on isolated bacterial strains (%) = (Number of studies carried out on the bacterial strain / Number of Total articles included in the study) x 100.

Prevalence of resistance to ß-lactams and/or quinolones from pathogens

Studies on the resistance of bacteria to antibiotics without mention of resistance to ß-lactams and/or quinolones were not included. For the rest of analyzes, articles that dealt only with

Enterobacteriaceae resistance without mentioning prevalence by species were excluded from the study (n = 35). Hence, 47 articles were subjected to meta-analysis. These articles addressed the prevalence of resistance or the epidemiology of resistance of pathogenic bacteria such as strains of *E. coli* (including VTEC / EHEC / ETEC / STEC / MNEC / UPEC or those mentioned as *E.coli* environmental), *Klebsiella pneumonia*, *Salmonella sp*. (With or without indication of species and serotypes) and *Pseudomonas aeruginosa*.

Fig. 2 shows that the average prevalence of resistance to ß-lactams of *E. coli* strains calculated among the publications examined (n = 46) was 46.81% (95% CI: 23.98 - 69.64, p <0.001). The average prevalence of quinolone resistance was 43% (95% CI 17.4-68.6) (n = 21). I^2 = 97.5%, signifies great heterogeneity between publications.

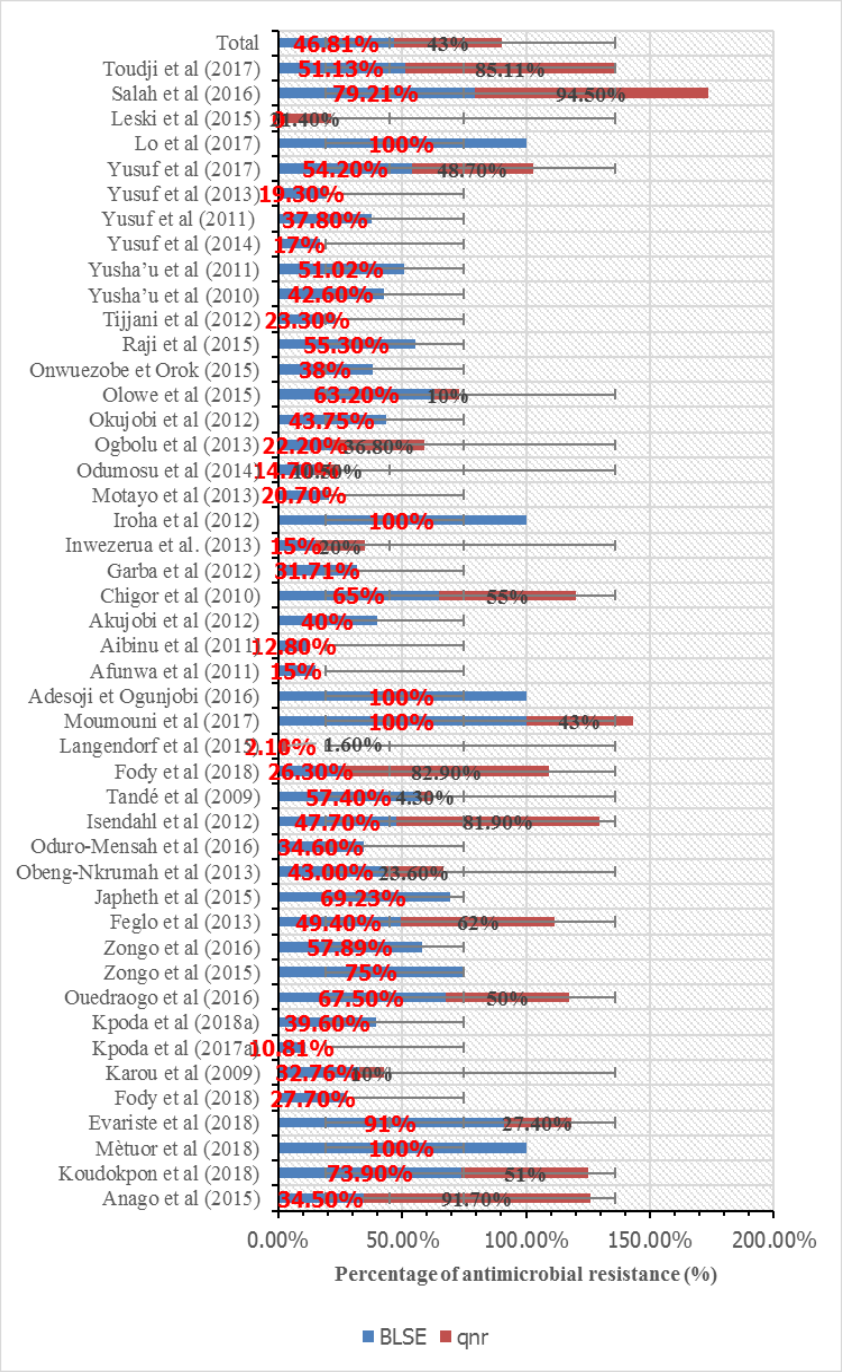

Figure No. 2: Prevalence of resistance to ß-lactams and quinolones from strains of Escherichia coli. (Confidence Interval (CI) 95%, I^2 = 95.7%, p <0.001). ESBL: Broad Spectrum ß-Lactamase, qnr = resistance to quinolones.

The average prevalence of resistance of *Salmonella Spp.* to ß-lactams as calculated from 14 publications, 15.29% (95% CI: 6.85 - 23.73, p <0.001). Average prevalence of quinolone resistance of *Salmonella* strains is 17.2% (95% CI: 08.54 - 25.86) (n = 07) (Fig. 3). There was also great heterogeneity among these publications (I^2 = 97.2%).

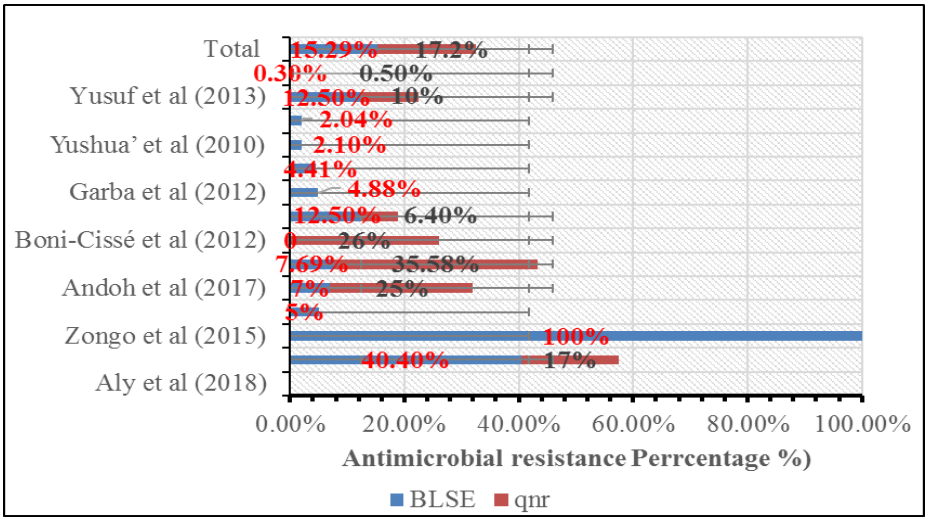

Figure No. 3: Prevalence of resistance to ß-lactams and quinolones from strains of Salmonella spp. (Confidence Interval (CI) 95%, I2 = 95.7%, p <0.001). ESBL: Broad Spectrum ß-Lactamase, qnr = resistance to quinolones.

The average prevalence of 18.42% (95% CI: 04.67 - 32.17, p <0.01) of resistance to ß-lactams was calculated from 07 publications in strains of *Pseudomonas aeruginosa* and the average prevalence of resistance to quinolones is 50% (n = 02) (Fig. 4).

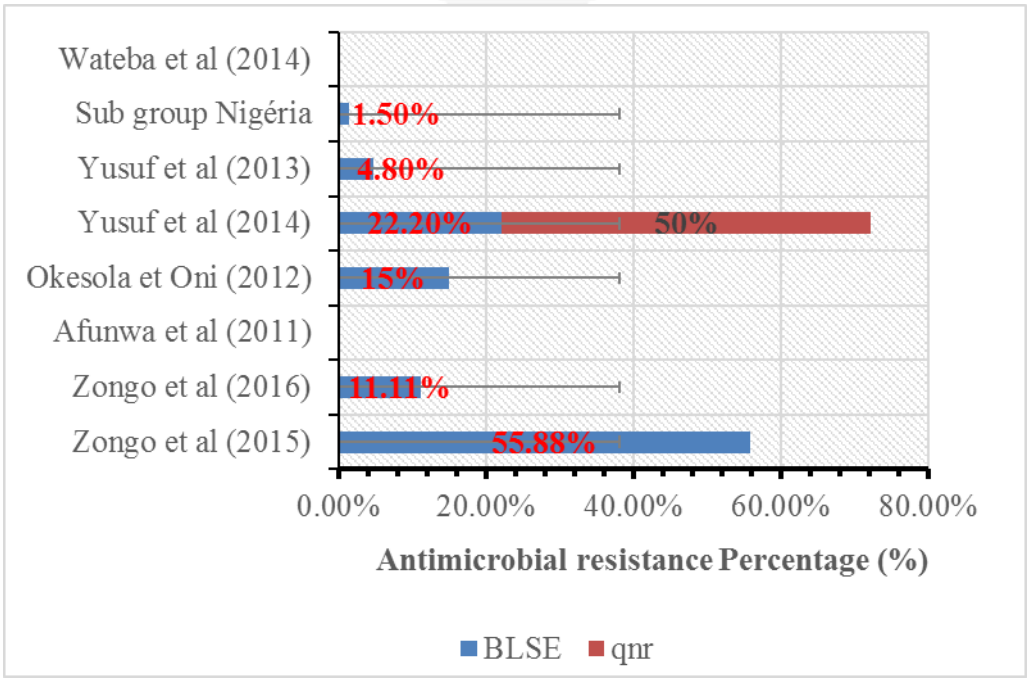

Figure No. 4: Prevalence of resistance to ß-lactams and quinolones from strains of Pseudomonas aeruginosa. (Confidence Interval (CI) 95%, I^2 = 95.7%, p <0.001). ESBL: Broad Spectrum ß-Lactamase, qnr = resistance to quinolones.

Fig. 5 shows the average prevalence of ß-lactam resistant strains of *Klebsiella pneumoniae* as calculated from 35 publications, 44.75% (95% CI: 19.65 - 69.85, p <0.001). The average prevalence of quinolone resistance of strains of *Klebsiella pneumoniae* is 49.3% (95% CI: 24.05 –74.55) (n = 11) (Fig. 5). There was also great heterogeneity among these publications (I^2 = 99.3%).

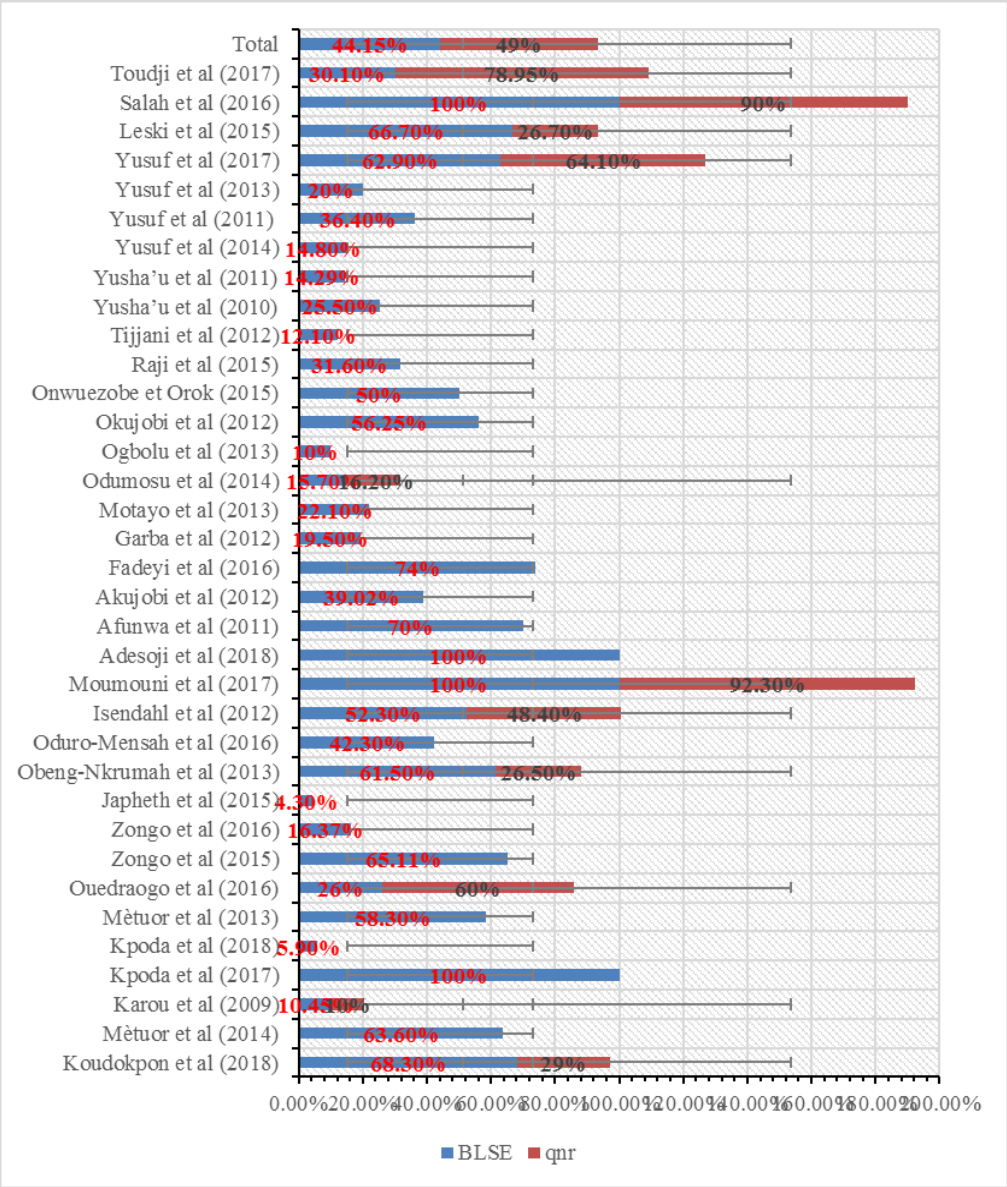

Figure No. 5: Prevalence of resistance to ß-lactams and quinolones from strains of *Klebsiella pneumoniae*. (Confidence Interval (CI) 95%, I2 = 95.7%, p <0.001). ESBL: Broad Spectrum ß-Lactamase, qnr = resistance to quinolones.

Prevalence of resistance by country and year

The average prevalence of overall resistance of pathogens resistant to ß-lactams is 42.62% (95% CI, 22.34 - 62.90%) and quinolones, 42.10% (95% CI: 21.67% - 62.53) and the difference in the prevalence of resistance among countries was statistically significant (p <0.001). The highest prevalence of resistance to ß-lactams is in Senegal 100% (p <0.015) and Togo (87.11% with 95% CI between 82.86 and 91.36, p <0.001) for the resistance to quinolones. The lowest prevalence of ß-lactams is at Ivory Coast (3.8% with a 95% CI between 02.60 and 05, p <0.05) and those of quinolones in Mali with 04.30 % (95% CI, 2.7 - 5.90, p <0.001) (Figure 6). The values of I^2 between 94.1% and 99.8% for all the countries imply that the studies of these countries have great heterogeneity.

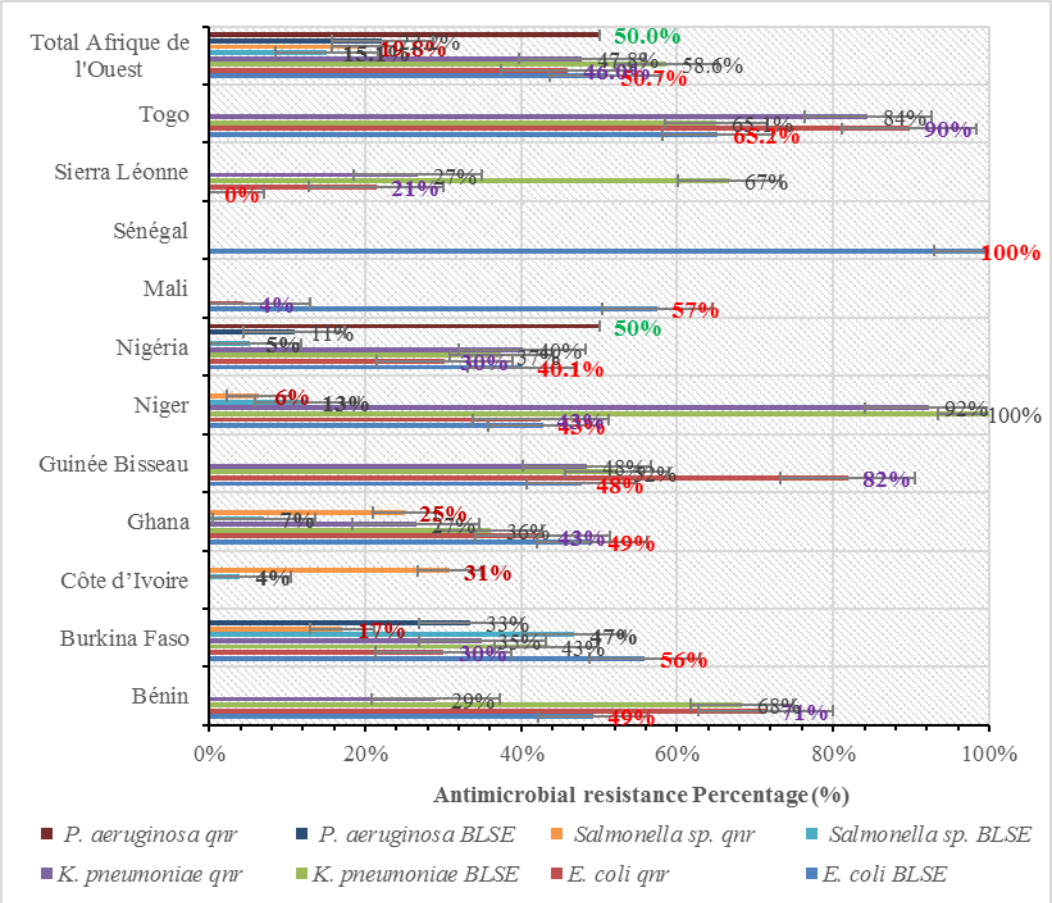

Figure No. 6: Prevalence of resistance to ß-lactams and quinolones from strains of *E. coli*, *K.pneumoniae*, *Salmonella spp.*, And *Pseudomonas aeruginosa*. (Confidence Interval (CI) 95%, 94.1 <I2 <99.8%, p <0.001). ESBL: Broad Spectrum ß-Lactamase, qnr: resistance to quinolones.

Fig.7 shows the emergence of resistance to ß-lactams and quinolones in West Africa from 2009 to 2018. The highest average prevalence of resistance in West Africa during our study in ß-lactams was 2018 (58.03% with 95% CI: 26.62 - 89.44, p <0.0001) and in 2016 (74% with 95% CI: 55.37 - 92.63, p <0.0001) for resistance to quinolones.

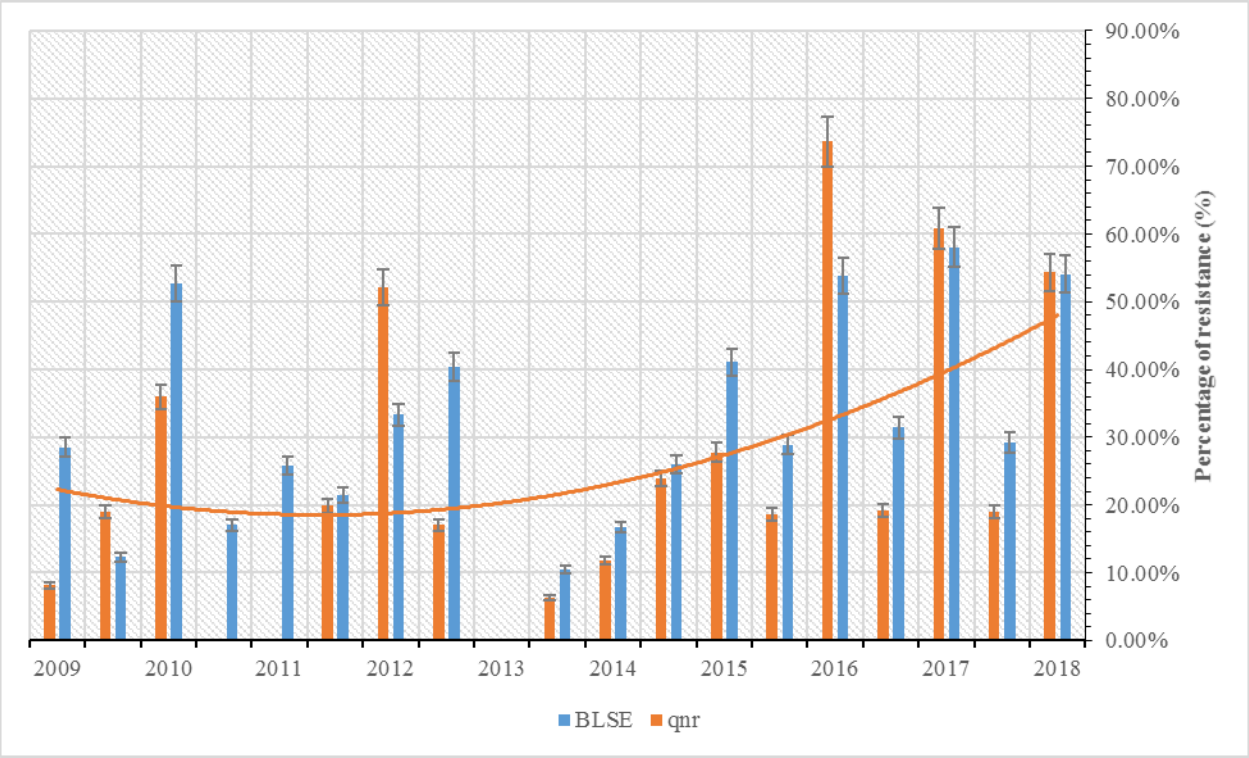

Figure No. 7: Emergence of resistance to ß-lactams and quinolones in West Africa from 2009 to 2018

The prevalence of ESBL genes (blaESBL) and resistance to quinolones (Qnr) circulating in West Africa

The prevalence of the Bla and Qnr genes in West Africa during our study period (2009 - 2018) (Fig. 8) is 43.77% respectively (95% CI: 14.08 - 73.46, p <0.001) and 55.70% (95% CI: 27.3 - 84.10, p <0.0001). The highest prevalence among the Bla_{ESBL} and Qnr genes in West Africa is CTX-M with 53.57% (95% CI: 26.58 - 80.56, p <0.001) (n = 26) and qnrS with 57.72% (95% CI: 33.3 - 82.14, p <0.01) (n = 2). SHV (29.66% with 95% CI between 04.07 and 55.25, p <0.001) (n = 19) and qnrB (32.72% with 95% CI between 07.12 and 58.28, p < 0.05) (n = 2) are the genes with the lowest prevalence observed among the Bla_{ESBL} and Qnr genes.

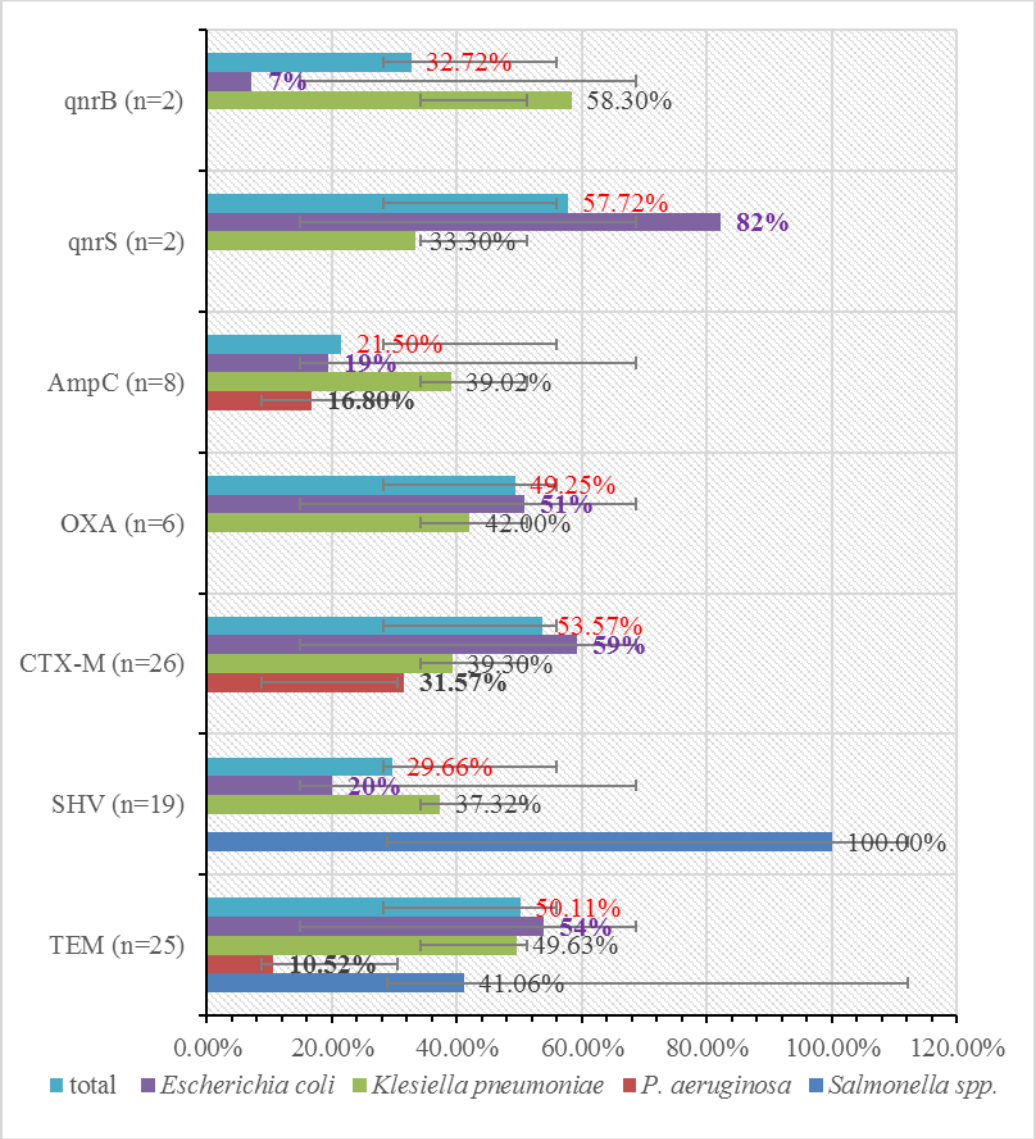

Figure No. 8: Prevalence of bla_{ESBL} and qnr genes in West Africa in the publications consulted from 2009 - 2018. (Confidence interval (CI) 95%, p <0.001).

DISCUSSION

Twelve countries in West Africa with different economic development statuses were included in the study. It is therefore unrealistic to expect similar levels of scientific progress and sophistication in terms of research results and methodologies. In addition, it has been reported that research publications in West Africa on resistance are very poorly represented (26) than South and North Africa which represent three-quarters (3/4) publications listed in international databases such as PubMed. Moreover, the quarter (1/4) of the remaining publications cover the rest of Africa. The twelve countries of West Africa are grouped in the remaining quarter. More than 65% of African research is published in local journal which are

not indexed in PubMed and Scopus (26), while others are accessible only in the form of reports or copies of documents in directories and university or hospital libraries. This could explain the recovery of less publication in our study.

Of the 82 publications reviewed for the 10-year period from 2009, almost 70% covered the period from 2014 to 2018. In part, it has indicates increased attention to the problems of resistance of bacterial strains to ß-lactams and quinolones in this region. The publications of research results also vary by country, Burkina Faso and Nigeria are the most active with the highest number of publications included in this study. Moreover, there have been many studies on human infections (27-29). This can be explained by the fact that the first discoveries of ESBL were made in hospital infections (30-32). In addition, the rapid evolution of this resistance and the possibility of horizontal transmission to other species via plasmids have widened research into community infections and the food and environmental production chain, in order to understand the mechanism of acquisition of these resistance genes between humans, animals and the environment (18, 20).

In a general context, the first plasmid β-lactamases (narrow spectrum penicillinases) (TEM-1/2, SHV-1) were initially described in the 1960s in *Escherichia coli* and *Klebsiella pneumoniae* and very quickly spread among other species (*Enterobacteria*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*) (32-34). Our study concludes that the microorganisms commonly studied in West African countries are the strains of *E. coli*, *Klebsiella pneumoniae, Salmonella Spp.*. and *Pseudomonas aeruginosa*. All of them have an average double-digit prevalence. The high prevalence of resistance to ß-lactams and quinolones from strains of *E. coli*, *Klebsiella pneumoniae* and *Salmonella spp* indicate a major problem in drug control (Consumption, sale, storage conditions, transport and waste management microbiological contamination).

Senegal and Togo appear to be the countries in West Africa with the highest prevalence of resistance to ß-lactams to quinolones in our study. The increased in resistance was shown in West Africa during our study period. However, studies have shown a prevalence of resistance to quinolones of 55.91% in the United States (21,35), 8% in Korea (36), 34.7% in Guangdong province in China (23,37), 91.4% in Poland (24,38) and 44% in South Africa (39, 40). Other studies on resistance to ß-lactams have shown prevalence ranging from 16.4 to 31.4% in Algeria (41, 42) and from 11 to 42.9% in Egypt (10, 27). In Libya, ESBL class A/D and carbapenemase were detected in 32.6% and 16% respectively (43). In Tunisia, ESBLs,

AmpCs and carbapenemases of class A and D were present, and the prevalence varied from 11.7 to 77.8% (44). In East Africa, more specifically in Ethiopia and Kenya, it is respectively 62% and 37.4 (45, 46).

The blaCTX-M and qnrS genes are the resistance genes with the highest prevalence in our study. Studies have shown that the blaCTX-M genes are generally associated with other types of genes for resistance to ß-lactams and quinolones. Strosberg [26] confirms this result in his study on ESBL-producing enterobacteria in Africa. This explains resistance to quinolones by ESBL-producing strains because the genes coding for resistance to beta-lactams and quinolones are located on the same plasmid and are thus transmitted together between different species of enterobacteria (32, 47).

In West African countries, the best characterization of genetic resistance to ß-lactams and quinolones is resistance mediated by plasmids (31, 48). The main molecular characterizations of the ESBL and quinolone resistance genes are carried out on Gram-negative bacteria originating from animals and in particular on the *E. coli* strains causing human extra-intestinal infections (49). The transmission of resistance by plasmids is diverse and we can cite among other things the geographical situation, the host animals and the host bacteria, in particular in the host animals such as in the production chains of poultry, pigs, and cattle. The main genes of bla_{ESBL} and *Qnr* have been identified in *E. coli* and *Klebsiella pneumonia* in humans, the host *Enterobacteriaceae* for the transmission of resistance by the plasmid in food and the environment included species of *Salmonella* and *E. coli* (50, 51). The genes coding for the bla_{ESBL} and *Qnr* described seem to vary proportionally and the blaCTX-M, are predominant in West Africa.

CONCLUSION

This study shows the emergence of resistance to ß-lactams and quinolones in West Africa over the past ten years. The use of β-lactams and fluoroquinolones in humans and animals should be urgently limited. This limitation may reduce the selection and persistence of predominant ESBL clones and the likely spread of conjugate plasmids among bacterial strains. This would also reduce not only the number of potential bla_{ESBL} donors but also the accumulation of antibiotic resistance genes on common genetic elements. But other studies deserve to be carried out on resistance to ß-lactams and quinolones in West African countries

in order to have more important data to determine the prevalence of this resistance in this area. Few studies are carried out in West Africa like other parts of Africa.

Conflicts of interest: Authors do not declare any conflict of interest.

Author contributions: B.G and A.M.D designed the research protocol; S.D.K., J.S. and Y.A.A revised the research protocol; B.G extracted the data; F.W.D., A.M.D., B.G and A.K.O. contributed to the data analysis and the draft of the manuscript; B.G. wrote the article.

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