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Review

Antimicrobial resistance patterns in bacteria causing febrile illness in Africa, South Asia, and Southeast Asia: a systematic review of published etiological studies from 1980-2015☆

Tamalee Roberts[1,2,*], Prabin Dahal[2,3], Poojan Shrestha[2,3], William Schilling[4], Rujan Shrestha[3], Roland Ngu[3], Vu Thi Lan Huong[5], H Rogier van Doorn[2,5], Vilayouth Phimolsarnnousith[1], Thyl Miliya[6], John A Crump[7], David Bell[8], Paul N Newton[1,2,3,9], Sabine Dittrich[10], Heidi Hopkins[9], Kasia Stepniewska[2,3], Philippe J Guerin[2,3], Elizabeth A Ashley[1,2], Paul Turner[2,6]

[1] *Lao-Oxford-Mahosot Hospital, Wellcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic*
[2] *Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK*
[3] *Infectious Diseases Data Observatory (IDDO), University of Oxford, Old Road Campus, Oxford, UK*
[4] *Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*
[5] *Oxford University Clinical Research Unit (OUCRU), Vietnam*
[6] *Cambodia Oxford Medical Research Unit, Angkor Hospital for Children, Siem Reap, Cambodia*
[7] *Centre for International Health, Otago Medical School, University of Otago, Dunedin, New Zealand*
[8] *Independent consultant, Issaquah, WA, USA*
[9] *London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK*
[10] *Foundation for Innovative New Diagnostics, Geneva, Switzerland*

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ABSTRACT

Objective: In this study, we aimed to conduct a systematic review to characterize antimicrobial resistance (AMR) patterns for bacterial causes of febrile illness in Africa and Asia.
Methods: We included published literature from 1980-2015 based on data extracted from two recent systematic reviews of nonmalarial febrile illness from Africa, South Asia, and Southeast Asia. Selection criteria included articles with full bacterial identification and antimicrobial susceptibility testing (AST) results for key normally sterile site pathogen-drug combinations. Pooled proportions of resistant isolates were combined using random effects meta-analysis. Study data quality was graded using the Microbiology Investigation Criteria for Reporting Objectively (MICRO) framework.
Results: Of 3475 unique articles included in the previous reviews, 371 included the target pathogen-drug combinations. *Salmonella enterica* tested against ceftriaxone and ciprofloxacin were the two highest reported combinations (30,509 and 22,056 isolates, respectively). Pooled proportions of resistant isolates were high for third-generation cephalosporins for *Klebsiella pneumoniae* and *Escherichia coli* in all regions. The MICRO grading showed an overall lack of standardization.
Conclusion: This review highlights a general increase in AMR reporting and in resistance over time. However, there were substantial problems with diagnostic microbiological data quality. Urgent strengthening of laboratory capacity, standardized testing, and reporting of AST results is required to improve AMR surveillance.

Background

Antimicrobial resistance (AMR) is a major threat to public health, resulting in adverse patient outcomes and higher healthcare costs (Founou et al., 2017; Shrestha et al., 2018). A recent modeling study estimated that 1.27 million deaths globally were

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* Corresponding author. Tamalee Roberts, Lao Oxford-Mahosot Hospital, Wellcome Trust Research Unit, Mahosot Hospital, Mahosot Road, Vientiane, Lao People's Democratic Republic. Ph: +856021250752.
E-mail address: tamalee.r@tropmedres.ac (T. Roberts).

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attributable to bacterial AMR in 2019, with a particularly high burden predicted for Sub-Saharan Africa (Antimicrobial Resistance Collaborators, 2022). Although these estimates support high-level actions to combat AMR, more granular data availability and robust national estimates are lacking for much of Africa and Asia (Sentry, 2022; World Health Organization, 2022). Given this limited available data, there is a dearth of reviews on AMR burden and trends in these regions. However, the few previous reviews available have highlighted the increase in AMR in community-onset infections over time (Ashley et al., 2011; Marchello et al., 2019). AMR-related activities are now increasing in Africa and Asia, including a focus on building laboratory capacity and AMR surveillance (e.g., the Fleming Fund [www.flemingfund.com] and Africa Centres for Disease Control and Prevention [CDC] Surveillance and Disease Intelligence). This is encouraging; however, some time will be needed to fill the data gap and for results to feed into focused policy making and changes in antimicrobial guidelines.

Therefore, the purpose of this review was to summarize existing data on AMR in bacteria that cause febrile illness in Africa and Asia and to also identify knowledge gaps and the limitations of diagnostic methods and capacity.

Methods

A systematic review was conducted on all published literature from 1980-2015 from Africa, South Asia, and Southeast Asia as part of a series of reviews on pathogens that may cause febrile illness in these regions (Elven et al., 2020; Shrestha et al., 2020). Data sources include case studies, case series, and population-based studies, not specifically laboratory-based studies or AMR surveillance reports. Hospital studies were not excluded.

Literature search strategy

The review was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) and is registered with the international prospective register of systematic reviews (PROSPERO CRD42016049281) with meta-analysis added as an objective after this registration. This review is based on two previous systematic literature searches on nonmalarial febrile illness from Africa, South Asia, and Southeast Asia that were carried out in six libraries: MEDLINE, Embase, World Health Organization (WHO) Global Health Library, PASCAL, CABI Global Health, and Bulletin de la Société Française de Parasitologie (Elven et al., 2020; Shrestha et al., 2020). The searches were conducted in English and French, restricted to articles published from 1980-2015 (Supplementary File 1; Methods 1).

Study selection and full-text review

For the original systematic reviews, independent reviewers screened titles and abstracts, then full-text articles, according to published selection criteria (Elven et al., 2020; Shrestha et al., 2020). From the original reviews' databases, this AMR review includes articles that reported on pathogen-drug combinations prioritized by the WHO Global Antimicrobial Resistance Surveillance System (GLASS) (Table 1) (World Health Organization, 2022) (inclusion and exclusion criteria in Supplementary File 2; Methods 1). Although GLASS does not cover all locally important pathogens, it includes the major globally important pathogens.

Data extraction

Bibliographic, meta-data, sample, and isolate information were extracted. If the article did not explicitly report the number of resistant isolates, it was derived using the number of susceptible and/or intermediate cases where possible (Supplementary File 2; Methods 2).

Table 1
List of organism and antibiotic combinations included in the systematic review of published aetiological studies from Africa, South Asia, and Southeast Asia, 1980-2015

Organism	Antibiotic class	Antibiotics included
Escherichia coli	Third-generation cephalosporin	Ceftazidime, ceftriaxone, cefotaxime
	Carbapenem	Meropenem, imipenem
	Aminoglycoside	Gentamicin
Klebsiella pneumoniae	Third-generation cephalosporin	Ceftazidime, ceftriaxone, cefotaxime
	Carbapenem	Meropenem, imipenem
	Aminoglycoside	Gentamicin
***Salmonella enterica.* (*S.* Typhi, *S.* Paratyphi and Non-Typhoidal Salmonellae)**	Third-generation cephalosporin	Ceftazidime, ceftriaxone, cefotaxime
	Fluoroquinolone / Quinolone	Ciprofloxacin, ofloxacin, nalidixic acid
	Macrolide	Azithromycin
***Shigella* spp.**	Third-generation cephalosporin	Ceftazidime, ceftriaxone, cefotaxime
	Quinolone	Ciprofloxacin, ofloxacin, nalidixic acid
	Macrolide	Azithromycin
Acinetobacter baumannii	Carbapenem	Meropenem, imipenem
Pseudomonas aeruginosa	Carbapenem	Meropenem, imipenem
Haemophilus influenzae	Penicillin/ Beta-lactamase activity	Ampicillin
Neisseria meningitidis	Quinolone	Ciprofloxacin
	Penicillin	Penicillin
	Miscellaneous	Chloramphenicol
Staphylococcus aureus	Methicillin	Cefoxitin, methicillin, oxacillin
	Glycopeptide	Vancomycin
***Enterococcus* spp.**	Glycopeptide	Vancomycin
Streptococcus pneumoniae	Penicillin	Penicillin
	Macrolide	Erythromycin

Geographical classification of countries and study population

Countries were classified by sub-region per United Nations designations (United Nations, 2022). Study populations were grouped into four categories: neonates (aged <28 days), infants (1 to <12 months), children (1 to <13 years), and older individuals (≥13 years). If a study reported any participants from each age group, they were grouped as participants of "all ages."

Definitions

The original systematic reviews identified reports of pathogen presence based on laboratory confirmation of infections; clinical definitions were not used. For this review, only confirmed detection of bacterial isolates from cultured samples from normally sterile sites (e.g., blood, cerebrospinal fluid [CSF], bone marrow, joint fluid, pleural fluid, and peritoneal fluid) were included. Years of study were grouped as shown in Supplementary File 2; Methods 3.

Categorization of resistance

For studies in which isolates were reported as susceptible, intermediate, or resistant to the tested antimicrobial, these interpretations were retained and used for analysis focusing on resistant results. Only studies with denominators were included in the review (Supplementary File 2; Methods 4).

Laboratory diagnosis grading

Studies were graded using the core requirements from the Microbiology Investigation Criteria for Reporting Objectively (MICRO) framework (Turner et al., 2019), resulting in a score out of 13. One reviewer (TR) reviewed all studies, then 20% were reviewed independently by two other authors (VP and TM), and the results were compared. Discrepancies were discussed with a fourth reviewer (PT), and a final consensus decision was made (Supplementary File 2; Methods 5).

Statistical analyses and sensitivity analysis

Statistical analysis and details of the two sensitivity analyses are described in Supplementary File 2; Methods 6. (Elven et al., 2020; Shrestha et al., 2020). Statistical analyses were carried out using R version 4.0.4 (R Core Team, 2021); meta-analyses were carried out using the meta package.

Results

Search results

Of 3475 unique articles included in the two previous reviews, 484 included laboratory information on the bacterial organism and AST results. Of these, 371 (10.6%) included target pathogen-drug combinations and were selected for further analysis (Figure 1, articles listed in Supplementary File 3, full list available from the non-malaria febrile illness [NMFI] surveyor - fever series [www.iddo.org]).

Spatial distribution

There were 371 articles describing data from 39 countries. The highest number of articles were from India (142, 38.3%), followed by Nepal (44, 11.9%), Pakistan (31, 8.4%), Bangladesh (16, 4.3%), Nigeria (13, 3.5%), South Africa (13, 3.5%), and Thailand (12, 3.2%). By region, there were 237 (63.9%) articles from South Asia (studies from 1991-2015), 82 (22.1%) from Sub-Saharan Africa (1986-2015), 39 (10.5%) from Southeast Asia (1995-2015), and 13 (3.5%) articles from Northern Africa (1990-2014) (Figure 2; panel A).

Study population

A total of 80 (21.6%) articles reported only on neonates, three (0.8%) on infants, 76 (20.5%) on children aged 1-13 years, and 31 (8.4%) on children and adults >13 years. A total of 130 (35.0%) included all age groups, whereas age was unspecified in the remaining 51 (13.7%) articles (Table 2).

Diagnostic method and susceptibility testing

Blood was the most common specimen type (301 articles, 81.1%). CSF was collected in 36 (9.7%) articles, a combination of blood and/or CSF in 24 (6.5%) articles, and various sterile body fluids in the remaining eight (2.2%) studies (Table 2). Kirby-Bauer disc diffusion and nonspecified disc diffusion were the main AST methods used (140 articles: 37.7% and 81 articles: 21.8%, respectively; Supplementary File 4; Table 1).

AST interpretative criteria per Clinical and Laboratory Standards Institute (CLSI) guidelines were the most common, with 201 (54.2%) articles, whereas 147 (39.6%) articles did not specify the AST guidelines used (Table 2).

AMR profiles

Unless stated otherwise, all results in the following section are presented as a proportion of isolates that were resistant derived from a random-effects meta-analysis (referred to as "pooled proportion" onwards) (x%) with 95% confidence intervals (CIs) (CI: x-x%), along with the number of resistant isolates/number of isolates tested (n/N) and the number of articles. *Salmonella enterica* were the most reported organisms with ceftriaxone and ciprofloxacin against *S. enterica,* the two most common combinations tested (30,509 and 22,056 isolates, respectively). Overall, when data were combined across all regions and time periods, *Klebsiella pneumoniae* tested against ceftriaxone had the highest pooled proportion of resistant isolates (71.8% [CI: 48.5-87.3%], 960/1499) of any pathogen-drug combination included in the review, and there was a higher proportion of extended-spectrum beta-lactamase (ESBL) producing *K. pneumoniae* compared with ESBL *Escherichia coli* (58.5% vs 36.5%). Only three articles reported on *Shigella* spp. (data presented in Supplementary File 4; Results 1).

Gram-negative bacteria

Escherichia coli. Pooled proportions of *E. coli* isolates resistant to third-generation cephalosporins remained above 50% in Asia since 2000 (Figure 3, Supplementary File 4; Table 2). Overall, ceftazidime resistance was reported in 56 articles (47.4% [CI: 38.7-56.2%], 806/1643), ceftriaxone in 55 articles (41.0% [CI: 28.9-54.3%], 957/2048), and cefotaxime in 59 articles (47.9% [CI: 38.3-57.6%], 1077/2259). Pooled proportions of resistance were higher in Asia than Africa for all three drugs (ceftazidime $P = 0.035$, ceftriaxone $P < 0.0001$, and cefotaxime $P = 0.041$). A total of 15 (36.5%) of 496 isolates ESBL positive. However, three of these studies did not state how ESBL status was determined. All studies reporting ESBLs were published after the year 2000; three from Africa and 12 from Asia. Pooled proportions of resistance to meropenem in Asia ranged from 1.1% (CI: 0.1-11.2%, 46/692) in 2000-2009 to 9.7% (CI: 1.7-39.8%, 17/196) in 2010-2015, and was lower in Africa (0.1% [CI: 0.0-14.4%], 1/530 in 2000-2009 and 0.0% [CI: 0.0-20.4%], 0/15 in 2010-2015) (Figure 3, Supplementary File 4; Table 3). Meropenem resistance was reported in 23 articles (1.0% [CI: 0.2-5.2%], 64/1433) and imipenem in 53 articles (0.8% [CI: 0.3-2.7%], 70/2254). Pooled proportions of resistance to gentamicin were 43.0% (CI: 36.1-50.2%, 1427/3051, 92 articles) for all age groups and 52.7% (CI: 44.8-60.5%, 756/1282, 50 articles) in the neonate age group.

Klebsiella pneumoniae. Third-generation cephalosporin resistance was more common in *K. pneumoniae* than *E. coli* for all regions. A total of 35 articles reported ceftazidime resistance (71.1% [CI: 54.1-83.7%], 657/1046), 30 articles reported ceftriaxone (71.8% [CI: 48.5-87.3%], 960/1499), and 33 articles reported cefotaxime (68.4% [CI: 51.6-81.4%], 1057/1744) (Supplementary File 4; Table 4). In Africa, pooled proportions of resistance to cefotaxime increased significantly over time from 0.0% (CI: 0.0-32.4%, 0/8) in 1980-1989 to 72.2% (CI: 60.8-81.3%, 52/72) in 2010-2015 (test for difference in estimates over time period; $P = 0.034$) (Figure 4). In Asia, pooled proportions of resistance to the three antibiotics decreased over time: cefotaxime from 86.5% (CI:67.3-95.3%, 651/792) in 2000-2009 to 59.2% (CI: 37.5-77.9%, 90/156) in 2010-2015 ($P < 0.0001$); ceftazidime from 90.2% (CI: 65.6-97.8%, 432/571) in 2000-2009 to 59.6% (CI: 44.4-73.2%, 87/149) in 2010-2015 ($P < 0.001$); and ceftriaxone from 88.6% (CI: 67.0-96.8%,574/638) in 2000-2009 to 30.7% (CI: 13.1-56.6%, 28/93) in 2010-2015 ($P = 0.0003$) (Figure 4). There were 14 articles that reported ESBL results with denominators: 384 (58.5%) of 656 isolates were ESBL positive. However, four articles did not state ESBL confirmation methodology. All studies reporting ESBLs were after the year 2000; two from Africa and 12 from Asia.

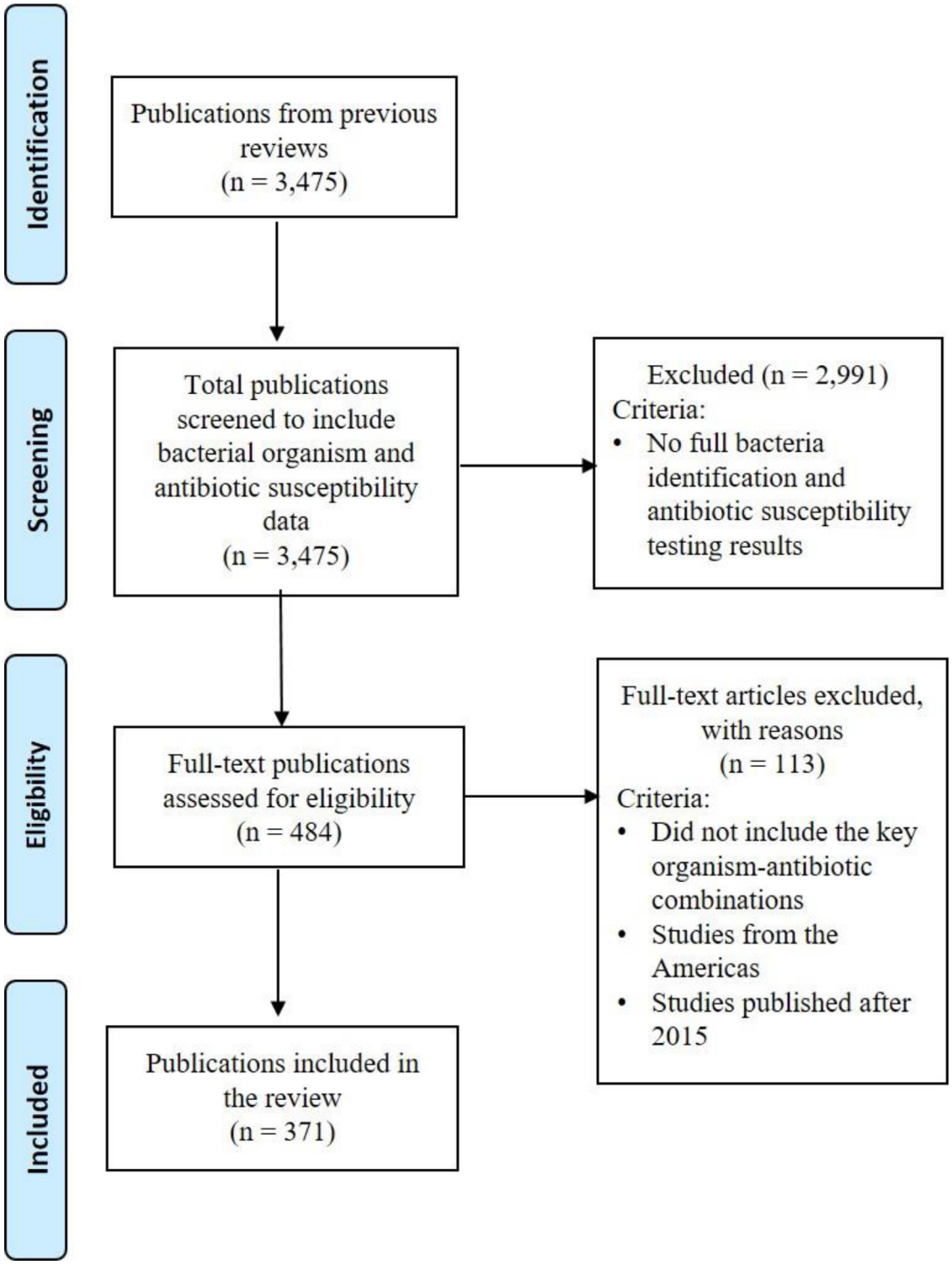

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of publications screened in a systematic review of aetiological studies and case reports from Africa, South Asia, and Southeast Asia, 1980-2015.

Pooled proportions of resistance for carbapenems were similar to *E. coli* and remained low within the regions and over time (Supplementary File 4; Table 5). Meropenem resistance was reported in 15 articles (1.7% [CI: 0.5-5.5%], 84/1513) and imipenem in 36 articles (0.2% [CI: 0.0-2.0%], 249/2597). Pooled proportion of resistance to gentamicin was 63.4% (CI: 48.2-76.9%, 1195/1958, 51 articles) for all age groups and 73.5% (CI: 56.4-85.7%,602/978, 27 articles) for neonates.

Salmonella enterica. *S. enterica* were the most reported organisms, and the most frequent combination tested was with ceftriaxone in 109 articles (0.2%, [CI: 0.1-0.4%], 212/30,509) (Supplementary File 4; Table 6). A total of 25 articles reported ceftazidime (2.9% [CI: 0.5-14.8%], 41/1821) and 56 articles reported cefotaxime (1.5% [CI: 0.5-4.2%], 391/5357). Overall, the pooled proportion of resistance to ceftriaxone and cefotaxime was less than 10% for all regions and time periods, whereas ceftazidime resistance reached 30.6% (CI:

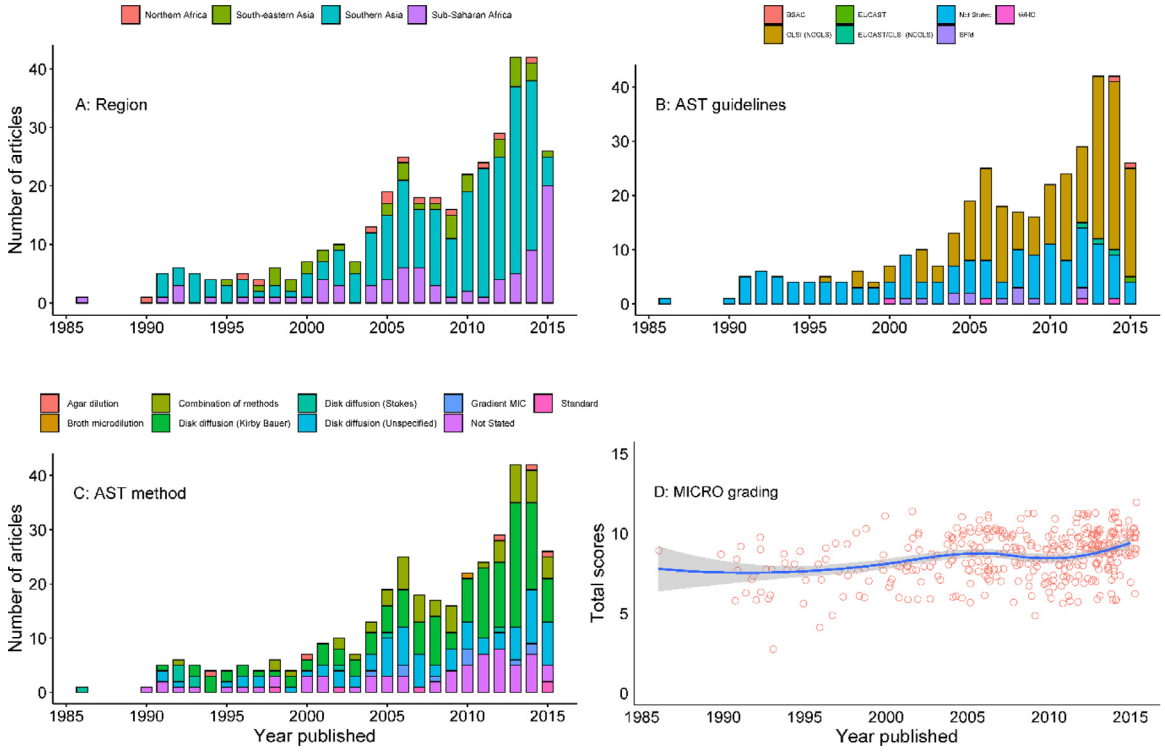

Figure 2. Temporal trends in characteristics of etiologic studies included from Africa, South Asia, and Southeast Asia, 1980-2015.
Legend: Number of publications from region over time (Panel A); Number of publications by AST guidelines over time (Panel B); Number of publications by AST method over time (Panel C); MICRO grading score in studies included over time with a locally weighted smoothing trendline (blue) and associated 95% confidence band (shaded). Jitters (random noise) were added to visualize the discrete scores (Panel D).
AST = antimicrobial susceptibility testing; MICRO = microbiology investigation criteria for reporting objectively.

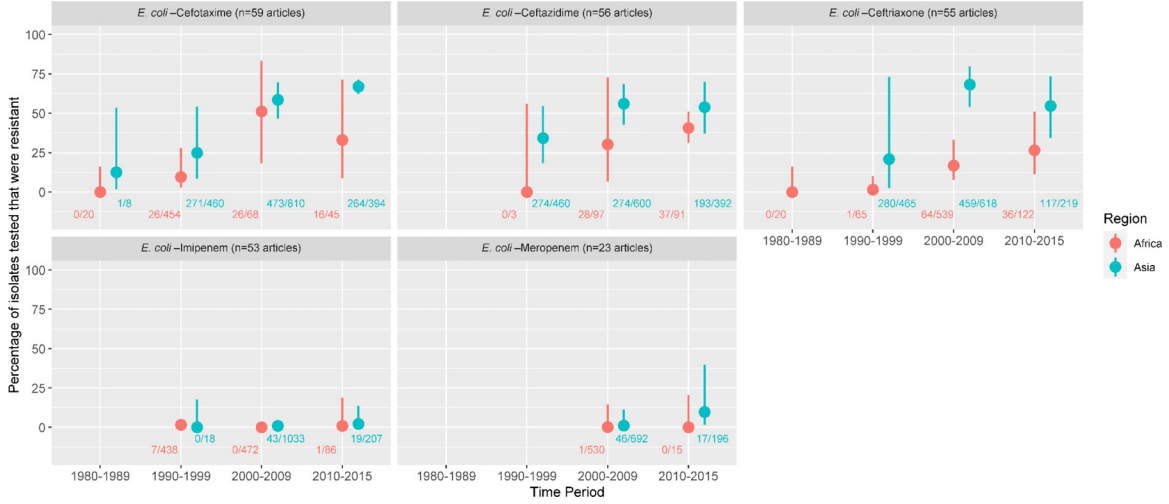

Figure 3. Pooled proportion of resistant *Escherichia coli*, third-generation cephalosporin and carbapenem antibiotics stratified by region and time period of sample collection in the systematic review of published aetiological studies from Africa, South Asia, and Southeast Asia, 1980-2015.
Legend: Lines indicate 95% confidence intervals. Numbers next to dots indicate number of resistant isolates and total number of isolates tested. Test for overall sub-group differences in the resistant proportion of isolates between Africa and Asia using a random-effects model were statistically significant for *E. coli*: ceftazidime ($P = 0.035$), *E. coli*: ceftriaxone ($P < 0.0001$), and *E. coli*: cefotaxime ($P = 0.041$). The number of articles represents studies that had nonmissing numerator (studies with missing numerator are not considered. All studies had a denominator).

21.0-42.1%, 22/73) in Asia between 2010-2015. There was no significant regional difference for ceftazidime ($P = 0.411$), ceftriaxone ($P = 0.101$), or cefotaxime ($P = 0.778$). Apart from nalidixic acid, used as a marker for fluoroquinolone resistance, fluoroquinolone resistance was uncommon in *S. enterica*. A total of 69 articles reported on nalidixic acid (56.0% [CI: 40.5-70.5%], 6920/10,938). There was an increase in resistance to nalidixic acid in Asia over time from 1.5% (CI: 0.0-60.3%, 14/133) in 1990-1999 to 88.9% (CI: 72.4-96.0%, 1404/1665) in 2010-2015 ($P = 0.008$ for the difference between time periods), whereas there was no significant increase in Africa ($P = 0.474$) (Figure 5). Ciprofloxacin was reported in 130 articles (1.5% [CI: 0.8-2.7%], 1116/22,056), ofloxacin in 36 articles (2.4% [CI: 0.8-7.3%], 4077/10,246), and azithromycin in 20 articles (2.6% [CI: 1.1-6.4%], 230/2966) (Supplementary File 4; Tables 7 and 8).

Acinetobacter baumannii. Six articles included *A. baumannii* and meropenem data (63.4% [CI: 7.9-97.2%], 170/308) and 14 articles reported imipenem (12.9% [CI: 1.4-60.4%], 192/403). There was an in-

Table 2
Description of studies included in the systematic review of published aetiological studies from Africa, South Asia, and Southeast Asia, 1980-2015

	Northern Africa (n = 13 articles)	Sub-Saharan Africa (n = 82 articles)	South-Eastern Asia (n = 39 articles)	Southern Asia (n = 237 articles)	Overall (n = 371 articles)
Publication year	1990-2014	1986-2015	1995-2015	1991-2015	1986-2015
Sample collection period	1988-2014	1985-2015	1985-2014	1986-2014	1985-2015
Age-group					
Neonates	1 (7.7%)	17 (20.7%)	7 (17.9%)	55 (23.2%)	80 (21.6%)
Infants	0 (0.0%)	0 (0.0%)	1 (2.6%)	2 (0.8%)	3 (0.8%)
Children	4 (30.8%)	24 (29.3%)	11 (28.2%)	37 (15.6%)	76 (20.5%)
Adults	1 (7.7%)	7 (8.5%)	9 (23.1%)	14 (5.9%)	31 (8.4%)
All ages	3 (23.1%)	27 (32.9%)	9 (23.1%)	91 (38.4%)	130 (35.0%)
Unspecified	4 (30.8%)	7 (8.5%)	2 (5.1%)	38 (16.0%)	51 (13.7%)
Samples collected					
Blood culture	10 (76.9%)	53 (64.6%)	29 (74.4%)	209 (88.2%)	301 (81.1%)
CSF	2 (15.4%)	24 (29.3%)	3 (7.7%)	7 (3.0%)	36 (9.7%)
Blood culture and/or CSF	1 (7.7%)	5 (6.1%)	5 (12.8%)	13 (5.5%)	24 (6.5%)
Peritoneal/pericardial/pleural fluid	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	4 (1.1%)
Vitreous humor	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	2 (0.5%)
Joint aspirate	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.4%)	2 (0.5%)
Bone Marrow	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	1 (0.3%)
Various sterile body fluids (unspecified)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
AST guidelines					
CLSI (NCCLS)	5 (38.5%)	38 (16.3%)	18 (46.2)	140 (59.1%)	201 (54.2%)
WHO	0 (0.0%)	2 (2.4%)	0 (0.0%)	2 (0.8%)	4 (1.1%)
EUCAST/CLSI (NCCLS)	0 (0.0%)	2 (2.4%)	0 (0.0%)	1 (0.4%)	3 (0.8%)
SFM	6(46.2%)	7 (8.5%)	0 (0.0%)	0 (0.0%)	13 (3.5%)
BSAC	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
EUCAST	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Not Stated	2 (15.4)	30 (36.6%)	21 (53.8)	94 (39.7%)	147 (39.6%)
AST Method					
Agar dilution	0 (0.0%)	0 (0.0%)	2 (5.1%)	3 (1.3%)	5 (1.3%)
Broth microdilution	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Disc diffusion (Kirby-Bauer)	4 (30.8%)	18 (22.0%)	11 (28.2%)	107 (45.1%)	140 (37.7%)
Disc diffusion (Stokes)	0 (0.0%)	3 (3.7%)	0 (0.0%)	6 (2.5%)	9 (2.4%)
Disc diffusion (unspecified)	5 (38.5%)	28 (34.1%)	11 (28.2)	37 (15.6%)	81 (21.8%)
Gradient MIC	0 (0.0%)	3 (3.7%)	3 (7.7%)	4 (1.7%)	10 (2.7%)
Combination of one or more of the previously mentioned methods	2 (15.4%)	17 (20.7%)	7 (17.9%)	27 (11.4%)	53 (14.3%)
Standard	0 (0.0%)	4 (4.9%)	0 (0.0%)	1 (0.4%)	5 (1.3%)
Not stated	2 (15.4%)	9 (11.0%)	5 (12.8%)	51 (21.5%)	67 (18.1%)

Column percentages presented in parenthesis; one study with specified samples used "various sterile body fluid specimens" without further description.
AST = antimicrobial susceptibility testing; BSAC = British Society for Antimicrobial Chemotherapy; CLSI (NCCLS) = Clinical and Laboratory Standards Institute (National Committee for Clinical Laboratory Standards); CSF = cerebrospinal fluid; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration; SFM = Société Française de Microbiologie; WHO = World Health Organization.

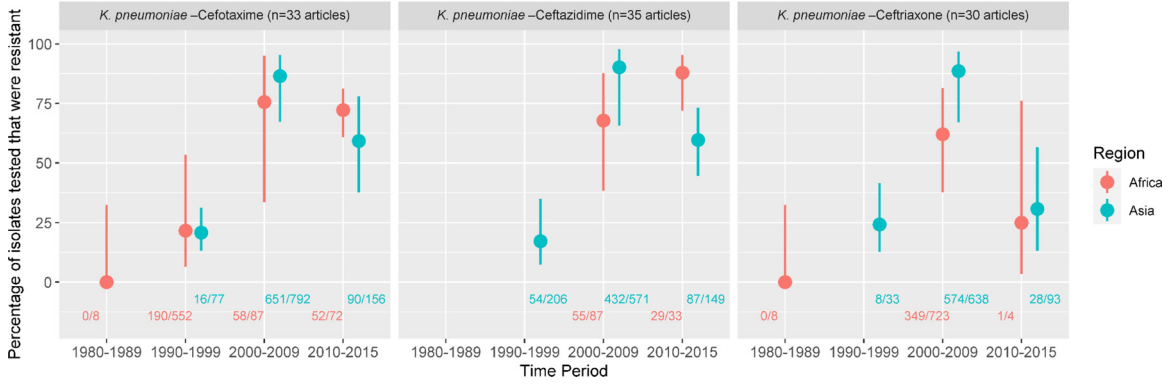

Figure 4. Pooled proportion of resistant *Klebsiella pneumoniae*: third-generation cephalosporin stratified by region and the time period of sample collection in the systematic review of published aetiological studies from Africa, South Asia, and Southeast Asia, 1980-2015.
Legend: Lines indicate 95% confidence intervals. Numbers next to dots indicate number of resistant isolates/total number of isolates tested. Test for sub-group differences in resistant proportion of isolates between Africa and Asia using a random-effects model were statistically nonsignificant for *K. pneumoniae*: ceftazidime ($P = 0.502$), *K. pneumoniae*: ceftriaxone ($P = 0.091$) and *K. pneumoniae*: cefotaxime ($P = 0.122$). In studies from Africa, the test for sub-group differences in the resistant proportion between time period: ceftazidime ($P = 0.131$), ceftriaxone ($P = 0.453$), and cefotaxime ($P = 0.034$). In studies from Asia, the test for sub-group differences in the resistant proportion between time period: ceftazidime ($P < 0.001$), ceftriaxone ($P = 0.0003$), and cefotaxime ($P < 0.0001$). The number of articles represents studies that had nonmissing numerator (studies with missing numerator are not considered. All studies had a denominator).

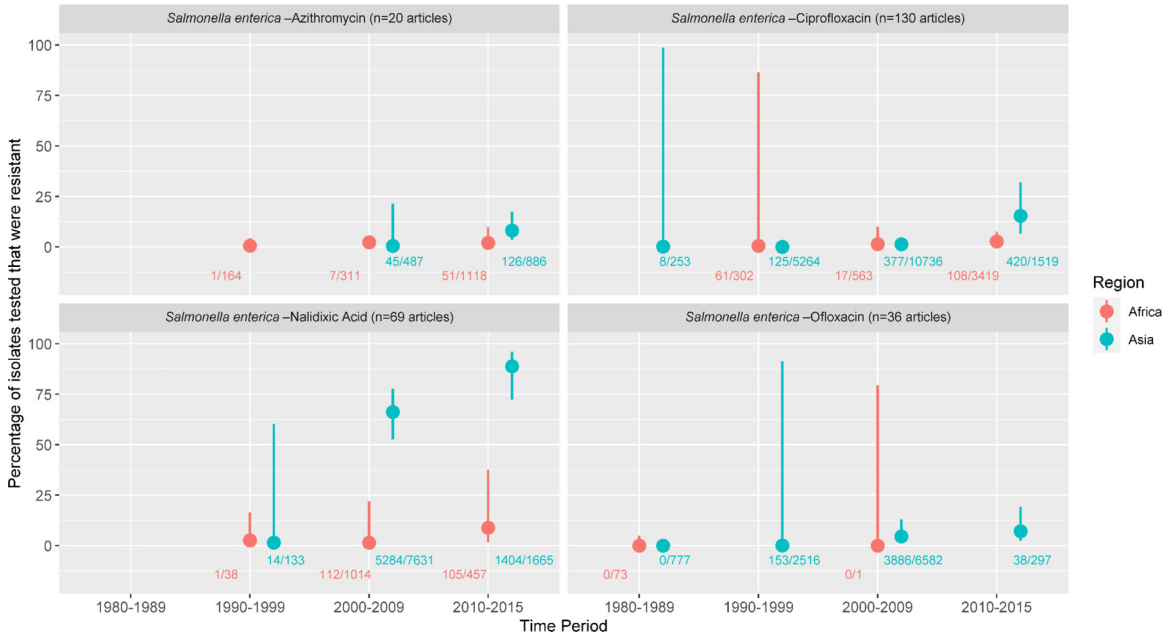

Figure 5. Pooled proportion of resistant *Salmonella enterica*: azithromycin and quinolones stratified by region and the time period of sample collection in the systematic review of published aetiological studies from Africa, South Asia, and Southeast Asia, 1980-2015.
Legend: Lines indicate 95% confidence intervals. Numbers next to dots indicate the number of resistant isolates/total number of isolates tested. Test for sub-group differences in the resistant proportion of isolates between Africa and Asia using a random-effects model was statistically nonsignificant for *S. enterica:* azithromycin ($P = 0.355$), *S. enterica:* ciprofloxacin ($P = 0.459$), and *S. enterica*: ofloxacin ($P = 0.999$), and statistically significant for *S. enterica*: nalidixic acid ($P < 0.001$). The number of articles represents studies with nonmissing numerator and denominator (studies with missing numerator are not considered. All studies had a denominator). Overall, there was a difference in resistance estimates during the four time periods ($P = 0.0027$, test for sub-group differences, random-effects meta-analysis). Sub-group differences in the time period were statistically significant in Asia ($P = 0.008$) but not in Africa ($P = 0.575$).

crease in the pooled proportions of resistance to meropenem and imipenem over time for both regions (Supplementary File 4; Table 9). There were no significant regional differences for either meropenem ($P = 0.450$) or imipenem ($P = 0.120$).

Pseudomonas aeruginosa. A total of 11 articles reported on *P. aeruginosa* and meropenem (26.6% [CI: 8.7-58.0%], 278/714) and 29 articles reported imipenem (11.7% [CI: 5.4-23.6%], 330/1001). The pooled proportion of resistance for *P. aeruginosa* isolates to imipenem increased over time in Africa and remained similar in Asia over the study period for both imipenem and meropenem (Supplementary File 4; Table 10). There was a significant difference between the regions for imipenem ($P = 0.030$) but not meropenem ($P = 0.851$).

Haemophilus influenzae. A total of 25 articles reported on *H. influenzae* and ampicillin (43.8% [CI: 32.1-56.3%], 348/904). There was an increase in the pooled proportion of resistance to ampicillin over time in both regions, from 25.6% (CI: 4.3-72.6%, 2/8) in 1980-1989 to 54.9% (CI: 35.3-73.1%, 48/99) in 2000-2009 for Africa, and 26.8% (CI: 9.4-56.2%, 205/622) in 1990-1999 to 77.5% (CI: 66.3-85.7%, 55/71) in 2000-2009 in Asia. There were no results for 2010-2015 for either region (Supplementary File 4; Table 11). There was no significant difference between the regions ($P = 0.999$).

Neisseria meningitidis. A total of 15 articles reported on *N. meningitidis* and penicillin (21.7% [CI: 5.4-57.4%], 40/223) and 17 articles reported on chloramphenicol (1.7% [CI: 0.0-4.6%], 11/289), with most isolates from Africa for both antibiotics (35/213 isolates resistant for penicillin and 9/236 isolates resistant for chloramphenicol, from Africa). A total of 10 articles reported on ciprofloxacin (9.6% [CI: 0.9-56.4%], 23/110), with the first resistant isolates noted in Africa between 2010-2015 and Asia from 2000-2009. The pooled proportion of resistance to ciprofloxacin was 7.3% (CI: 1.0-39.1%, 3/38) in Africa, and 30.5% (CI: 1.4-93.0%, 20/72) in Asia (Supplementary File 4; Table 12). There was no regional difference for either of these antibiotics ($P = 0.112$ for penicillin, $P = 0.447$ for chloramphenicol, and $P = 0.400$ for ciprofloxacin).

Gram-positive bacteria

Staphylococcus aureus. For *S. aureus* and methicillin, 13 articles reported cefoxitin (40.1% [CI: 28.5-53.0%], 284/640), 17 reported methicillin (32.3% [CI: 21.1-46.0%], 481/1470), and 33 reported oxacillin (38.4% [CI: 29.4-48.3%], 746/2053) (Supplementary File 4; Table 13). The pooled proportion of resistance to methicillin increased over time in Asia from 17.2% (CI: 7.9-33.5%, 88/515) in 1990-1999 to 45.3% (CI: 30.4-61.0%, 316/756) in 2010-2015. Cefoxitin had the highest pooled proportion of resistance for both regions. In Africa, data on cefoxitin and methicillin were limited; the overall pooled proportion of resistance was 65.9% (CI: 11.5-96.7%, 13/25) for methicillin and 16.9% (CI: 5.0-44.0%, 4/23) for cefoxitin. There were no regional differences for any antibiotics (cefoxitin $P = 0.062$, methicillin $P = 0.272$, and oxacillin $P = 0.463$).

Reported vancomycin resistance was very low, with an overall pooled proportion of resistance of 0.1% (CI: 0.0-3.3%, 28/1638) in Africa and 0.03% (CI: 0.0-0.96%, 41/2744) in Asia (Supplementary File 4; Table 14). There was no regional difference ($P = 0.579$). Vancomycin-resistant isolates were reported from 14 studies; five were from neonates, and one was from <5-year-olds. However, five of these studies used disc diffusion, which CLSI has not recommended since 2009 (all study periods for these five articles were after 2009), so the results may be unreliable (Clinical and Laboratory Standards Institute, 2009). Two studies also used CLSI guidelines from several years before the study was carried out. Four studies did not state the methodology for vancomycin resistance detection.

Enterococcus *spp.* A total of 37 articles reported on *Enterococcus* spp. and vancomycin (1.02% [CI: 1.01-1.04%], 144/1246). The

pooled proportion of resistance to vancomycin was 0.0% (CI: 0.0-91.1%, 2/286 resistant isolates) from Africa and 2.4% (CI: 0.4-12.1%, 142/960) from Asia, with no regional difference ($P = 0.404$) (Supplementary File 4; Table 15).

Streptococcus pneumoniae. A total of 47 articles reported on *S. pneumoniae* and penicillin (2.4% [CI: 0.8-7.2%], 285/2937). The pooled proportion of resistance to penicillin increased in Africa over time from 0.0% (CI: 0.0-8.6%, 0/41 resistant isolates) in 1980-1989 to 17.4% (CI: 8.9-31.1%, 8/45) in 2010-2015 with an overall pooled proportion of resistance of 4.7% (CI: 1.5-13.6%, 218/1824). Penicillin resistance was rarely reported in Asia, with a pooled proportion of resistance of 0.4% (CI: 0.0-8.0%, 67/1113). There were 28 articles that reported on *S. pneumoniae* and erythromycin (2.8% [CI: 0.5-15.0%], 109/1147) with a higher pooled proportion of resistance in Asia, 7.5% (CI: 1.5-30.4%, 92/608) compared with Africa 0.0% (CI: 0.0-72.2%, 17/539). However, there were no significant regional differences for both antibiotics ($P = 0.139$ for penicillin and $P = 0.213$ for erythromycin) (Supplementary File 4; Table 16).

Laboratory diagnosis grading

None of the 371 studies graded using the MICRO criteria core items checklist scored 13. Most studies scored between 8-10, with the most common score being nine (99/371 studies, 27%, Figure 2D, Supplementary File 4; Table 17). All studies described the specimen type and denominators, and almost all described the sampling period (369/371) and geographic setting (370/371). Approximately 2% (8/371) stated whether the laboratory participates in an external quality assurance (EQA) scheme and 9% (33/371) described their strategy for dealing with duplicate or sequential isolates. Just over half of the studies reported the full information for their AST method (52%, 193/371) (Supplementary File 4; Table 18, Supplementary File 5). Approximately 26% (51/193) of studies that reported their AST method used AST guidelines from several years before the start of the study and not the most up-to-date versions. Nine studies reported *Klebsiella* spp. isolates as ampicillin sensitive, although *Klebsiella* spp. are defined as intrinsically resistant by CLSI.

Sensitivity analysis

See Supplementary File 4; Results 2, Tables 19 and 20.

PRISMA Checklist

PRISMA Checklist is shown in Supplementary File 6.

Discussion

Our analyses provide a detailed overview of AMR in key bacterial species as reported in published literature across Africa and Asia over 35 years. As expected, because of considerable testing and methodologic heterogeneity, it is difficult to compare and draw robust conclusions from the data (Pezzani et al., 2021). However, there is a clear trend of an increasing number of studies reporting AMR data over time (from one study published in 1986 to 39 studies published in 2014), which might reflect increased AMR research in the regions. Many studies reported third-generation cephalosporin resistance in Asia for *E. coli* and *K. pneumoniae* and in Africa for *K. pneumoniae.* There were significant regional differences for resistance against third-generation cephalosporins in *E. coli,* with higher pooled proportions of resistant isolates seen in Asia than in Africa. In both regions, the pooled proportion of resistance to fluoroquinolones in *S. enterica* isolates increased over time. Nalidixic acid resistance, previously tested as a marker for decreased ciprofloxacin susceptibility, was particularly high in Asia (88.9% [CI: 72.4-96.0%] in 2010-2015) compared with Africa (8.9% [CI: 1.6-37.5%] for the same period) suggesting overuse of fluoroquinolones, potentially because of the high burden of typhoid, and to empiric use for other indications in the region and the easy accessibility of the drugs (Do et al., 2021; Ingle et al., 2018). The limited data from Africa hampers a comparison of resistance prevalence in *S. enterica* between regions. Considerable heterogeneity in the definition of multidrug resistance precluded analyses of this important resistance phenotype in *S. enterica.* There are a limited number of reviews on AMR from Africa and Asia. However, they have all confirmed moderate to high rates of resistance for common pathogen-drug combinations and also highlighted the paucity of data at the country level (Ashley et al., 2011; Bernabé et al., 2017; Deen et al., 2012; Lubell et al., 2011; Tadesse et al., 2017; Williams et al., 2018).

The lack of a fully standardized global AST methodology leads to large AMR data heterogeneity across the studies and hampers our ability to analyze the pooled dataset. Although CLSI were the most common susceptibility guidelines and interpretive criteria used in the studies (54.2%), many studies reported using out-of-date versions at the time of testing. This may impact reported results as zone diameter and minimum inhibitory concentration interpretations change over time, resulting in differences in the proportion resistant. Some examples of CLSI changes are the 2008 guidelines for *S. pneumoniae* and penicillin, resulting in isolates previously classified as resistant now classified as susceptible (Clinical and Laboratory Standards Institute, 2008), the 2010 and 2011 guidelines for *Enterobacterales* and cephalosporins resulting in isolates previously classified as susceptible now resistant (Clinical and Laboratory Standards Institute, 2010, 2011), and the 2012 guidelines for fluoroquinolones and *S. enterica* with previously susceptible isolates now resistant (Clinical and Laboratory Standards Institute, 2012). Changes in the detection of decreased fluoroquinolone susceptibility, i.e. from nalidixic acid to pefloxacin disc testing, also complicate the assessment of resistance proportions and time trends in *S. enterica.* Access to raw susceptibility testing data would have enabled reanalysis using a single standard and permitted assessment of multidrug resistance, but this was not possible in the current study. For future studies, data availability through data repositories would make reanalysis of data with current standards possible. Of the 3475 etiology studies identified in the previous reviews, approximately 10% conducted and reported analysis of AST data. Considering the increasing impact of AMR and the paucity of resistance surveillance, prospective microbial etiology studies should embed AMR as an important research outcome.

The inclusion of laboratory quality grading is an important strength of our study (Ashley et al., 2018). Based on the MICRO grading checklist, no studies included all core reporting elements. The large range in scores emphasizes the variation in reporting practice and, therefore, the potential challenges to assessing the data quality. Notably, few laboratories reported whether they were part of an EQA system. Including this information helps signpost whether laboratories are invested in continual quality improvement and provides reassurance that results should meet a recognized standard.

It is a frequent practice in low and middle-income countries to collect microbiology specimens only after failure of empiric treatment(s) or in patients with severe infection if microbiology services are available at all (Om et al., 2016). Therefore, the results from this study may have implications for empiric treatment guidelines. Ceftriaxone is a common first-line treatment for severe infection in many locations (Durham et al., 2017; Mandell et al., 2007), but with a pooled proportion of approximately 50% of *E. coli* and *K. pneumoniae* isolates resistant in this dataset, this needs to be urgently reconsidered. Gentamicin resistance may also com-

promise empiric treatment of neonatal sepsis, with a pooled proportion of 52.7% *E. coli* and 73.5% *K. pneumoniae* isolates from this age group being resistant. However, patient selection criteria may have led to an overestimation of resistance. Results from this review can be used to compare to GLASS data to determine how well research studies and publications reflect routine AMR surveillance within countries and regions.

There are several limitations to this review. The selection criteria may have resulted in a bias toward case studies, which do not provide a true representation of the overall AMR prevalence in Asia and Africa; thus, results should not be over-interpreted. The focus on blood, CSF, and other normally sterile sites may have resulted in the exclusion of other clinically relevant organisms, such as *Shigella* spp. and explain the low number of isolates overall. For most of the studies, it was not known whether isolates were from hospital or community-acquired infections, nor the clinical or symptomatic status of the source individual. Hospital-based studies were not excluded, which may have led to the inclusion of some hospital-acquired infections. The analysis within this review focuses on regions without specific country analysis. Because of the lack of data at the country level for many countries, it was not possible to do a more in-depth analysis. There was moderate-large heterogeneity in the estimates obtained from the meta-analysis. Therefore, the estimates from the meta-analysis should be used as an approximate guide to gauge the level of resistance rather than an exact estimate. Finally, this analysis is based on the original series of reviews that searched data until 2015. Although the more recent publications are not included in this review, this presents a summary of the evidence over 35 years and identifies key themes and trends. However, despite these limitations, these analyses fill a part of the considerable knowledge gap regarding AMR in Africa and Asia.

Conclusions

This review highlights a general increase in AMR reporting and resistance over time among clinical bacterial isolates in Africa, South Asia, and Southeast Asia. There are many reports of third-generation cephalosporin resistance in both regions. In addition, Quinolone resistance in *S. enterica* is increasing in Asia. However, this review highlights the general paucity of data, a lack of standardization, and data quality assurance. Strengthening of laboratory capacity and standardized testing and reporting of AST results is required to improve surveillance of AMR, both nationally and regionally. Furthermore, prospective studies reporting the etiology of bacterial illness should add AMR as a key outcome of their findings.

Abbreviations

AMR = Antimicrobial resistance; AST = Antimicrobial susceptibility testing; BSAC = British Society for Antimicrobial Chemotherapy; CLSI = Clinical and Laboratory Standards Institute; CSF = Cerebrospinal fluid; EQA = External quality assurance; EUCAST = European Committee on Antimicrobial Susceptibility Testing; ID = Identification; MIC = Minimum inhibitory concentration; MICRO = Microbiology Investigation Criteria for Reporting Objectively; MDR = multidrug-resistant; NTS = nontyphoidal *Salmonella*; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SFM = Société Française de Microbiologie; WHO = World Health Organization.

Competing interests

DB and HH were previously employed at the Foundation for Innovative New Diagnostics (FIND), and SD is currently employed by FIND. HH's salary at the London School of Hygiene and Tropical Medicine (LSHTM) was previously covered through the ACT Consortium, funded through a grant from the Bill and Melinda Gates Foundation to the LSHTM.

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Ethics approval and consent to participate

Not applicable.

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Author contributions

PJG, PNN, DB, JAC, SD, and HH conceived the idea. PS, RS, VTLH, RN, and RVD were involved in data curation. PD, KS, TR, and WS were involved in formal analysis. PD, KS, and TR created the methodology. PD visualized the data. PD, TR, VP, MT, and PT were involved in data validation. PJG, HH, and SD were involved in funding acquisition. HH coordinated working groups for the original systematic reviews of pathogens causing nonmalaria febrile illness. PJG and PS were involved in project administration. PJG was involved in resources. PS, RVD, PJG, and PT supervised the project. TR, PD, PT, and EAA wrote the first draft of the manuscript. All authors edited drafts and read and approved the final version.

Availability of data and materials

All data generated and analyzed in this review are openly available from the IDDO webpage as a downloadable resource (Non-malaria febrile illness (NMFI) surveyor - fever series (iddo.org)). The script used for generating all the figures, tables, and the estimates presented in the manuscript is available from: https://github.com/PrabinDahal/IDDO_NMFI_Antimicrobial-Resistance.

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.018.

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