Prevalence and outcome of bloodstream infections due to third-generation cephalosporin-resistant Enterobacteriaceae in sub-Saharan Africa: a systematic review

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Background: The prevalence of bacterial bloodstream infections (BSIs) in sub-Saharan Africa (sSA) is high and antimicrobial resistance is likely to increase mortality from these infections. Third-generation cephalosporin-resistant (3GC-R) Enterobacteriaceae are of particular concern, given the widespread reliance on ceftriaxone for management of sepsis in Africa.

Objectives: Reviewing studies from sSA, we aimed to describe the prevalence of 3GC resistance in Escherichia coli, Klebsiella and Salmonella BSIs and the in-hospital mortality from 3GC-R BSIs.

Methods: We systematically reviewed studies reporting 3GC susceptibility testing of E. coli, Klebsiella and Salmonella BSIs and Salmonella BSIs and the in-hospital mortality from 3GC-R BSIs.

Results: We identified 40 articles, including 7 reporting mortality. Median prevalence of 3GC resistance in E. coli was 18.4% (IQR 10.5 to 35.2) from 20 studies and in Klebsiella spp. was 54.4% (IQR 24.3 to 81.2) from 28 studies. Amongst non-typhoidal salmonellae, 3GC resistance was 1.9% (IQR 0 to 6.1) from 12 studies. A pooled mortality estimate was prohibited by heterogeneity.

Conclusions: Levels of 3GC resistance amongst bloodstream Enterobacteriaceae in sSA are high, yet the mortality burden is unknown. The lack of clinical outcome data from drug-resistant infections in Africa represents a major knowledge gap and future work must link laboratory surveillance to clinical data.

Introduction

The emergence and spread of antimicrobial resistance (AMR) in bacteria is recognized as a global public health problem. Drug-resistant infections (DRIs) caused by AMR bacteria threaten human health worldwide, with the greatest mortality burden expected to occur in low- and middle-income countries. In settings where antibiotics and advanced diagnostics are available and affordable, DRIs can be treated with tailored regimens using second- or third-line antibiotics; however, these agents cost more and increase healthcare expenditure. In sub-Saharan Africa (sSA), where bacterial bloodstream infection (BSI) is a major cause of morbidity and mortality, diagnostic facilities are scarce and antibiotics such as carbapenems and semi-synthetic aminoglycosides (e.g. amikacin) are either unavailable or prohibitively expensive, the morbidity and mortality from DRIs is predicted to be high.

In many sSA hospitals, limited nursing capacity favours the use of broad-spectrum antimicrobials with a once-daily dosing regimen and this has led to the widespread adoption of the third-generation cephalosporin (3GC) ceftriaxone for the empirical management of hospitalized patients with suspected sepsis.
ESBL-producing Enterobacteriaceae, which are resistant to penicillins and 3GCs, represent a threat to the treatment of BSI in this setting and have been identified as priority pathogens on which all national AMR programmes should focus their surveillance and reporting.\(^2,7\)

Comprehensive AMR surveillance in sSA is limited by lack of quality-assured diagnostic microbiology laboratories, but knowledge of the prevalence and spatiotemporal trends of 3GC-resistant (3GC-R) Enterobacteriaceae is critical to inform national and international antibiotic prescribing guidelines. Additionally, securing access to effective second- and third-line antibiotics in Africa will not only require an understanding of the prevalence of 3GC resistance, but also of the burden and impact of these pathogens on patients and healthcare systems.\(^8\) We have therefore systematically reviewed published reports of 3GC susceptibility amongst key Enterobacteriaceae in sSA, including surveillance data and clinical cohorts. Robust clinical outcome data are needed to support the estimates and assumptions that the greatest global burden associated with AMR will occur in sSA\(^9\) and we have therefore also reviewed studies that describe mortality from 3GC-R BSI. The aim of this systematic review was to determine the prevalence of 3GC resistance amongst Escherichia coli, Klebsiella spp. and Salmonella spp. in sSA and to provide an estimate of the associated mortality burden from these infections.

**Methods**

**Search strategy and selection criteria**

We systematically reviewed articles published between 1 January 1990 and 31 August 2019, according to a pre-specified protocol, prepared in February 2017 (Table S1, available as Supplementary data at JAC Online) with no language restrictions, following PRISMA guidelines (Table S2). We searched PubMed and Scopus according to a predefined strategy with search terms relating to BSI and susceptibility testing (Table S3). A search string that included all sSA countries as defined by the UN list of 54 African sovereign states returned more articles than a string using ‘Africa’ alone. References cited in selected articles were reviewed for additional articles and authors were contacted to obtain original data, where percentages but not absolute numbers of resistant organisms were provided.

Studies were included if they tested E. coli, Klebsiella spp. or Salmonella spp. for 3GC resistance. Methods of confirmatory ESBL testing, such as double-disc synergy or PCR, were extracted from articles if they were reported, but we did not exclude studies that did not confirm ESBL status. We included surveillance data in addition to studies reporting clinical cohorts, but excluded case reports, case series, expert opinions and reviews.

**Data extraction**

Two authors (R.L. and P.M.) independently searched the literature and screened the abstracts of all retrieved records. The full text of remaining English articles was reviewed by one author (R.L.) and of French language articles by another (N.V.G.). Articles in other languages were not found in the search. Disputes about article inclusion were resolved through discussion, with recourse to a third reviewer (N.A.F.) if required. Predefined variables were extracted from each article (Table 1). Variables included study design and setting, clinical data such as age and HIV prevalence of clinical cohorts, and information on laboratory methods including antimicrobial susceptibility testing (AST) method and guideline, and method of ESBL confirmation. Mortality data were extracted as they were reported in the articles, as case-fatality rates, ORs or relative risks (RRs).

**Data analysis**

Prevalence is described as proportions of 3GC-R isolates, calculated from numbers of isolates of E. coli, Klebsiella spp., non-typhoidal Salmonella (NTS) or Salmonella Typhi tested against a 3GC and the number of resistant strains. Forest plots were generated, illustrating proportion estimates for each study with 95% CI calculated using the Wilson’s score method. The I\(^2\) statistic was calculated to quantify heterogeneity.

Our initial analysis plan aimed to calculate a pooled proportion of 3GC resistance for each pathogen, using random-effects meta-analysis with subanalysis by African region. However, high levels of heterogeneity amongst included studies precluded meaningful meta-analysis and we therefore present median prevalence of 3GC resistance for each pathogen, with corresponding IQR to provide an assessment of the wide range in resistance prevalence. Medians were calculated for sSA and for each African region as defined by the United Nations Statistics Division.\(^9\)

Heterogeneity of proportion estimates was explored using predefined subgroup analysis by African region and a post hoc subgroup analysis by age group of study population. Visual inspection of resulting forest plots was carried out and a test for subgroup differences applied where visual inspection suggested a likely difference in subgroup proportion estimates and where more than two studies contributed to each subgroup. We additionally examined for trends in proportions estimates over time using visual inspection of forest plots, ordered by year of publication, and a linear meta-regression model. Analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Risk of bias assessment**

In terms of delineating a population estimate, we noted that the most likely risk of bias is patient selection. Additionally, the laboratory techniques and their implementation may differ in sensitivity and specificity and could also introduce bias. We modified the Critical Appraisal Skills Programme (CASP) checklist to design a risk-of-bias assessment to fit our research question, assessing risk of bias in patient recruitment and laboratory techniques used (Table S4). The assessment was performed by both R.L. and P.M. and any disagreements were resolved by consensus.

To explore for indirect evidence of publication bias, we examined 3GC resistance estimates against the number of isolates included in the study, as smaller studies may be subject to publication bias.

**Results**

The online database search combined with reference review from key papers generated 1401 articles and, of these, 185 abstracts were selected for full-text review (Figure 1). Original data for one article were retrieved by direct communication with authors.\(^10\) Forty articles met the inclusion criteria and were included in the systematic review, which synthesizes 11 404 isolates. Of these, 20 articles reported proportions of 3GC resistance in E. coli and 28 in Klebsiella spp. Twelve studies reported proportions of 3GC resistance in NTS and four in S. Typhi.

Table 1 presents the characteristics of all included studies. Data were available from 12 countries across all four sSA regions (Figure 2), with the highest proportion of studies (11/40) from South Africa. All studies were observational. There were 30 studies that recruited cohorts of patients with confirmed or suspected BSI, 16 of which were prospective, 13 retrospective and 1 mixed. Four studies were cross-sectional reviews of isolates and three tested isolates collected as part of longitudinal multisite surveillance. There was one case–control study, designed to estimate mortality from 3GC-R BSI.\(^11\)
| First author | Country, year of publication | Years of data collection | Study type | Healthcare setting | Age category | HIV, n (%) | Blood culture method, organism identification | AST method, AST breakpoint guideline | ESBL confirmatory test | External lab QC | Blood culture positivity in study population, n (%) | Prevalence of 3GC resistance, n (%) | Other findings |
|--------------|-----------------------------|--------------------------|------------|-------------------|--------------|------------|-----------------------------------------------|-----------------------------------|-------------------|----------------|-----------------------------------------------|-------------------------------|------------------|
| Acquah⁴¹     | Ghana, 2011–12              | Retrospective analysis of positive blood cultures | Urban referral hospital | Paediatric       | NR           | Manual Disc diffusion then automated Etest | CLSI                             | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 1/12 (8.3) | NR               |  |
| Apondi⁴²     | Kenya, 2002–13              | Retrospective analysis of Klebsiella isolates | Urban referral hospital | All ages         | NR           | Manual Automated Disc diffusion | NR                | Yes            | NR             | 86/331 (26.0) | Klebsiella spp. 68/78 (20.7) | NR               |  |
| Bejon⁴³      | Kenya, 1994–2001            | Retrospective analysis of Gram-negative bacilli | Rural district hospital | Paediatric (<1998) | NR           | Manual Automated Disc diffusion | NR                | Yes            | NR             | 86/331 (26.0) | Klebsiella spp. 4/63 (1.2) | NR               |  |
| Blomberg⁴⁷   | Tanzania, 2007              | Prospective cohort of children with suspected systemic infection | Urban referral hospital | Paediatric (0–7 years) | NR           | Automated Disc diffusion and Etest | CLSI                             | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 9/52 (17.0) | NTS 1/39 (2.6) | Significantly higher 3GC resistance in HAI than CAI |
| Breurec⁴⁸    | Senegal, 2007               | Prospective cohort of neonates with suspected systemic infection | Urban referral hospital | Paediatric (neonates) | NR           | Manual Disc diffusion | Etest, PCR           | NR                | NR             | 86/331 (26.0) | Klebsiella spp. 3/39 (84.6) | NR               |  |
| Brink⁴⁹      | South Africa, 2007          | Prospective review of bacterial isolates | Private urban hospitals (12 sites) | All ages         | NR           | Mixture of disc diffusion and automated VITEK 2 CLSI | Mixture of VITEK 2 and double-disc synergy | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 47/471 (10.0) | Klebsiella spp. 293/636 (46.0) | Higher 3GC resistance in HAI than CAI and CAI; no statistical analysis |
| Buys³¹       | South Africa, 2006–11       | Retrospective review of K. pneumoniae isolates | Urban referral hospital | Paediatric       | 82/410 (20.0) | Automated Automated VITEK 2 | Mixtures of VITEK 2 and disc diffusion then automated | Mixtures of VITEK 2 and double-disc synergy | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 3/39 (84.0) | Klebsiella spp. 3/39 (84.0) | Higher 3GC resistance in HAI than CAI and CAI; no statistical analysis |
| Crichton⁵⁰  | South Africa, 2012–15       | Cross-sectional review of BSI | Urban referral hospital | Paediatric       | 18/141 (12.8) | Automated Automated VITEK 2 | Mixtures of VITEK 2 and disc diffusion | CLSI                             | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 47/471 (10.0) | Klebsiella spp. 293/636 (46.0) | Higher 3GC resistance in HAI than CAI and CAI; no statistical analysis |
| Dramowski⁵²  | South Africa, 2009–13       | Retrospective cohort of HA neonatal BSI | Urban referral hospital | Paediatric (neonates) | NR           | Automated Automated VITEK 2 | Mixtures of VITEK 2 and disc diffusion | CLSI                             | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 3/39 (84.0) | Klebsiella spp. 3/39 (84.0) | Higher 3GC resistance in HAI than CAI and CAI; no statistical analysis |
| Dramowski⁵³  | South Africa, 2008–13       | Retrospective review of paediatric BSI | Urban referral hospital | Paediatric (excluding neonates) | (13.4) | Automated Automated VITEK 2 | Mixtures of VITEK 2 and disc diffusion | CLSI                             | NR                | Yes            | 86/331 (26.0) | Klebsiella spp. 3/39 (84.0) | Klebsiella spp. 3/39 (84.0) | Higher 3GC resistance in HAI than CAI and CAI; no statistical analysis |

**Table 1.** Characteristics of included studies
| Study | Country | Years | Study Type | Setting | Age(s) | HIV Status | Sample Size | Methodology | Resistance | Species | Trends | Comments |
|-------|---------|-------|------------|---------|---------|------------|-------------|-------------|------------|---------|--------|----------|
| Eiaheh49 | Ghana | 2007–09 | Prospective cohort of patients with fever or history of fever or suspected neonatal sepsis | Rural district hospital | All | NR | | Automated VITEK 2 EUCAST | Double-disc synergy and PCR | NR | E. coli 5/50 (10) Klebsiella spp. 3/41 (82.9) NTS0/25 | Possible lower 3GC resistance in CAI, but no statistical analysis |
| Kalani60 | South Africa | 2011–14 | Multisite prospective surveillance of Salmonella BSIs | Urban referral and private hospital | Pediatric (3 months–9 years) | NR | | Disc diffusion ± Etest CLSI | Double-disc synergy and PCR | Yes | NTS4/977 (6.3) S. Typhi 0/164 | NTS0/198 |
| Kalu61 | Kenya | 2002–05 | Cross-sectional review of NTS isolates over 12 years | Rural district hospital | Children (0–13 years) | NR | | Automated Disc diffusion | Yes | NA | NTS0/36 | Trends reported, no change over time |
| Ka62 | South Africa | 2002 | Prospective cohort of patients with CAK. pneumoniae | Urban multisite | Adults >16 years | 7/40 (18) | | Automated Disc diffusion | Yes | NA | K. pneumoniae 3/40 (7.5) | CAI only |
| Ko63 | Kenya | 2003–08 | Retrospective analysis of positive blood cultures | Urban referral | All | 123/10 (1.1) | | Automated Disc diffusion | Yes | 109/18 750 (5.8) | E. coli 10/69 (15.4) Klebsiella spp. 5/38 (13.1) NTS0/13 | No obvious difference in 3GC resistance between CAI, HAI and HCAI but no statistical analysis |
| Lau64 | Ghana | 2010–13 | Retrospective review of Salmonella blood culture isolates | Urban referral | All | NR | | Automated Disc diffusion | Yes | 276/23 278 (11.7) | E. coli 3/192 (33.7) Klebsiella spp. 68/88 | |
| Lohan65 | South Africa | 2011–13 | Retrospective cohort of children with culture-confirmed BSI | Urban referral | Pediatric | 17/5.24 (13.4) | | Automated Disc diffusion | Yes | 958/16 951 (5.7) | E. coli 3/192 (33.7) Klebsiella spp. 68/88 | |
| Lungaya66 | DRC | 2007–11 | Prospective cohort of invasive NTS | Mixed multisite—full details NR | All | NR | | Disc diffusion ± Etest CLSI | Yes | 989/364 (10.3) | NTS3/23 (1.3) |
| Mohend67 | Tanzania | 2013 | Prospective cohort of children with fever or history of fever | Rural district hospital | Neonates | 10/17 (58.8) | | Automated Disc diffusion CLSI | Yes | 58/503 (11.5) | E. coli 10/4 (14.3) Klebsiella spp. 4/22 (18.2) | Differs in LOS and ETS but not by AMR patterns |
| Matsha68 | Burundi | 2012–13 | Prospective cohort of children with fever or signs of severe illness | Rural district hospital and health centre | Neonates | 4/21 (19.0) | | Disc diffusion ± Etest CLSI | Yes | 60/304 (19.7) | E. coli 3/192 (16.0) Klebsiella spp. 68/88 | |
| Marando69 | Tanzania | 2018 | Prospective cohort of neonates with suspected sepsis | Neonates | Manual | 60/304 (19.7) | | Automated Disc diffusion CLSI | Yes | NTS0/25 (80.8) | K. pneumoniae 21/26 (80.8) |
| Mengo70 | Kenya | 2004–06 | Cross sectional study of S. Typhi isolates | Urban referral and private hospital | All | NR | | Disc diffusion ± Etest CLSI | Yes | 26/808 (3.2) | S. Typhi 1/17 (5.9) |
| Mhado71 | Tanzania | 2009–19 | Prospective cohort of neonates with suspected sepsis | Neonates | Manual | 60/304 (19.7) | | Automated Disc diffusion CLSI | Yes | 63/711 (8.9) | S. Typhi 0/12 |
| Markel72 | South Africa | 2008 | Prospective cohort of positive blood cultures on NICU | Urban referral hospital | Pediatric neonates | 9/54 (16.6) | | Automated Disc diffusion ± Etest CLSI | Yes | 5/503 (11.5) | E. coli 3/192 (16.0) Klebsiella spp. 4/22 (18.2) | Differs in LOS and ETS but not by AMR patterns |

Continued
| First author | Country, year of publication | Years of data collection | Study type | Healthcare setting | Age category | HIV, n (%) | Blood culture method, organism identification | AST method, AST breakpoint guideline | ESBLE confirmatory test | External lab QC | Blood culture positivity in study population, n (%) | Prevalence of 3GC resistance, n (%) | Other findings |
|--------------|-----------------------------|--------------------------|------------|-------------------|--------------|-----------|----------------------------------|----------------------------------|--------------------------|----------------|---------------------------------|-----------------------------|-----------------|
| Mshana57     | Tanzania 2009               | NR                       | Cross-sectional review of Gram-negative isolates from blood/urine/swabs | Urban referral hospital | NR | NR | Disc CLSI | Double disc synergy | Yes | NR | Klebsiella spp. 29/33 (93.5) |                 |                 |
| Musicha5     | Malawi 2017                 | 1998–2016                | Retrospective isolate surveillance from patients admitted with suspicion of sepsis | Urban referral hospital | All | NR | Automated Manual, confirmed with WGS | Disc CLSI | Double disc synergy | Yes | 29.183/194 5.39% | E. coli 14/1311 (10.7) | Klebsiella spp. 260/542 (48.0) | Trends show increase in 3GC resistance over time |
| Ndi11        | Senegal 2016                | 2012–13                  | Case-control of patients with Enterobacteriaceae in blood | Urban referral | Paediatric | NR | Manual | Disc FSM | Double disc | 173/1800 (9.6) | E. coli 7/12 (58.3) | Klebsiella spp. 33/40 (82.5) | HAI only |
| Obeng-Nkurumah60 | Ghana 2008           | Prospective cohort of patients with Enterobacteriaceae in blood culture | Urban referral | All ages | NR | Automated Manual | Disc diffusion CLSI | Double disc | NR | NR | E. coli 5/7 (29.4) | Klebsiella spp. 13/26 (50.0) |                 |
| Obeng-Nkurumah60 | Ghana 2010–13          | Retrospective analysis of children with BSI | Urban referral (excluding neonates) | Paediatric | NR | Automated Manual | Disc diffusion CLSI | NR | NR | 145/1583 (9.3) | E. coli 63/112 (56.2) | Klebsiella spp. 40/68 (58.8) |                 |
| Ogunlesi51    | Nigeria 2011               | Mixed prospective/referential cohort of neonates with presumed or probable sepsis | Urban referral | Neonates | NR | Broth | Disc diffusion CLSI | NR | Yes | 174/1050 (16.6) | E. coli 6/16 (37.5) | Klebsiella spp. 12/33 (36.4) |                 |
| Onela62       | Kenya 2015                 | Prospective cohort of children with invasive NTS (nested cohort in RTS5 trial) | Rural district | Paediatric | 13/1696 (7.7) | Automated Manual | Disc diffusion and broth microdilution CLSI | NR | Yes | 134/1692 (7.9) | NTS 17/102 (16.7) |                 |
| Oni19         | Tanzania (Zanzibar) 2015   | Prospective cohort of patients with suspected septic systemic infection | Urban referral | All ages | NR | Manual, confirmed with automated VITEK 2 EUCAST | Mixed disc diffusion, confirmed with ESBLE Etest and PCR | Yes | 66/670 (14.0) | E. coli 1/10 (10) | Klebsiella spp. 5/11 (45.5) |                 |
| Paterson63    | South Africa 2004          | Prospective cohort of patients with *K. pneumoniae* BSI | Urban multisite | Adults >16 years of age | NR | Automated Manual | Mixed | NR | Broth dilution | NR | Klebsiella spp. 28/76 (37.0) | Reports mortality data for 3GC resistance but not split by country |                 |
| Peravi64      | South Africa 2014          | Multi-site prospective surveillance of *K. pneumoniae* isolates | Academic urban centres (multi-site) | All | NR | Automated (VITEK 2) | MiraScan CLSI/EUCAST and/or MicroScan guidelines | 14% confirmed with PCR from each region | NR | NR | Klebsiella spp. 1895/2774 (68.3) |                 |                 |
| Reference | Country    | Year(s)  | Study Design | Setting | Study Population | Age(s) | Recovery Method(s) | Antimicrobial Susceptibility | CAI, DRC, EOS, FSM, HAI, HCAI, LOS | CAI, DRC, EOS, FSM, HAI, HCAI, LOS |
|-----------|------------|----------|--------------|---------|------------------|--------|-------------------|-------------------------------|--------------------------------|----------------------------------|
| Preziosi  | Mozambique | 2011–12  | Prospective cohort of adults with fever | Urban referral hospital | Adults ≥18 years | 652/841 (77.5) | Automated Disc diffusion | NR | E. coli 1/14 (7.1) NTMs 10/34 (40.0) | E. coli 1/14 (7.1) NTMs 10/34 (40.0) |
| Sangare   | Mali       | 2014     | Prospective cohort, patients with suspected systemic infection referred from other health centres | Urban referral hospital | All | NR | Manual CLSI | NR | E. coli 2/34 (23.5) | E. coli 2/34 (23.5) |
| Seboxa    | Ethiopia   | 2012–13  | Prospective cohort of adults with clinically suspected sepsis and retrospective study of blood cultures positive for Gram-negative bacilli | Urban referral hospital | All | 123/399 (30.1) | Automated Disc diffusion | NR | Klebsiella 10/34 (29.4) | Klebsiella 10/34 (29.4) |
| Washihun  | Ethiopia   | 2014     | Prospective cohort of febrile outpatients, no antibiotics for 2 weeks | Urban referral hospital | All | NR | Manual | NR | E. coli 9/16 (56.2) | E. coli 9/16 (56.2) |

CAI, CA infection; DRC, Democratic Republic of the Congo; EOS, early-onset sepsis; FSM, French Society of Microbiology; HAI, HA infection; HCAI, HCA infection; LOS, late-onset sepsis; NR, not reported.
3GC resistance amongst NTS was low, at a median of 1.9% (IQR 0 to 6.1) in isolates from 12 studies (Figure S5). The highest proportion of 3GC resistance in NTS came from eastern Africa (Kenya and Mozambique) but subgroup analysis by African region did not explain interstudy variability (Figure S1). Four studies in this review carried out 3GC susceptibility testing on S. Typhi isolates. Of these, two studies from Kenya and Tanzania found 3GC resistance with prevalence of 6% (6/100) and 5.9% (1/17), respectively. These studies did not report confirmatory ESBL testing on cephalosporin-resistant S. Typhi strains.

The earliest published reports of 3GC resistance in Gram-negative BSI are from 2002. Graphical exploration of forest plots, ordered by year of publication (Figures 3–5), suggested a trend towards increased 3GC resistance over time for Klebsiella, NTS and E. coli. Meta-regression by year of publication supported a significant trend towards increased resistance over time for Klebsiella (P<0.01), NTS (P=0.02) and E. coli (P=0.02).

Studies reporting mortality estimates from 3GC-R BSI are shown in Table 3. Only one study, a paediatric case–control study in Senegal, was designed to determine attributable mortality from 3GC resistance as a primary outcome, finding that 3GC-R BSI remained the only significant independent risk factor for death in multivariable logistic regression, (OR=2.9, 95% CI 1.8–7.3, P=0.001) regardless of antibiotic treatment choice. Seven further studies provide mortality estimates for patients with 3GC-R BSI, but were not designed to estimate attributable mortality from these infections. These studies were a mixture of retrospective and prospective designs, variably providing ORs, RRs and case-fatality rates and incorporating different characteristics in multivariable models. It was therefore not possible to combine these into a single mortality estimate using meta-analysis. Where available, case-fatality rates from individual studies were high, ranging from 60% to 100%, with all but one study concluding 3GC-R BSI to be a predictor of fatal outcome in patients.

Additional study population characteristics are shown in Table 1. There were 22 studies in paediatric populations, including 6 exclusively in neonates. Four studies recruited adults over 16 years of age, 13 recruited from all age groups and one study did not report age of participants from which blood cultures were obtained. Given that age categories were generally well reported and could explain differences between proportion estimates, we carried out post hoc stratified analysis by age group (Figure S2). Visual inspection of resulting forest plots suggested no difference in proportion estimates by age group for E. coli (Figure S2a), but potentially higher proportion estimates for 3GC-R Klebsiella in children than in adults (Figure S2b). A higher proportion estimate for 3GC resistance in NTS was seen in adults (Figure S2c) but there was only one study in this age group.

Results of the risk-of-bias assessment are shown in Figure 6. Bias in prevalence estimates was most likely introduced through selection of study participants. Many studies did not report criteria for blood culture sampling in the population recruited and many were conducted in special populations such as neonatal ICUs (NICUs). Most studies described blood culture methods well, but few reported external quality control (QC) in laboratory methods, resulting in a moderate risk of bias introduction across this domain for most studies.

As a measure of potential publication bias, plots of 3GC resistance estimates against study size, for E. coli and Klebsiella spp., are

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**Figure 1.** Study selection.
shown in Figure S2. For *E. coli* and *Klebsiella*, the larger studies tended to report lower resistance estimates (Figure S3), suggesting a potential for publication bias against studies reporting a smaller number of isolates.

Blood culture processing techniques varied. An automated system for blood culture incubation was used in 18 studies, whilst manual systems were used in 10. Three studies reported a mixture of manual and automated techniques and nine did not report which methods were used. AST methods varied, but most laboratories used disc diffusion (22/40). Four studies used VITEK 2, with the remainder using Etest, MicroScan or a mixture of techniques. Three studies did not report which AST methods were used. Most studies (30/40) used CLSI breakpoint guidelines, with the remainder using national or international guidelines as shown in Table 1. Twenty-two studies carried out ESBL confirmatory testing in 3GC-R isolates. Of these, 10 used double-disc synergy, with the remainder using broth dilution, PCR or a mixture of methods.

The classification of isolates by source, for example whether community-acquired (CA) or hospital-acquired (HA), or urban versus rural, is key to the interpretation of these data. Thirty studies tested BSIs from patients presenting to public referral or private hospitals in urban settings, with nine recruiting from rural district hospitals and one from a mixed urban/rural setting. HIV status of individuals who had blood culture sampling was recorded in only 11 studies and 1 study was exclusively a cohort of HIV-infected individuals. Six studies investigated the difference in blood culture pathogens and prevalence of resistance between CA and HA or healthcare-associated (HCA) infection. Of these, five found a higher prevalence of 3GC resistance in HA infections. Two studies were cohorts of patients with HA infection and one study included...
### Table 2. Median prevalence of 3GC resistance in *E. coli*, *Klebsiella* spp. and NTS BSI, shown by African region

| Pathogen | overall 3GC resistance | Prevalence, % (IQR) |
|----------|-------------------------|---------------------|
|          | eastern | middle | western | southern |
| *E. coli* | 18.4 (10.5–35.2) | 14.3 (10.0–24.3) | no data | 33.5 (25.0–51.6) | 12.4 (12.1–22.2) |
|          | 20 studies | 9 studies | 6 studies | 5 studies |
| *Klebsiella* spp. | 54.4 (24.3–81.2) | 46.7 (17.3–84.5) | no data | 58.3 (34.6–82.6) | 63.6 (39.1–76.2) |
|          | 28 studies | 10 studies | 8 studies | 10 studies |
| NTS | 1.9 (0–6.1) | 0 (0–9.6) | 1.3, 6.3 | 4.8 (2.4–5.4) | no data |
|          | 12 studies | 7 studies | 2 studies | 3 studies |

| First author, year | Resistant | Total strains | Proportion (%) | [95% CI] |
|--------------------|-----------|---------------|----------------|---------|
| Bejon, 2005        | 0         | 141           | 0.0            | [0.0; 2.7] |
| Brink, 2007        | 47        | 471           | 10.0           | [7.6; 13.0] |
| Blomberg, 2007     | 9         | 37            | 24.3           | [13.4; 40.1] |
| Kohli, 2010        | 10        | 69            | 14.5           | [8.1; 24.7] |
| Ogunlesi, 2011     | 6         | 16            | 37.5           | [18.5; 61.4] |
| Mhada, 2012        | 2         | 14            | 14.3           | [4.0; 39.9] |
| Obeng–Nkrumah, 2013 | 5       | 17             | 29.4           | [13.3; 53.1] |
| Preziosi, 2015     | 1         | 14            | 7.1            | [1.3; 31.5] |
| Dramowski, 2015a   | 7         | 58            | 12.1           | [6.0; 22.9] |
| Onken, 2015        | 1         | 10            | 10.0           | [1.8; 40.4] |
| Wasihun, 2015      | 9         | 16            | 56.2           | [33.2; 76.9] |
| Seboxa, 2015       | 8         | 16            | 50.0           | [28.0; 72.0] |
| Dramowski, 2015b   | 12        | 97            | 12.4           | [7.2; 20.4] |
| Obeng–Nkrumah, 2016 | 63     | 112           | 56.2           | [47.0; 65.1] |
| Ndír, 2016         | 7         | 12            | 58.3           | [32.0; 80.7] |
| Eibach, 2016       | 5         | 50            | 10.0           | [4.3; 21.4] |
| Sangare, 2016      | 8         | 34            | 23.5           | [12.4; 40.0] |
| Musicha, 2017      | 140       | 1311          | 10.7           | [9.1; 12.5] |
| Lochan, 2017       | 31        | 90            | 34.4           | [25.4; 44.7] |
| Crichton, 2018     | 8         | 36            | 22.2           | [11.7; 38.1] |
| **Total**          | 379       | 2621          |                |         |

**Heterogeneity: I^2 = 93%**

**Figure 3.** Proportion of 3GC resistance in 2621 *E. coli* BSI isolates from 20 studies.
only patients with suspected CA BSI. Of the six neonatal studies, two differentiated early-onset from late-onset neonatal sepsis but did not report on differences in proportions of 3GC resistance between the two groups.

**Discussion**

Our systematic review has synthesized over 11 000 blood culture isolates from patients in sSA, finding high levels of 3GC resistance amongst the key Enterobacteriaceae, *E. coli* and *Klebsiella* spp., and emerging resistance amongst salmonellae. Ceftriaxone is one of the most widely used broad-spectrum antibiotics in Africa, indicated in the empirical management of adult and paediatric patients at district-, regional- and tertiary-level care facilities. Limited access to carbapenems and aminoglycosides may make 3GC-R BSI untreatable in some settings. The striking lack of mortality data we describe in this review is therefore a major barrier to a comprehensive understanding of the burden of AMR in this setting.

**Figure 4.** Proportion of 3GC resistance in 5688 *Klebsiella* spp. BSI isolates from 28 studies.
We found a high median prevalence of 3GC resistance in E. coli BSI, greater than estimates from high-income countries, which are typically less than 10%. Interpreting the significance of proportion estimates in the absence of trend data is challenging and the latter will require long-term, high-quality surveillance. Some of the most comprehensive published trend data come from Malawi, where blood culture surveillance for 18 years has shown a recent, rapid rise in 3GC resistance amongst Enterobacteriaceae in adult and paediatric patients. Between 2003 and 2016, the proportion of 3GC-R E. coli rose from 0.7% to 30.3%, with similar trends in other non-Salmonella Enterobacteriaceae. The alarming trends described in Malawi highlight the urgent need for systematic AMR surveillance data from Africa that will inform both policy on access to antimicrobials and public health programmes aimed at reducing DRIs.

Resistance amongst Klebsiella spp., at 50.0%, was higher than for E. coli. Klebsiella spp. frequently acquire AMR genes and are a common cause of BSI in vulnerable populations, often causing localized outbreaks in settings such as NICUs and paediatric ICUs (PICUs). 3GC-R Klebsiella spp. are a particular challenge in neonatal infection as, in addition to the vulnerability of this age group to severe bacterial infection, many antimicrobials are either relatively contraindicated (e.g. chloramphenicol) or not locally available as IV agents (e.g. ciprofloxacin). In the single study from this review in which mortality from 3GC-R Klebsiella was recorded, all patients died; clearly, prospective studies investigating transmission dynamics of this nosocomial pathogen are required in order to support targeted interventions to reduce their development and spread.

Although resistance to first-line antimicrobials, such as ampicillin, chloramphenicol and co-trimoxazole, is common among NTS in SSA, 3GC resistance has remained low, but may represent an emerging problem (Figure 5). Our review found sporadic cases of ceftriaxone resistance amongst S. Typhi from three countries, but these studies did not carry out confirmatory testing for the presence of ESBL genes. Although not captured by our inclusion criteria, ESBL-producing S. Typhi have been detected in SSA. In light of the recent outbreak of fluoroquinolone-resistant and ESBL-producing S. Typhi in Pakistan, resulting from the acquisition of ESBL-encoding plasmids by the H58 haplotype (genotype 4.3.1) known to be prevalent in Africa, this is concerning. Surveillance of S. Typhi non-susceptibility in Africa will be essential, as emergence of drug-resistant strains is associated with increase in transmissibility of typhoid and resurgence of disease.

We found marked heterogeneity amongst 3GC resistance proportion estimates, which was not explained by differences in African region or age group of patients. Prevalence of resistance amongst key pathogens is likely to be influenced by a variety of clinical parameters including HIV status, healthcare attendance and prior antibiotic use, but these data were rarely reported and subgroup analysis by these factors was impossible. Detailed clinical and demographic parameters should be collected by studies that aim to understand the epidemiology of DRIs and the drivers of transmission of AMR pathogens.

We aimed to provide an estimate of the mortality burden from 3GC-R BSI, but this was prohibited by the scarcity of outcome data and heterogeneity of study designs. DRIs are associated with adverse patient outcomes in high-income settings, including high

![Figure 5. Proportion of 3GC resistance in 2567 NTS BSI isolates from 12 studies.](image-url)
Table 3. Studies reporting mortality in patients with 3GC-R BSI

| Study publication year | Study type | Population | Country | Total patients in study | Pathogens | Case-fatality rate, 3GC-R/3GC-S (%) | Adjusted mortality estimate from 3GC-R BSI (95% CI) | Author conclusions |
|------------------------|------------|------------|---------|-------------------------|-----------|------------------------------------|-----------------------------------------------|---------------------|
| Blomberg17 2007         | Prospective cohort | Paediatric; 0–7 years Urban referral hospital Children with suspected systemic infection based on IMCI | Tanzania | 1632 | Mixture of Enterobacteriaceae | 15/21 (71.0) | OR 12.87 (4.95–33.48) | Multivariable model adjusted for age <1 month, sex, HIV status, malaria, other underlying disease, polymicrobial blood culture | Inappropriate antimicrobial therapy due to 3GC-R resistance predicts fatal outcome |
| Dramowski10 Retrospective cohort 2015 | Prospective cohort | Paediatric; 0–14 years South Africa | 864 | Mixture of Enterobacteriaceae | 21/122 (17.2) | Not reported by AMR type | NR | AMR not associated with BSI mortality |
| Onken19 2015 Prospective cohort | All ages, no range reported Urban referral hospital Patients with fever (≥38.3°C in adults, ≥38.5°C in children) or hypothermia (<36.0°C), tachypnoea >20/min, tachycardia >90/min or suspected systemic bacterial infection | Zanzibar | 469 | Mixture of Enterobacteriaceae | 3/5 (60.0) | OR 2.85 (1.94–4.21) | Not reported | |
| Sebasa18 2015 Prospective cohort | Adults; 13–98 years Urban referral hospital Patients with clinical suspicion of sepsis and 2 of the 3 following criteria: axillary temperature ≥38.5°C or ≤36.5°C, pulse ≥90 beats/min and frequency of respiration ≥20/min | Ethiopia | 232 | Mixture of Enterobacteriaceae | 11/11 (100) | RR 9.00 (1.42–57.12) | No multivariable analysis | Inappropriate antimicrobial therapy due to 3GC-R infections predicts fatal outcome |
| Buys21 2016 Retrospective cohort | Paediatric; IQR 2–16 months Urban referral hospital Electronic list of Klebsiella bloodstream isolates from hospital database | South Africa | 410 | Klebsiella spp. | 1/10 (10) | OR 1.09 (0.55–2.16) | Multivariable model adjusted for age, gender, nutrition, HIV, ESBL, patient in PICU, patient needing to go to PICU, continuous IV infusion for >3 days before the BSI, Klebsiella BSI without source, chronic underlying medical condition excluding HIV, and skin erosions | MDR K. pneumoniae BSI is associated with high mortality in children |
| Eibach30 2016 Prospective cohort | All ages; IQR 1–18 years Rural primary healthcare centre Patients with fever ≥38°C or history of fever within 24 h after admission or neonates with suspected neonatal sepsis | Ghana | 7172 | Mixture of Enterobacteriaceae | NR | OR 3.0 (1.2–7.3) | No multivariable regression reported | 3GC-R BSI is associated with higher mortality than non-3GC-R, but this is highly dependent on age | No mortality difference from 3GC-R infections in neonates and higher overall mortality |
In Africa, where the prevalence of bacterial sepsis is high, late presentation to secondary care is common and the availability of alternative antimicrobials and advanced laboratory diagnostics is limited, the impact of AMR on patients is predictable, but currently unknown. This review has a number of limitations. Heterogeneity is highly likely with reviews of this nature and the variety of populations described make a true general population estimate difficult. Potential sources of heterogeneity that we have not explored include the diversity of laboratory microbiological methods used, both for organism identification and for AST. Most studies did not report whether or how they engaged with external quality assurance programmes. We did not exclude these from the review, as they likely represent the vast majority of facilities in SSA, but this may be an important source of variation in estimates.

The limitations of available data we highlight in this review, together with the high level of unexplained interstudy heterogeneity, prompt the need for standardisation of AMR research. Further studies should collect and report clinical metadata associated with the sample, including empirical antibiotic regimens, HIV status, and the clinical setting, using standardised sampling criteria. In future, studies should be required to provide a clear account of the microbiological sampling criteria, study or surveillance sampling frame and laboratory methods used to generate resistance data. Studies should collect and report clinical metadata associated with the sample, including empirical antibiotic regimens, HIV status, and the clinical setting, using standardised sampling criteria. In future, studies should be required to provide a clear account of the microbiological sampling criteria, study or surveillance sampling frame and laboratory methods used to generate resistance data. Studies should collect and report clinical metadata associated with the sample, including empirical antibiotic regimens, HIV status, and the clinical setting, using standardised sampling criteria.

We have documented proportions of 3GC-R BSI from a large number of bloodstream isolates across SSA, expanding on previous reviews that have focused on clinical syndromes, paediatric populations or limited African regions. Using inclusion criteria that captured surveillance studies in addition to clinical cohorts, we have, to our knowledge, captured the largest AMR dataset available from SSA and therefore provide the most comprehensive summary of 3GC-R BSI in the continent. Using inclusion criteria that captured surveillance studies in addition to clinical cohorts, we have, to our knowledge, captured the largest AMR dataset available from SSA and therefore provide the most comprehensive summary of 3GC-R BSI in the continent.

| Study, publication year | Study type | Population | Country | Total patients in study | Pathogens | Case-fatality rate | Adjusted mortality estimate from 3GC-R BSI (95% CI) | Author conclusions |
|-------------------------|------------|------------|---------|-------------------------|-----------|-------------------|-----------------------------------------------|---------------------|
| Ndiri et al. 2016       | Case-control | Paediatric; 0–17 years | Senegal | 173 | Mixture of Enterobacteriaceae | NR (54.8) | OR 2.9 (1.8–7.3) | 3GC-R BSI is associated with fatal outcome in HA-BSI |
| Marando et al. 2018     | Prospective cohort | Neonates; IQR 4–8 days | Tanzania | 304 | Mixture of Enterobacteriaceae | NR (34.4) | OR 2.71 (1.22–6.03), multivariable model adjusted for age and sex | Neonates infected with 3GC-R BSI have significantly higher mortality than EBSL negative or non-bacteraemic patients |

3GC-S, 3GC susceptible; IMCI, integrated management of childhood infection.
economic outcome data, to allow for a true understanding of the burden of AMR on patients and health systems.

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**Transparency declarations**

None to declare.

**Supplementary data**

Tables S1 to S4 and Figures S1 to S3 are available as Supplementary data at JAC Online.

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