The Global Geospatial Distribution Of Antimicrobial Resistance In Selected Gram-Negative Bacterial Infections



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Abstract

Antimicrobial resistance of Gram-negative bacteria is increasingly reported worldwide, rendering multiple antibiotics ineffective. *Shigella* is the second leading cause of diarrheal mortality, with an estimated 264 million episodes of shigellosis and 220,000 deaths annually. *Escherichia coli* and *Klebsiella pneumoniae* are the most common causes of community- and hospital-acquired Gram-negative bloodstream infections. Identifying the spatial and temporal trends in the distribution of drug-resistant Gram-negative bacteria are important to identify hotspots of disease, close gaps in knowledge, and inform policy regarding the use of antibiotics.

A systematic review compiled a global dataset of the proportion of *Shigella* isolates with nalidixic acid resistance, linked to time and geographic location. Data were extracted from the published literature, from 1990 to 2018. A meta-analysis of nalidixic acid resistance was calculated and presented by region and 5-year time periods. A second systematic review was initiated to determine the proportion of antimicrobial resistance in *Escherichia coli* isolates. Data were also extracted from the published literature, from 1990 to 2018. A meta-analysis of seven antimicrobials was calculated and presented by antimicrobial, region, and 5-year time periods.

The proportion of antimicrobial resistant isolates globally were predicted using a geospatial modeling framework on a national level. Maps were produced to identify trends in resistance over a 30-year period in each country worldwide.

This thesis documents high rates of fluoroquinolone resistance in *Shigella* and *Escherichia coli* and carbapenems resistance in *Escherichia coli* and 3rd generation cephalosporin resistance in *Escherichia coli*. The prevalence of AMR in *Shigella* and *Escherichia coli* is provided in detail, and global trends across time are examined. These estimates can be used as a baseline to inform intervention and the development of policies to combat AMR.

Acknowledgments

I would like to acknowledge my supervisors who have been on this journey with me from the beginning. Christiane, Susie, Paul, and Benn, thank you for your guidance, insight, and patience throughout my DPhil. Thank your support throughout this opportunity. I am so grateful for it, it has been an unparalleled experience.

I would like to thank my team members on the GRAM project for working alongside me throughout my DPhil and for being a great team to collaborate with.

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Declaration of Work and Contributors

The work contained in this thesis is my own, but could not have been done without the scientific guidance of my supervisors Christiane Dolecek, Susie Dunachie, Paul Turner, and Benn Sartorius and the assistance of several others, outlined below.

GRAM Team

This project is part of a larger project, GRAM (Global Research on AntiMicrobial resistance). Our group, the Oxford GBD (Global Burden of Disease) Group was established in July 2018 at the University of Oxford's Big Data Institute and Centre for Tropical Medicine and Global Health to work in partnership with the Institute for Health Metrics and Evaluation (IHME) at the University of Washington to conduct strategic research in epidemiology and public health.

The team consists of: two principal investigators, Christiane Dolecek and Chris Murray; scientific lead by Susanna Dunachie; three data analysts; two post-doctoral researchers; a scientific communications officer; line manager, Catrin Moore; the IHME team; and myself.

GRAM has additionally subcontracted parts of the systematic review work to Oxford students. Throughout the past four years, GRAM has subcontracted about thirty students. These students were interviewed, trained, and managed by me. I provided a 90-minute training to each student and was available to answer questions they had, scheduled meetings with students, checked student work for accuracy, and constantly improved my training according to student feedback.

The *shigella* work was mainly carried out myself, double extraction was done by; myself, one data analyst, and three subcontracted students. The *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae,* and *Staphylococcus aureus* systematic review was carried out by; myself, two data analysts, and twenty-eight students. Students contributed about 10 hours per week or less of time, worked on the project for three months at a time, and worked on various stages of the systematic review. My work on the *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae,* and *Staphylococcus aureus* systematic review included: appending the original search strategy after realizing it was not exhaustive, deduplicating the library, writing up the variables of information to be extracted from the papers, creating the extraction template, managing those working on the *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae,* and *Staphylococcus aureus* systematic review, and I planned each step of the review. I checked all extracted work for accuracy.

Thesis

Chapter Two - Antimicrobial Drug Resistance in Shigella Isolates Worldwide, from 1990 to 2018: A Systematic Review of the Literature.

- Christiane Dolecek constructed the search strategy for the *shigella* systematic review.
- Eli Harris, Oxford librarian performed the database searches.
- I was the first reviewer and the second reviewer for the systematic review was a team of seven medical students whom I trained and managed and three research assistants at the Big Data Institute, University of Oxford. All work from the students was double-checked by myself.

Chapter Three – Global Geospatial Modelling Of Antimicrobial Drug Resistance In *Shigella*

- The code for the spatial-temporal Gaussian process regression (ST-GPR) model was provided by Benn Sartorius.

Chapter Four – Systematic Review Of Antimicrobial Drug Resistance In *Escherichia coli* From 1990-2018

- Christiane Dolecek constructed the search strategy for the *Escherichia coli* systematic review.
- Eli Harris, Oxford librarian performed the database searches.
- The first reviewer consisted of myself, Georgina Haines-Woodhouse, or Emmanuelle Kumaran, second reviewer for the systematic review was a team of 24 medical students whom I trained and managed at the Big Data Institute, University of Oxford. All work from the students was double-checked by myself.

Chapter Five – Global Geospatial Modelling Of Antimicrobial Drug Resistance In E. Coli 1990-2018

- The code for the ST-GPR model was provided by Benn Sartorius.

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List Of Acronyms and Abbreviations

3GC	Third-Generation Cephalosporins
4GC	Fourth-Generation Cephalosporins
AMR	Antimicrobial Resistance
ABACUS	AntiBiotic ACcess and USe
ACORN	A Clinically Oriented antimicrobial Resistance Network
AST	Antimicrobial Sensitivity Test
ATLAS	Antimicrobial Testing Leadership and Surveillance
AURA	Antimicrobial Use and Resistance in Australia Surveillance System
BMJ	British Medical Journal
BSAC	The British Society for Antimicrobial Chemotherapy
BSI	Blood Stream Infection
CAESAR	Central Asian and European Surveillance of Antimicrobial Resistance
CAI	Community-Acquired Infections
CDC	Centers for Disease Control and Prevention
CLSI	Clinical Laboratory Standards Institute
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus Disease of 2019
CRE	Carbapenem-resistant Enterobacteriaceae
CSF	Cerebrospinal Fluid
EARS-Net	The European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	The European Economic Area
EQA	External Quality Assessment
ESBL	Extended-spectrum beta-lactamases
EU	The European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FQ	Fluoroquinolone
FQR	Fluoroquinolone Resistance
GAM	Generalized Additive Model
GARPEC	Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children
GASP	Gonococcal Antimicrobial Surveillance Program
GATHER	Guidelines for Accurate and Transparent Health Estimates Reporting
GBD	Global Burden of Disease
GEMS	Global Environment Monitoring System
GLASS	Global Antimicrobial Resistance Surveillance System
GLMM	Generalized linear mixed models
GRAM	The Global Research on Antimicrobial Resistance

HAI	Hospital-Associated Infections
HCAI	Healthcare-Associated Infections
HIC	High-income Countries
ICU	Intensive Care Unit
INICC	International Nosocomial Infections Control Consortium
ISO	International Organization for Standardization
JANIS	Japan Nosocomial Infections Surveillance
JSTOR	Journal Storage
KNN	K-nearest Neighbors
LIC	Low-income Countries
LMIC	Low-middle Income Countries
LOESS	Locally Weighted Scatterplot Smoothing
LSHTM	The London School of Hygiene & Tropical Medicine
MAD	Median Absolute Deviation
MBG	Model Based Geostatistics
MBIRA	Mortality from Bacterial Infections Resistant to Antibiotics
MCMC	Markov chain Monte Carlo
MDR	Multidrug Resistance
MIC	Minimal Inhibitory Concentration
MICRO	Microbiology Investigation Criteria for Reporting Objectively guidelines
MRSA	Methicillin-resistant Staphylococcus aureus
MSM	Men who have sex with men
NAR	Nalidixic Acid Resistance
NCCLS	National Committee for Clinical Laboratory Standards
NNCLS	National Committee for Clinical Laboratory Standards
NNET	Neural Networks
NSAR	National Surveillance of Antimicrobial Resistance in Malaysia
PAHO	Pan American Health Organization
PBM	African Pediatric Bacterial Meningitis Surveillance Network
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMSE	Root-mean-square Deviation
SIR	Sensitive Intermediate Resistant
SLIPTA	Stepwise Laboratory Improvement Process Towards Accreditation
SMART	Study for Monitoring Antimicrobial Resistance Trends
SOAR	Survey of Antibiotic Resistance
SSA	sub-Saharan Africa
STGPR	Spatial Temporal Gaussian Process Regression
STRATAA	Strategic Typhoid Alliance Across Africa and Asia
TSAP	The Typhoid Fever Surveillance in Africa Program
UTI	Urinary Tract Infections
WHO	The World Health Organization

CHAPTER 1

Introduction to Antimicrobial Resistance in Select Gram-negative Bacterial Infections

1.1 GLOBAL THREAT AND IMPORTANCE OF ANTIMICROBIAL RESISTANCE

The introduction of antimicrobials changed the world. They made modern medical procedures possible and have contributed to modern life expectancies.[1] It was the most significant medical discovery in the 20th century. In 1937, the first antimicrobials, sulfonamides, were available for human use on a mass scale, however, only a year later, the first antimicrobial-resistant infections developed.[2]

Antimicrobial resistance (AMR) is the process in which pathogens adapt themselves to fight the drugs created to kill them. These pathogens can be bacteria, fungi, parasites, or viruses, and when infections are more challenging to treat, it can increase the severity of the infection, increase the chances of spreading the infection to others, and increase mortality from the infection.[3] This phenomenon affects all countries worldwide and leaves even those with the most advanced medical care with limited or no options for treatment. Additionally, AMR infections are costly due to extended hospital stays, more intensive treatments, and potential long-term health consequences from untreated infections. The costs of AMR vary by country due to the large variety of healthcare systems worldwide. Not only does AMR have high economic costs, but it also costs many people their lives.

The Global Research on Antimicrobial Resistance (GRAM) study estimates 1.27 million deaths in 2019 were due to drug-resistant infections, making AMR a leading cause of death globally, particularly impacting low and middle-income countries (LMICs).[4] AMR is not a problem limited to humans; large volumes of antimicrobial use in animals have led to a high prevalence of resistance in animals. Of all the antimicrobials in the world sold for use, it is estimated that 73% are used in raising animals for food.[5] This practice raises the risk of AMR in both animals and humans. AMR is described as one of the most significant global threats of the 21st century as it directly affects progress in healthcare, food production, and human life expectancy.[6]

AMR is a multifactorial issue, with different drivers of resistance and several approaches to improvement. Suspected drivers of AMR include inappropriate antimicrobial use (e.g., due to lack of regulation or non-adherence to treatment guidelines), poor infection control in hospitals, and lack of clean water and sanitation leading to quicker spread of resistant bacteria.[3,7] AMR worsens not only through human use of antibiotics but also through its use in agriculture. Antimicrobials are commonly used in animals to avoid infections in crowded living conditions and to aid in the quick growth of the animal. As many antimicrobials given to animals are the same as those given to humans, this can contribute to developing and spreading resistant bacteria to common antimicrobials in humans.

AMR is a worldwide threat with progressively fewer efficacious treatment options available each year. Unfortunately, the incentive for pharmaceutical companies to develop new antimicrobial classes is low. Additionally, access to appropriate antimicrobials is often limited in resource-limited regions. Over-prescription and misuse of antimicrobials are

rampant and general public education on the appropriate use of antimicrobials is lacking. In high-income countries, over-prescription is driven by the insistence of the patient, appointment time constraints lead to empirical treatments, uncertain diagnoses, or decision fatigue.[8,9] Taking antimicrobials for an illness in which they are an inappropriate treatment can wipe out naturally occurring susceptible bacteria in the gut and contribute to resistance in bystander bacteria. This can leave the patient more susceptible to infections in the future. Over-prescription in low and middle-income countries is often driven by a lack of resources, including microbiology laboratory capacity, skilled medical care, and treatment guidelines informed by local evidence.

The clinical implications of AMR affect each stage of medical care. Prescription of an antimicrobial for the infection presented can differ by country due to the differences in policy, antimicrobial stewardship, diagnostic procedure, and cost. The specific antimicrobial prescribed will also vary by country due to; the resistant infection presented, whether antimicrobial sensitivity tests are performed, and the availability of different antimicrobials in the country. With resistance on the rise, it increases the probability of contracting a resistant infection and limits the ability to treat it. Much of modern medicine relies on effective antimicrobials and infection control within hospitals. There are many modes of transmission of drug-resistant infections within a hospital including unwashed hands or unsterilized equipment, length of hospital stay, the proximity of patients to one another, shared bathroom facilities, invasive surgical procedures, intense therapies, and patient age.[8] Many surgical procedures with a high risk of infection, such as organ transplants and joint replacement surgeries, are standard in modern medicine with the help of antimicrobials. However, with increasingly limited antimicrobial options, these

surgeries could one day be deemed too risky to perform with no way to treat possible infection afterward.

In many LMICs, it is common for pharmacies to sell antimicrobials over the counter without a prescription. This can result in unnecessary consumption of antimicrobials or an incorrect dosage, increasing the likelihood of bacterial AMR developing. Little information is commonly available and dispersed regarding proper antimicrobial use and practices. Globally, over-prescription of antimicrobials is a problematic and common occurrence. Despite antimicrobial resistance developing naturally, clear human actions amplify and facilitate this process.

The global pandemic of COVID-19 has only exacerbated this problem in the past three years. A review conducted in 10 African countries: Ghana, Kenya, Uganda, Nigeria, South Africa, Zimbabwe, Botswana, Liberia, Ethiopia, and Rwanda, reported antimicrobials were prescribed for COVID-19 management for 2,097/2,834 (74%) patients, yet only 499 (17.6%) patients had evidence of secondary bacterial infections.[10] A study conducted in Spain reported 12,238/13,932 (89%) patients presenting at a hospital were prescribed antibiotics for COVID-19. Mortality was higher in those prescribed antibiotics, and these patients were more often transferred to the intensive care unit (ICU).[11] Additionally, a systematic review of publications from China, USA, Spain, Thailand, and Singapore collected data on 3,506 patients, highlighting significant misuse of antibiotics in COVID-19 cases. Of the 3,338 patients evaluated for a bacterial infection, 281 (8.4%) patients had a bacterial infection, and 2,517 (71.8%) patients received antibiotics.[12] In Egypt, 413 pharmacies collected data on 90,542 patients, in which 84,205 (93%) patients received antibiotics either through a physician's prescription (82%) or without a prescription (18%)

when presenting with COVID-19 symptoms at either a doctor's office or pharmacy. Further, 28,097 (33.4%) patients had a recurrent case and requested a repeat of the same antibiotics previously dispensed. All patients were classified as "presumptive COVID-19 patients" with no COVID-19 test taken. [13] Over the past two years, many studies looking at antibiotics use during the COVID-19 pandemic are overwhelmingly reporting overuse of antibiotics.

1.2 ANTIMICROBIAL RESISTANCE IN GRAM-NEGATIVE BACTERIA

Antimicrobial resistance of Gram-negative bacteria is progressively reported worldwide, resulting in many first- and second-line treatments ineffective. ICUs are increasingly under pressure as Gram-negative bacteria account for 45-75% of ventilator-associated pneumonia, 20-30% of catheter-related bloodstream infections, and frequently are responsible for ICU-acquired sepsis or urinary tract infections (UTIs).[14] Gram-negative bacteria are more susceptible to gaining resistance to antimicrobials when compared to Gram-positive bacteria, due to structural differences. Gram-negative bacteria have an outer membrane that serves as a barrier and a tool to resist different antimicrobials that Gram-positive bacteria do not have.

There are multiple mechanisms by which Gram-negative bacteria gain antimicrobial resistance. Innate resistance due to the impermeable membrane - this is the case with vancomycin as it cannot penetrate the cell membrane of Gram-negative bacteria. Bacteria can also acquire resistance through mutation in the cell DNA. Horizontal gene transfer of resistance is a mechanism that allows bacteria to exchange genetic material from one bacterial cell to another..[15] This process is conducted by creating a channel from one cell to another when in close contact.[15] Some antimicrobials are hydrophilic or hydrophobic and

use specific channels to pass through the cell membrane. The bacteria can genetically change components of their membrane, thus rendering these channels unusable. These mutations may create efflux pumps, transporting the antimicrobial out of the cell before it can impact it. An example of this process is how *Escherichia coli (E. coli)* has become resistant to fluoroquinolones by creating a channel in which it pumps the antimicrobial out through the outer membrane.[16] Bacteria may undergo genetic changes that make protein components and receptors that become either unrecognizable by the antimicrobial or inactivate the antimicrobial. This process causes third-generation cephalosporin-resistant *E. coli* by the spread of extended-spectrum β-lactamases (ESBLs) worldwide.[17] Additionally, carbapenemases may be produced which causes carbapenem resistance in *E. coli*. [18]

AMR sensitivity testing is performed in the laboratory to determine which antimicrobials the bacteria is resistant to. A sample from the patient is tested for the presence of bacteria, this can be a sterile or non-sterile site, depending on the infection presented. To determine the resistance or sensitivity of the bacteria, there are multiple methods available to grow microorganisms using a culture medium. This involves measuring the diameter of the area without bacterial growth, the minimum inhibitory concentration (MIC) value is estimated from the size of this diameter. Antimicrobial susceptibility testing guidelines are used to interpret the MIC value as resistant or sensitive. This is the lowest antibiotic concentration at which the bacteria will be effectively prevented from growing.[19]

This thesis will focus on the selected Gram-negative pathogens, *E. coli* and *Shigella spp,* within the Enterobacteriaceae family. These pathogens can easily move from the gut into the bloodstream causing deadly complications. Some species are also known to cause

diarrheal diseases. Fluoroquinolones were an antimicrobial of focus due to the WHO global priority pathogen/antibiotic list featuring fluoroquinolone-resistant *Shigella* and fluoroquinolone-resistant *E.coli*. The WHO recommends azithromycin or ceftriaxone as a treatment for fluoroquinolone resistance infections. These three antimicrobials were the focus of the *Shigella* systematic review analysis. Carbapenem-resistant *E.coli* and third-generation cephalosporin-resistant *E.coli* are also on the WHO global priority pathogen/antibiotic list and these pathogen/antibiotic combinations were the focus of the *E.coli* analysis.

1.2.1 *E. COLI*

E. coli was first detected in the late 19th century by a Bavarian pediatrician, Theodor Escherich.[20] *E. coli* is found in the gut flora of over 90% of people in the world and is one of the first bacteria to colonize a neonate's gut at birth.[21] *E. coli* are anaerobic, flagellated, and non-spore forming.[22] There are many *E. coli* pathotypes that are characterized by their virulence determinants and unique characteristics. Some pathotypes are classified as causing different types of diarrhea in different populations worldwide, including diarrhea in children under five, traveler diarrhea, and diarrhea in adults. Other pathotypes are classified based on causing wound infections, urinary tract infections, peritonitis, pneumonia, meningitis, and septicemia.[23]

E. coli can be broadly categorized into three phylogenetically and epidemiologically different groups: commensal, pathogenic (enteric/diarrheagenic), and extraintestinal pathogenic *E. coli.*[24] *E. coli* can remain commensal bacteria in the human gut or can cause intestinal and diarrheal diseases and extraintestinal infections.[24] Intestinal pathogens can cause gastroenteritis when *E. coli* has spread person to person by hand-to-mouth contact.

It is most often ingested by eating or drinking contaminated food or water.[25] *E. coli* can also be found in common areas with high human contact such as on paper currency, coins, and on the floor of hospitals and long-term care facilities.[22,26] The severity of gastroenteritis ranges from mild gastroenteritis to deadly disease. The seven main diarrhea-causing pathotypes are enteropathogenic *E. coli* (EPEC), Enterohaemorrhagic *E. coli* (EHEC), Shiga toxin-producing *E. coli* (STEC), *Shigella*/enteroinvasive, *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), diffusely adherent *E. coli* (DAEC), and enterotoxigenic *E. coli* (ETEC), and adherent invasive *E. coli* (AIEC). Additionally, extraintestinal disease can form when *E. coli* in the gut move to other parts of the body. The most frequent extraintestinal infections are urinary tract infections, ventilator-associated pneumonia, and community-acquired pneumonia, and blood-stream infections. Additional pathotypes have been identified that cause extraintestinal diseases (Intestinal pathogenic *E. coli* (IPEC)); sepsis (Sepsis-associated *E. coli* (SEPEC)); neonatal sepsis and meningitis (Neonatal meningitis *E. coli* (NMEC)); and urinary tract infections (Uropathogenic *E. coli* (UPEC)).[27]

In community and hospital settings, AMR in *E. coli* poses a significant threat. *E. coli* is the most common cause of community and hospital-acquired Gram-negative bloodstream infections and the most common aetiologies of urinary tract infections, causing nosocomial outbreaks within and between hospitals.[28] Additionally, *E. coli* is a leading cause of neonatal meningitis.[29] More than half of all infections caused by *E. coli* are now resistant to fluoroquinolones.[30] Fluoroquinolones are the most commonly used antibiotic in treating urinary tract infections and are no longer effective in more than half of patients treated.[3]

1.2.2 *SHIGELLA*

Shigella was first discovered by the Japanese physician Kiyoshi Shiga in Japan in 1898.[31] Epidemic dysentery was often seen in the late 1800s, with a mortality rate of 25% and killing over 22,00 people in 1897.[31] Dr. Shiga described *Shigella* as "the most dreaded disease of children from its fulminating course and high mortality".[31] *Shigella* are non-spore-forming, nonmotile prokaryotic rods that are anaerobic.[32] Shigellosis is an enteric infection caused by bacteria of the genus *Shigella* and is clinically manifested by diarrhea.[33] *Shigella* is highly infectious as ingestion of only ten organisms can cause disease.[34] Once ingested, *Shigella* is mostly resistant to stomach acid and begins multiplying and moves to the colon where it produces *Shigella* enterotoxins. *Shigella* thrives in unsanitary living conditions. It is spread by direct contact with an infected person, eating contaminated food, or drinking contaminated water. Shigellosis is usually self-limiting with proper hydration. Antimicrobial treatment may be necessary depending on the severity of the disease, patient age, or risk of spreading the illness to others.[34]

Shigella is grouped into four species, *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei,* which share many traits and some distinct differences. *S. dysenteriae* has 15 serotypes, *S. flexneri* has 8 serotypes, *S. boydii* has 19 serotypes and *S. sonnei* has one serotype.[31] *S. flexneri* is usually found in LMICs, while *S. sonnei* is more common in high-income countries (HICs). *S. boydii is* commonly found in Bangladesh and Southeast Asia, and *S. dysenteriae* is most often found in outbreak settings such as refugee or war camps.[35] Most *Shigella* cases are caused by *S. flexneri* and *S. sonnei.*

Shigellosis is endemic in many LMICs and is the most critical cause of bloody diarrhea worldwide, with an estimated 264 million episodes and 220,000 deaths annually.[36] In the

United States, *Shigella* is estimated to cause around 450,000 episodes annually.[36] A majority of the deaths caused by shigellosis involve children less than five years old.[33] Antimicrobial-resistant *Shigella* isolates are increasingly reported worldwide. *Shigella* isolates were earlier susceptible to ampicillin, chloramphenicol, co-trimoxazole, and nalidixic acid but now have developed resistance against fluoroquinolones, cephalosporins, and azithromycin.[37]

1.2.3 *SHIGELLA* AND *E. COLI* INFECTIONS

Fluoroquinolone-resistant *Shigella,* fluoroquinolone-resistant *E. coli*, third-generation cephalosporin *E. coli*, and carbapenem-resistant *E. coli* are on the WHO AMR priority pathogens list, highlighting the need for more research and development to help alleviate this global health problem.[30] Major obstacles in managing infections caused by *Shigella* and *E. coli* include the ease with which they spread from person to person and the rapid development of antimicrobial resistance.[38,39] According to the WHO, once *Shigella* become resistant they tend to remain resistant, it is rare for strains to reappear in a region sensitive over time.[33] Drivers of AMR in *Shigella* and *E. coli* include overcrowding, poor sanitation, and unregulated antimicrobial access and consumption.[33,40] This affirms the need for better sanitation and clean water in many LMICs suffering from a high prevalence of these infections.

Shigella and *E. coli* outbreaks often occur in childcare centers worldwide due to poor hand hygiene and sanitation. Children under the age of five have yet to develop proper and adequate hygiene practices. Enforcing good hand washing multiple times a day for a large group of young children can prove to be very challenging and difficult to maintain efficacy. Many of these children contract the illness, return home, and spread it to their families.

Children in childcare are known to take more antibiotics compared to children who are not.[41,42] Outbreaks in childcare centers have been reported worldwide, including in the United States, Canada, Brazil, Japan, Vietnam, Nigeria, and Spain.[43–50]

Vaccines have been challenging to develop due to changes in the dominant *Shigella* species within a country or community. *S. flexneri* is commonly seen in LMICs or communities with poor sanitation. In the past, once these countries improved their sanitation and infrastructure, the dominant species then shifted to *S. sonnei*.[51–53] In Israel, when sanitation improved in the 1970s, the dominance of *S. flexneri* moved to *S. sonnei*, except for within traditional Bedouin communities. The likely cause is sanitation and general hygiene practices remained unchanged within these communities and allowed for *S. flexneri* to remain prominent.[54] Native Americans are another vulnerable community living secluded from the general population on reservations. These reservations are known to have poor water quality and sanitation, combined with a lack of health education, which lead to an ideal environment for *Shigella* to spread.[55] There are approximately one million Native Americans living on reservations, and they have the highest incidence of *Shigella* in the United States.[56] Indigenous communities in Australia are another high-risk group for contracting *Shigella* due to overcrowding and poor hygiene within the community.[57]

Vaccine development for protection from *E. coli* also comes with its challenges. When creating a vaccine for *E. coli*, some of the main goals involve affordability and availability in LMICs, aiming to reduce mortality and morbidity in children under the age of five. There is no licensed *E. coli* vaccine yet, this has been a WHO priority for the past 20 years and they have recently published a report outlining the preferred characteristics of an *E. coli* vaccine.[58] There are currently several oral and parenteral vaccine candidates in

development. These vaccines are essential for children under the age of five, and of great benefit to international travelers and military personnel. Effective vaccines for both *Shigella* and *E. coli* will reduce the use of antimicrobials in the population and significantly reduce mortality in children under the age of five.

Understanding the true impact of AMR worldwide is challenging due to the lack of data from many countries. The GRAM study estimates 1.27 million deaths were due to drug-resistant infections, making AMR a leading cause of death globally, particularly impacting LMICs.[4] *E. coli* was found to be responsible for the most deaths attributable to AMR. Identifying the spatial and temporal trends in the prevalence of drug-resistant *E. coli* and *Shigella* are essential to identify hotspots of disease, close gaps in knowledge, and inform policy regarding the use of antibiotics.

1.3 DATA COVERAGE ON THE PREVALENCE OF AMR

The aim of this thesis is to gather and collate a global dataset of available AMR data to provide a global picture of AMR in selected pathogen-antibacterial drug combinations. This process combines surveillance data, academic and industry data, unpublished data from researchers, and data gathered from the literature. The creation of such a comprehensive database will allow the use of geospatial modeling techniques to predict AMR in locations where no data is collected or reported.

HICs produce the most considerable amount of data available, this is made possible by ample funding and resources to do so. LMICs are unable to report AMR data at the same rate, resulting in the population most vulnerable to AMR with the least amount of data to

help inform prevention strategies. Additional factors leading to minimal AMR data reported from LMICs comprise of lack of laboratory capacity, over-reliance on empirical treatment, barriers to accessing healthcare, and a lack of clinical data linked to laboratory data.[7] Systematic reviews and extensive academic studies have helped fill this gap, however, data in many LMICs remains sparse.

A systematic review was the first approach taken to collect data. Systematic reviews are structured to identify, collect, appraise and analyze all available data to answer a specific research question. This process requires access to online databases to search for publications that may contain data of interest. This can be an excellent method to collect data from high, middle, and low-income countries if language is not restricted in the search criteria. However, systematic reviews can be time-consuming, difficult to assess data quality, and subjected to several biases.

Extensive academic studies and unpublished data from academic researchers can provide AMR data at a higher standard. Many of those studies had a transparent and comprehensive methodology, and data from high-quality laboratories. Data may be collected from many locations using the same methodology, this helps make meaningful comparisons of AMR across countries and regions, and years.

Surveillance systems are essential for reducing AMR by focusing policy and infection control efforts and monitoring the impact on communities. Surveillance systems vary as they can be implemented in specific hospitals or districts within a country, are nationwide or transnational. Each surveillance system has focused on particular pathogens and

antimicrobial combinations, and the vast majority have collected less than ten years of data. This data helps look at the specific targeted picture intended by the creation of the surveillance system rather than the macro picture. The use of secondary data has its benefits and challenges in AMR data. If a country has several district surveillance systems, this could be helpful in creating an overall picture of AMR in that country. However, if each surveillance system focuses on a different pathogen or antimicrobial and collects different variables of information, this data cannot be collated. This challenge makes it incredibly difficult to fill gaps in data between surveillance systems to achieve a global picture of AMR in the pathogen and antimicrobial of interest when compiling a global dataset.

In addition to the challenge of gaps in data, it can be very difficult to assess the quality of AMR data. There are potential problems of duplication of data in different publications and across different surveillance systems. Most data is collected through passive surveillance systems, in which the methodology of data collection and the population sampled is unknown. Additionally, data is often from tertiary-level referral hospitals, where the most severe cases are seen and resistant infections are more likely. This can introduce bias and lead to a potential overestimation of AMR. In Chapter 6, I will review the challenges in estimating the prevalence of resistance and will discuss bias in the collection of AMR data.

Countries	Surveillance Systems		Report Dates	Pathogen
EU	EURO/GASP	European gonococcal antimicrobial surveillance program	2009-2020	*Neisseria gonorrhoeae*
EU/EEA (ECDC)	EARS-Net	European Antimicrobial Resistance Surveillance Network	1998-2021	*Acinetobacter spp, Enterococcus faecalis, Enterococcus faecium, E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae*

Central Asia & Eastern Europe (12 Countries)	CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance	2015-2020	*Acinetobacter spp, Enterococcus faecalis, Enterococcus faecium, E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella species, Staphylococcus aureus, Streptococcus pneumoniae*
Sub-Saharan Africa	PBM	African Paediatric Bacterial Meningitis Surveillance Network	2001-2008	*Haemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae*
Sub-Saharan Africa and South Asia	GEMS	Global Enteric Multicenter Study	2007-2011	Enteric pathogens
East Africa	netSPEAR	Network for Surveillance for Pneumococcal Diseases in the East African Region	2003-2007	*Haemophilus influenzae, Streptococcus pneumoniae*
Latin America	ReLAVRA	Latin American Surveillance Network of Antimicrobial Resistance	2000-2016	*Acinetobacter baumannii, Enterobacteriaceae, Enterococci spp, E. coli, Haemophilus influenzae, Klebsiella spp, N. meningitidis, Pseudomonas aeruginosa, Streptococcus pneumoniae, Salmonella, Shigella, Staphylococcus aureus*
Global (54 Countries)	SMART	Study for Monitoring Antimicrobial Resistance Trends	2002-2020	Gram-negative bacteria
Global (60 Countries)	INICC	International Nosocomial Infection Control Consortium	2008-2020	Hospital-acquired infections
Global (72 Countries)	ATLAS	The Antimicrobial Testing Leadership and Surveillance database, Pfizer Inc.	2004-2017	*Acinetobacter spp, Bacteroides fragilis, Citrobacter spp, Clostridium spp, Enterobacter spp, Enterococcus faecalis, Enterococcus faecium, E. coli, Haemophilus influenzae, Klebsiella spp, Moraxella catarrhalis, Morganella morganii, Peptostreptococcus spp, Prevotella spp, Proteus mirabilis, Proteus vulgaris, Providencia spp, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus ,Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae*
Global (50 Countries)	GLASS	Global Antimicrobial Resistance Surveillance System	2014-2020	*Acinetobacter, E. coli, Klebsiella pneumoniae, Neisseria gonorrhoea, Non-typhoidal salmonella, Salmonella typhi and paratyphi, Shigella, Staphylococcus aureus, Streptococcus pneumoniae*
Global (22 Countries)	SOAR	GSK – Survey of Antibiotic Resistance	2011-2020	Community-acquired respiratory tract infections related pathogens

Table 1.1: Transnational AMR Surveillance Systems.References: EURO/GASP[59], EARS-Net[60], CAESAR[61], PBM[62], GEMS[63], netSPEAR[64], ReLAVRA[65], SMART[66], INICC[67], ATLAS[68], GLASS[69], and SOAR[70].

There are five global surveillance systems (SMART, INICC, ATLAS, GLASS, SOAR), however, each surveillance system focuses on a different set of countries and collects data on various pathogens and antimicrobials of interest. Almost all HICs currently have a national surveillance system, and extensive academic studies are in place to cover some

other countries worldwide, yet a significant data gap remains in sub-Saharan Africa. Table 1.1 shows the surveillance systems in sub-Saharan Africa and East Africa, which focus on a few pathogens, and have only a limited number of years of data.

1.4 THESIS AIMS

1.4.1 AIMS AND OBJECTIVES

This DPhil aims to estimate the prevalence of antimicrobial-resistant *E. coli* and *Shigella* infections in humans worldwide, from 1990-2018. The goal is to raise awareness of the critical situation the world is in regarding antimicrobial resistance, inform physicians, nurses, and other healthcare workers of the prevalence of resistance in their countries, and provide data to decision-makers to inform policy. The hope is that this data will help to incite policy changes and regulation of antimicrobial use and availability.

My thesis objectives are the following:

- To consolidate, review, and analyze all available data on antimicrobial-resistant *E. coli* and *Shigella* worldwide, combining surveillance system data, research data, and systematic review data from the literature.
- Produce maps of the prevalence of antimicrobial-resistant *E. coli* and *Shigella* infections, using machine learning and geospatial modeling techniques to predict the prevalence of *E. coli* and *Shigella* at the finest spatial resolution possible from 1990-2018.

1.4.2 CHAPTERS OVERVIEW

Chapter One: Introduction to Antimicrobial Resistance in Select Gram-negative Bacterial Infections

Chapter One of my thesis begins with a general introduction, the global threat of AMR, the importance of AMR, and the challenges of AMR in Gram-negative bacteria and *Shigella* and *E. coli* specifically. I will review the rationale for the pathogen and antimicrobial combinations I focus on. Finally, I discuss different data types, current data coverage, and data gaps in the prevalence of AMR. This chapter also includes my aims and objectives, and my thesis outline.

Chapter Two: Antimicrobial drug resistance in *Shigella* isolates globally, 1990 to 2018: A systematic review of the literature

Chapter Two describes the systematic review of antimicrobial drug-resistant *Shigella* infections. I discuss how a global dataset was compiled of the proportion of *Shigella* isolates (this included all four *Shigella* species) with nalidixic acid resistance, linked to the year of isolation and geographic location. The pooled prevalence of nalidixic acid resistance (as a proxy for fluoroquinolone resistance), ceftriaxone, and azithromycin were calculated and presented by region and 5-year time periods.

Chapter Three: Global Geospatial Modelling of Antimicrobial drug resistance in *Shigella* infections

In Chapter Three, I present the global geospatial modeling of antimicrobial drug resistance in *Shigella*. The proportion of *Shigella* exhibiting fluoroquinolone resistance globally is predicted using a geospatial modeling framework on a national level. The maps produced

identify trends in resistance over a 28-year period in each country worldwide. Sufficient data were available to create additional maps of the prevalence of resistance in all four *Shigella* species, separately.

Chapter Four: Systematic Review of Antimicrobial Drug Resistance in *E. coli* in Africa from 1990-2018

Chapter Four describes the methods of the systematic review of antimicrobial drug resistance in *E. coli*. I discuss the study characteristics and global data coverage obtained from the systematic review. Additionally, I present the meta analysis of resistant *E. coli* to the following antimicrobials:

- Fluoroquinolones
- Carbapenems
- Third-generation cephalosporins
- Fourth-generation cephalosporins
- Piperacillin-tazobactam
- Aminopenicillins
- Aminoglycosides

Chapter Five: Global Geospatial Modelling of Antimicrobial Drug Resistance in *E. coli* infections 1990-2018.

Chapter Five presents the global geospatial modeling of antimicrobial drug resistance in *E. coli* infections. The proportions of *E. coli* infections with resistance to third-generation cephalosporins, fluoroquinolones, and carbapenems are modeled at a national level globally and are predicted using a geospatial modeling framework. The maps I produced

identify trends in resistance over a 28-year period in each country. Data gaps in the systematic review have been supplemented by data from surveillance systems and unpublished research from collaborators to produce more robust estimates of the prevalence of AMR. Lastly, I discuss the implications my results can have on clinical practice and policy.

Chapter Six: Data Bias and Missing Information

Chapter Six will focus on data biases, missing information, and solutions for mitigating these biases. This project highlights the importance of having quality control indicators published in papers to assess and rank the overall quality of the study. Many papers in the systematic reviews did not report essential variables of information, introducing potential bias with no way to quantify this bias. Lastly, I discuss various methods for adjusting for identified biases when estimating the prevalence of AMR.

Chapter Seven: Conclusion and Future Work

Finally, Chapter Seven will be an overview of the proceeding chapters, including a discussion of the methodology and a summary of the results from Chapters Two and Four. Additionally, I discuss why spatial and temporal trends in the distribution of AMR Gram-negative bacteria are important, closing gaps in knowledge, and future work to expand on this project.

CHAPTER **2**

Antimicrobial Drug Resistance in *Shigella* Isolates Worldwide, from 1990 to 2018: A Systematic Review of the Literature

2.1 INTRODUCTION

Shigellosis is an enteric infection caused by the bacterium of the genus *Shigella* and is clinically manifested by diarrhea.[33] Disease can be caused by any of the four *Shigella* species: *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*. Each of the four *Shigella* species has unique epidemiological properties. *S. boydii* and *S. sonnei* are less virulent and usually present a mild infection. *S. flexneri* and *S. dysenteriae* present in a more severe infection and are more often responsible for epidemic and endemic shigellosis with high transmission rates and significant fatality rates in lower-income countries.[28] *S. flexneri* is usually found in lower-income countries and can be found across Africa and Asia, while *S. sonnei* is more commonly found in high-income countries. *Shigella* is spread by directly contacting an infected person, eating contaminated food, or drinking contaminated water. Only small numbers of bacteria are needed to cause disease, making it very easy to spread quickly. Shigellosis is endemic in most low-income countries and is the most important cause of bloody diarrhea worldwide, with an estimated 264 million episodes of shigellosis and 1.1 million deaths annually.[36,71] Most of the deaths caused by shigellosis involve children in the age group below five years old.[33] Currently there is no licensed *Shigella* vaccine and diminishing effective antimicrobials due to the rise in resistance.[72]

A *Shigella* infection commonly causes symptoms of bloody diarrhea and abdominal cramps.[33] There is an incubation period of one to four days and most patients recover within ten days. However, serious complications can occur, such as; metabolic abnormalities, sepsis, convulsions, rectal prolapse, toxic megacolon, intestinal perforation, and haemolytic-uraemic syndrome. If antimicrobials are not used for treatment, *Shigella* can be shed in stool for up to six weeks after symptoms resolve. Those at highest risk of complications are: infants, adults over 50 years of age, children who are not breastfed, children recovering from measles, malnourished children and adults, any patient who develops dehydration, unconsciousness or hypo- or hyperthermia, or has a history of convulsion.[33]

Some challenges in the control of shigellosis include the ease with which *Shigella* spreads from person to person, horizontal gene transfer, and the rapidity with which it develops antimicrobial resistance.[38] According to the WHO, once *Shigella* become resistant, they tend to remain resistant, it is rare for strains to reappear in a region sensitive over time.[33] Drivers of *Shigella* and antimicrobial resistance include overcrowding, poor sanitation, and unregulated antimicrobial access and consumption.[33] *Shigella* in high-income countries is mainly due to international travel, poor hygiene practices in vulnerable communities, and is sexually transmitted among men who have sex with men (MSM). *Shigella* in men who have sex with men (MSM) was first reported in the mid-1970s in San Francisco, and soon after, reports also emerged from Berlin and London and then in 2011 in Japan.[30,73–75] Shigellosis then became known as a sexually transmitted disease. Studies in Australia, England, and the United States have reported high rates of resistance to azithromycin in their MSM populations and are no longer able to use azithromycin as an effective treatment for shigellosis.[3,76–79]

Vaccines have been challenging to develop due to changes in the dominant *Shigella* species within a country or community.[35] This affirms the need for better sanitation and clean water in many LMIC countries suffering from high cases of *Shigella*. *Shigella* and fluoroquinolones are on the WHO antibiotic-resistant priority pathogens list, highlighting the need for more research and development to help alleviate this global health problem. Identifying the spatial and temporal trends in the prevalence of drug-resistant *Shigella* is important to distinguish hotspots of disease, increase knowledge on the state of AMR, and inform policy regarding the use of antibiotics.

In this chapter, I will discuss the methods used to conduct the systematic review of antimicrobial drug resistance in *Shigella*, a summary of the data collected, and meta-weighted estimates of prevalence by geography and time of AMR in *Shigella* worldwide. I focus on nalidixic acid resistance in *Shigella* and included data on resistance to azithromycin and ceftriaxone and their trends in resistance over time. Lastly, I discuss the limitations of the data collected and the challenges that come with working with AMR data.

2.2 MATERIALS AND METHODS

2.2.1 SEARCH STRATEGY AND SELECTION CRITERIA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were followed and the protocol was registered with the international prospective register of systematic reviews, PROSPERO 2019 CRD42019127603.[80] The systematic search combined Medical Subject Heading terms with free text terms in the title and abstract fields for *Shigella* or Shigellosis with the terms for antimicrobial drug resistance (Table A1). The systematic search included publications from 1990 to 2018. There were no

language or study type restrictions. The reference lists of relevant studies were checked to identify secondary references.

The endnote library was deduplicated and imported into the proprietary software DistillerSR (DistillerSR. Version 2.35. Evidence Partners; 2021. https://www.evidencepartners.com). DistillerSR is a project management tool for systematic reviews used widely by the Cochrane Reviews team. It is a web-based systematic review software created to manage, track, and streamline systematic reviews' screening, data extraction, and reporting process. This software allows for systematic reviews to be transparent, auditable, and reproducible by recording all decisions and user input at each step. All inclusion criteria are imported into the software as a questionnaire built in DistillerSR. The software ensures each criterion is met and checked to include or exclude the reference. All 3,663 references were screened at the title and abstract stage according to the following inclusion criteria:

- Samples must be confirmed as *Shigella*
- Antimicrobial susceptibility testing of the isolates must have been performed, and the denominator must be available (data were recorded as a percentage)
- The sample tested must be from humans
- All populations may be included in the study
- Samples were isolated from 1990 onwards
- Data must be linked to a location and must be a reasonable assumption that the site is linked to the acquisition of the infection

There were 1,827 references included and these references were then screened a second time at the full-text level to confirm they reported the resistance profile of *Shigella* isolates

to clinically relevant antimicrobials. Next, 1,310 studies were excluded at the full-text screening, the main reasoning for exclusion is: 251 studies did not include human samples, 243 studies included a small study size (<10 isolates), 130 studies did not disaggregate the AMR data by country and 190 studies were conducted before 1990. All reasons for exclusion can be found in the PRISMA flow chart (Figure 2.3). All studies must meet the inclusion criteria, and the reasoning for exclusion was recorded. This was all tracked within DistillerSR.

2.2.2 DATA EXTRACTION

Data was extracted directly into the DistillerSR software. Extracted data comprised of the following variables: author, year of publication, study site, and location, start and end date of the study, characteristics of the study population (age, sex), clinical outcome, number of patients screened, number of patients with positive stool culture for *Shigella*, species and serotype, lab internal and external quality controls, number of susceptible, intermediate and resistant *Shigella* isolates against specific antimicrobials, antimicrobial susceptibility testing method used, control strains used, and antimicrobial susceptibility testing guidelines used. In addition, if available, the following data were extracted: previous antibiotic use, clinical outcomes reported, molecular data reported, presence or occurrence of severe disease manifestations and complications, and fatal outcomes.

Guidelines used to determine resistance, study design, control strain used, and number of stool cultures performed were recorded to assess study quality. Where possible, data were disaggregated by the year and study location of the *Shigella* species (*S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*). Studies on duplicate isolates were excluded from the

analysis, and studies that show inconsistencies or conflicting data, that cannot be resolved by additional information from the authors were excluded.

Two authors screened the studies independently and reviewed them against the inclusion and exclusion criteria. A short description of the reason for exclusion was recorded. The two authors extracted the data independently, and discrepancies were resolved by discussion. Any disagreements were resolved through discussion with a senior researcher. Extracted data was exported from DistillerSR into an excel spreadsheet, where it was cleaned and prepared for analysis.

2.2.3 DATA ANALYSIS

Analysis was limited to stool culture (stool sample or rectal swab), all other sample types were excluded. Prevalence of antimicrobial resistance amongst *Shigella* isolates was defined as the percentage of isolates being resistant out of the total number of isolates tested for the specific drug. A meta-analysis was performed for each pathogen-antimicrobial combination by taking the total number of isolates tested and the number of resistant isolates to generate effect size and standard error. The 95% confidence intervals were estimated using the Agresti-Coull method.[81] The effect size and standard error were then used to pool the estimates of AMR. Freeman-Tukey double arcsine transformation was used to stabilize variance and a random-effects meta-analysis was performed to pool the estimates to allow for heterogeneity in the data. The meta-analysis was calculated using R statistical software (Version 1.2.1335) using the statistical software package "metafor". This analysis is presented by region and 5-year time periods (1990-1994; 1995-1999; 2000-2004; 2005-2009; 2010-2014; 2015-2018) based on the midyear of the study. If study dates were not provided, the midyear was imputed as the median difference between the

publication date and midyear for the remaining studies in the dataset. As the data is presented by region and five-year time periods, in some areas data is very limited and results in wide 95% confidence intervals. Geographical regions are defined according to the Global Burden Disease (GBD) regional classification system.[82] Analysis was done by time period and on all four species aggregated together and on all four species separately. The percentage of isolates from each study with antimicrobial-resistant strains of *Shigella* isolated from stool culture were analyzed, and intermediate resistant strains were classified as resistant. Several studies have shown that nalidixic acid can be a good indicator of ciprofloxacin susceptibility since ciprofloxacin breakpoints changed in 2018, leading to an underestimation of AMR without adjusting to the new breakpoints.[83–85]

2.2.4 RISK OF BIAS ASSESSMENT FOR EXTRACTED DATA

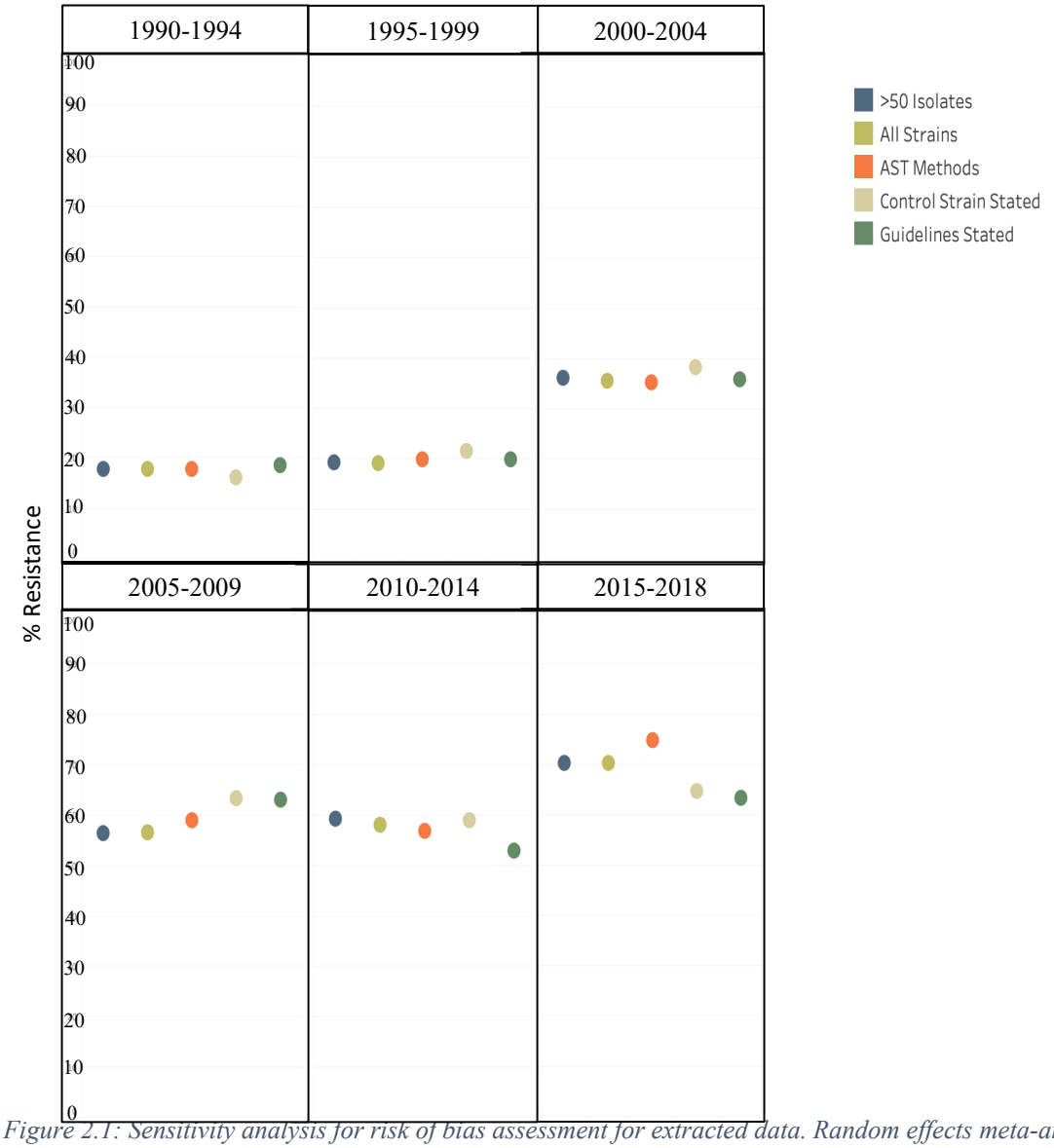

Figure 2.1: Sensitivity analysis for risk of bias assessment for extracted data. Random effects meta-analysis results for studies on Shigella and nalidixic acid by five-year time periods. Each plot compares the pooled prevalence of resistance for: all studies, more than 50 isolates, a control strain stated, guidelines stated, and AST methods.

According to the conducted sensitivity analysis, none of the conditions that were looked into had a meaningful impact on the combined prevalence of resistance (Figure 2.1). The pooled prevalence of MDR and fluoroquinolone resistance (FQR) was calculated for each location and time period using data from all research, and these findings confirmed the choice not to omit any studies based on the risk of bias assessment.

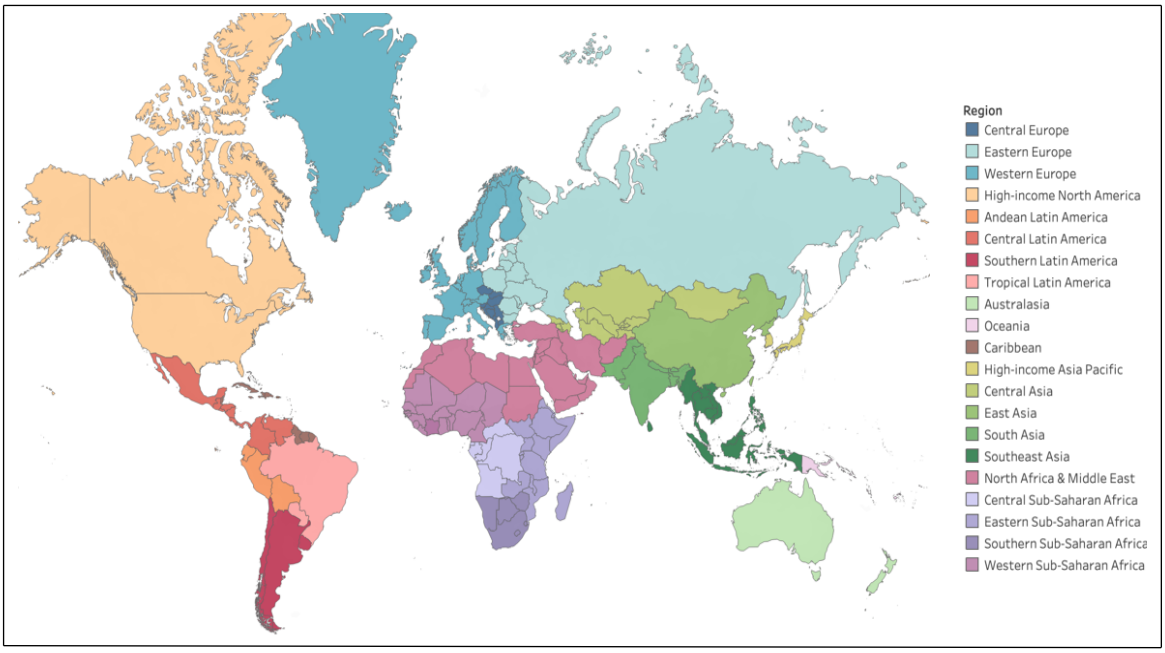

Figure 2.2: Map of GBD study regions.

2.3 RESULTS

2.3.1 SUMMARY OF STUDIES

The literature search identified 3,633 articles, and 521 full texts were extracted. Countries which had the most studies were India (56 studies), Iran (54 studies), and China (52 studies), which described all four *Shigella* species and included both children and adults. Method sections were often incomplete, failing to state the susceptibility testing methods, which testing standards (e.g. CLSI) were followed, and whether internal controls were used. Multidrug resistance (MDR) was reported in 30% of studies, however, the definition of MDR varied greatly.

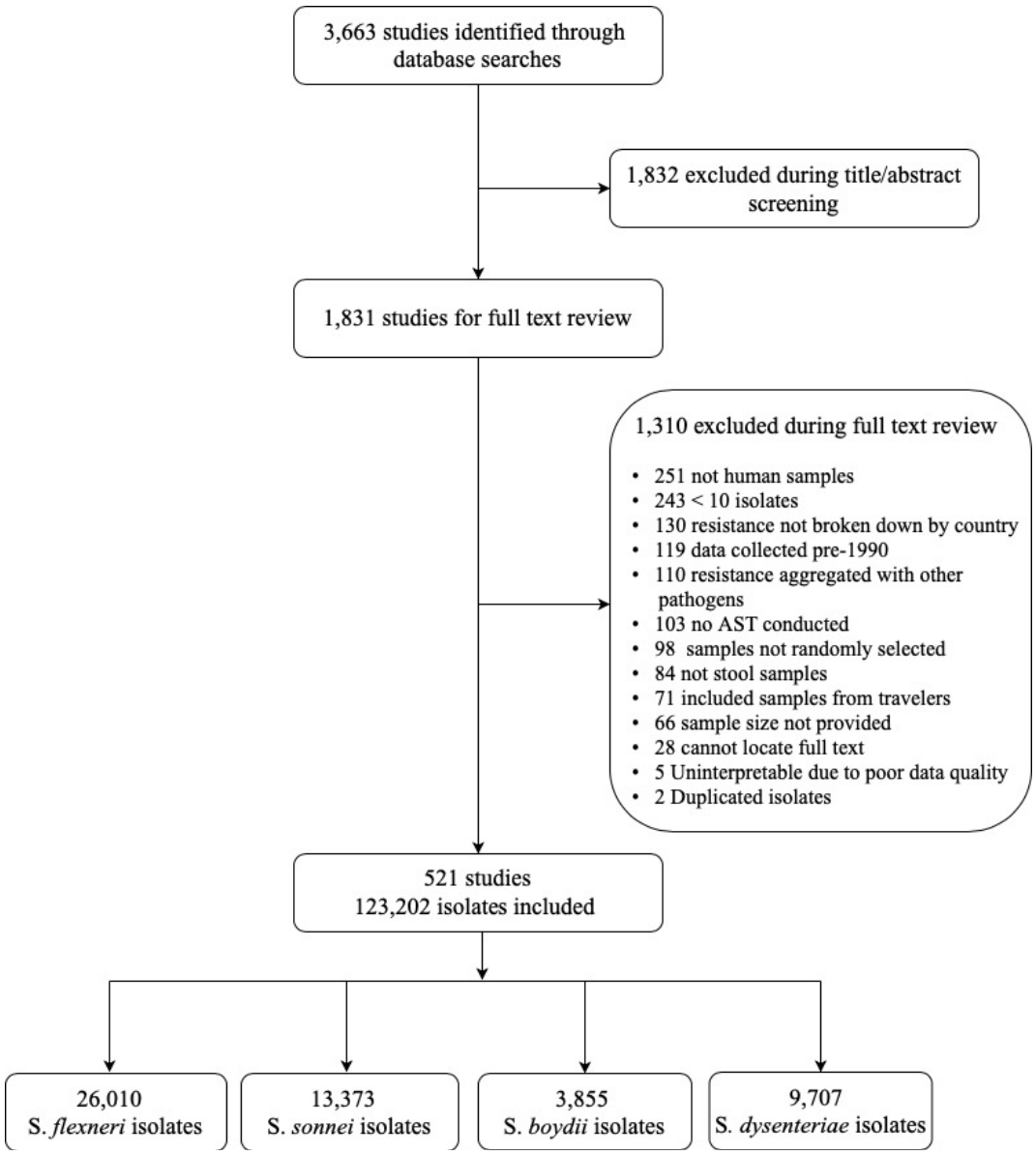

Figure 2.3: PRISMA Flow chart depicting study screening and selection.



Figure 2.4: Data availability by year and country. All included data are plotted by country (y-axis) and year (x-axis), grouped by GBD region. The size of the point depicts the number of studies for each country year.

Study Characteristics	Number of studies
Study design	
Clinical trial	4
Prospective	187
Retrospective	208
Other	21
Number of Stool Samples	
0-99	32
100-499	97
500-999	60
1000-4999	90
5000+	47
Not stated	94
Method of antimicrobial susceptibility testing	
Disk-diffusion	348
E-test	6
Microdilution Assay	12
Automated methods	7
Disk-diffusion & MIC determination	22
Not stated	25
Breakpoints for antimicrobial resistance	
BSAC/EUCAST	3
CLSI/NCCLS	171
Other	28
Not stated	318
Control strains clearly stated	
Yes	184
No	236
Specific age groups	
Adults only	17
Children only	171
No specified age /Adults and children	232
Reported pre-admission antibiotic use	
0%	0
1-25%	13
26-50%	9
51-75%	5
76-100%	2
Not stated	391
Reported case fatality rate	
0%	13
1-5%	7
6-10%	1
11-15%	4
16-20%	1
21-25%	2
Not stated	392

Table 2.1: Study characteristics

Study Distribution		Number of Studies
Time Period		
	1990-1994	45
	1995-1999	85
	2000-2004	114
	2005-2009	115
	2010-2014	95
	2015-2018	17
GBD Super Region		
Latin America & Caribbean		**38**
	Bolivia	1
	Peru	4
	Mexico	4
	Venezuela	2
	Chile	6
	Argentina	6
	Uruguay	2
	Brazil	10
	Cuba	2
	French Guiana	1
Eastern Europe & Central Asia		**3**
	Bulgaria	1
	Lithuania	1
	Uzbekistan	1
High-income		**3**
	United States of America	1
	Japan	2
South Asia		**108**
	Bangladesh	23
	Nepal	13
	Pakistan	17
	Bhutan	1
	India	54
Southeast Asia, East Asia and Oceania		**80**
	Cambodia	2
	Indonesia	7
	Laos	2
	Malaysia	4
	Myanmar	4
	Thailand	5
	Viet Nam	8
	Taiwan	5
	China	36
	Korea	4
	Papua New Guinea	3
North Africa & Middle East		**86**
	Egypt	7
	Iran	46
	Jordan	1
	Oman	2
	Palestine	2
	Saudi Arabia	3
	Tunisia	1
	Turkey	15
	Sudan	2
	Israel	6
	Libya	1
Sub-Saharan Africa		**59**
	Central African Republic	3
	Ethiopia	22
	Kenya	16
	Madagascar	2
	Rwanda	1
	Tanzania	3
	Uganda	2
	Zambia	3
	Burundi	5
	South Sudan	2

Table 2.2: Study distribution over time and GBD super region.

Most studies were observational, either retrospective or prospective (208 studies (49.5%) and 187 studies (44.5%) respectively), with only 4 clinical trials included. The sample size varied greatly, with 189 studies (45%) having over 100 samples. The most common antimicrobial susceptibility testing method was disk diffusion, with 345 studies (82%) reporting this as their testing method. The guidelines used to determine breakpoints for antimicrobial resistance were CLSI/NCCLS in 282 studies (67%), however, in 122 (29%) studies guidelines were not stated. Most studies failed to mention the control strain used, with only 181 studies (43%) reporting this information.

Only children were studied in 168 studies (40%) and 17 studies (4%) looked solely at adult patients; the remaining 236 studies (56%) either did not report the age of the patients (40%) or included both children and adults (60%). Reporting of patients who took pre-admission antibiotics was rarely done, with this information being stated in only 30 papers (7%). Case fatality was also rarely recorded and was stated in only 30 papers (7%). There was missing information on patient type: 67 studies (16%) were done on inpatients, 54 studies (13%) on outpatients, 80 (19%) included both inpatients and outpatients, and 219 (52%) were not specified.

There were 280 studies which tested *Shigella* isolates for nalidixic acid susceptibility. Of the 280 studies, 133 studies tested *S. flexneri* isolates, 114 studies tested *S. sonnei* isolates, 99 studies tested *S. dysenteriae* isolates, and 62 studies tested *S. boydii* isolates. There were 166 studies which tested *Shigella* isolates for ceftriaxone susceptibility and 41 studies which tested for azithromycin susceptibility. Fluoroquinolones were the antimicrobial of focus due to the WHO global priority pathogen/antibiotic list featuring *Shigella* and fluoroquinolones.[30] The WHO recommends nalidixic acid as a proxy marker for

fluoroquinolone resistance, based on a high correlation between nalidixic acid resistance and fluoroquinolone resistance in *Shigella*.[33] The breakpoint guidelines for nalidixic acid have been well established over the study period whereas, ciprofloxacin's breakpoints have changed several times and vary across different guidelines, making ciprofloxacin a less reliable proxy for fluoroquinolone resistance. [30,74,75] During data collection MIC § were not provided in a vast majority of studies, making it impossible to adjust the ciprofloxacin data according to the new breakpoints. The WHO recommends azithromycin or ceftriaxone as a treatment for fluoroquinolone resistant infections.[86]

Multidrug resistance (MDR) was reported in 30% of studies. Seventy-six studies reported MDR, defined as "resistant to three or more classes of antibiotics." China, Ghana, Cuba, Bangladesh, Venezuela, Cambodia, Kenya, Vietnam, Egypt, Nigeria, Nepal, and Papua New Guinea reported over 80% MDR, defined as "resistant to three or more classes of antibiotics." Currently, there is no standard definition for MDR in *Shigella*, resulting in various definitions and patterns of MDR reported in the studies. MDR was most commonly defined as resistance to "three or more antibiotics", however, many studies failed to list the names of the three or more antibiotics. If the definition used for MDR was missing or incomplete, the author was contacted.

2.3.2 PREVALENCE OF NALIDIXIC ACID RESISTANCE META-ANALYSIS

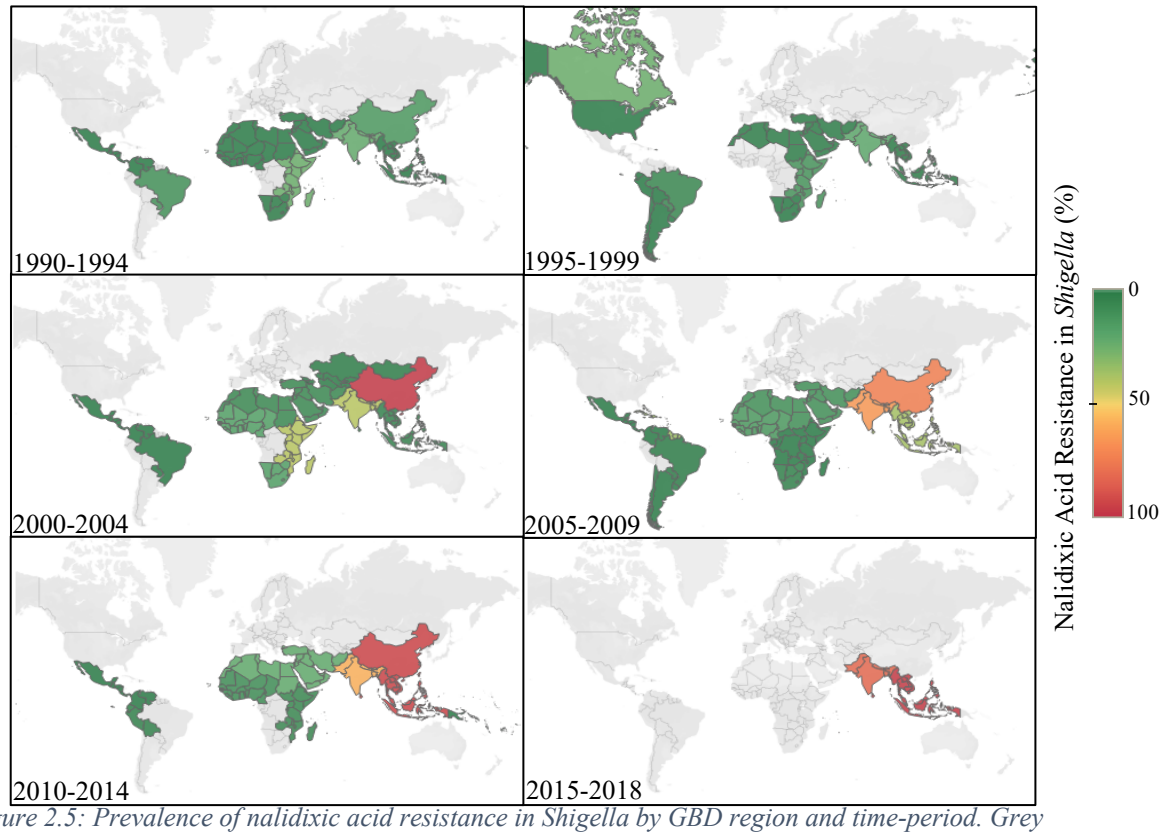

Figure 2.5: Prevalence of nalidixic acid resistance in Shigella by GBD region and time-period. Grey shading indicates no data.

The meta-analysis shows a high prevalence of nalidixic acid resistance starting in 2000 with 98% in South Asia, and 75% in 2005 in Southeast Asia. Nalidixic acid resistance has remained high in these regions throughout the study period until 2018. The data collected from studies conducted in China mainly had large numbers of isolates and were from all over the country, most often either *S. flexneri* or *S. sonnei* was reported. Data from Korea comprised of isolates from only two regions in the country. Two studies included are from Taiwan, they are from different regions of the country, with one reporting 98% resistance in 2001 and the other 0% resistance in 2005. Data from Vietnam is mainly from Ho Chi Minh city. Data from India, Bangladesh, Pakistan, and Indonesia have more significant isolate numbers in the studies overall and are from surveillance networks and larger

hospitals. Data from Nepal had smaller isolate numbers from each study, but the isolates were collected from all over the country.

The data shows that nalidixic acid susceptibility in Southern Sub-Saharan Africa, North Africa and the Middle East has persisted over time. Data collected from South Africa are all from the Northeast part of the country. Data from Iran and Israel are based on large isolate numbers in the studies and are from surveillance networks and larger hospitals in the country. Data from Yemen is from a central laboratory that serves the entire country. The data from Saudi Arabia is from just the Al-Hasa region and is based on a small number of isolates. Data from Oman is little but was from the only two hospitals in the country with culture facilities.

Sparse data were available from most of Europe, HIC, Latin America and Caribbean, and Oceania. In Brazil, the data collected was on large numbers of isolates and were from all over the country, most often specific *Shigella* species were not identified. Data from Cuba was collected from all over the country, however, only small samples of isolates were studied. Data were only collected from three Eastern European countries (Lithuania, Bulgaria, and Uzbekistan). Data from the United States is from one study conducted in Portland, Oregon. Most of the data from high-income countries came from surveillance systems and was reported aggregated in a way that could not be extracted for this review. *Shigella* isolates are often aggregated with other gram-negative pathogens, or the data for multiple neighboring countries are aggregated together.

Sparse and heterogeneous data was available from Eastern, Western, and Central Sub-Saharan Africa. High rates of nalidixic acid resistance were seen in Kenya from 2000-2004,

data from Kenya have more significant isolate numbers in the studies overall and are from surveillance networks and larger hospitals. Data from Ethiopia was mainly from the Northern and Western regions of the country. Data from Nigeria comes from smaller isolate numbers and are concentrated in a few regions in the country. Data from Rwanda is comprised of many isolates but from just one hospital.

Of the *Shigella* data collected, 74% of studies reported antimicrobial susceptibility data disaggregated by species. The data shows that *S. flexneri* has remained the dominant species over the study period in Europe and the Americas, with *S. sonnei* incidence increasing in 2005. No data was found on *S. boydii* and *S. dysenteriae* in Europe and the Americas. In the Middle East and Africa, *S. sonnei* and *S. flexneri* were most prominent from 1990-2014. In Asia, *S. flexneri* and *S. dysenteriae* were the most common species from 1990-1999 until the number of *S. sonnei* began to increase. From 2000-2009 *S. flexneri* remained the most dominant species in Asia, and slowly numbers of *S. sonnei* increased until both species were detected at a similar rate in 2010-2014. In Asia, the Middle East, and Africa, very few isolates of *S. dysenteriae* and *S. boydii* were reported from 2010-2014 (Figure 2.6). In Table 2.3, the pooled prevalence and interquartile range of each species are reported. Data was assigned to subgroups according to *Shigella* species, GBD study region, and five-year time periods in which the infection was acquired. A meaningful comparison between regions and time periods is difficult to interpret with high heterogeneity in the number of studies and isolates included in each region and time period.

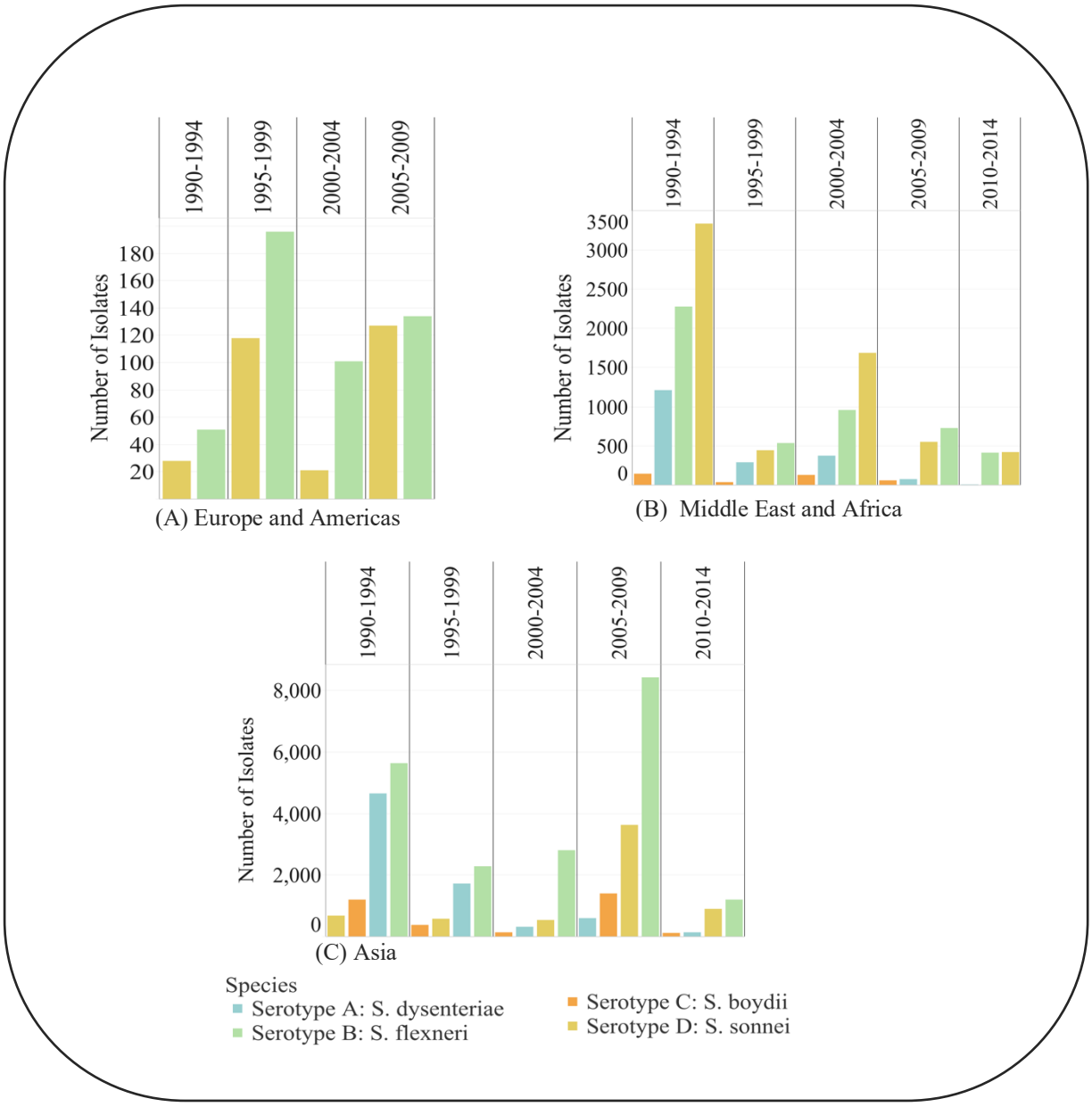

Figure 2.6: Incidence of Shigella serotypes in countries grouped into three large regions; (A)Europe and Americas, (B) the Middle East and Africa, and (C) Asia. The number of isolates is shown for each region by species and time period. The color shows details of the species; blue is S. dysenteriae, green is S. flexneri, orange is S. boydii, and yellow is S. sonnei.

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
Nalidixic acid- *Shigella*						
Andean Latin America	-	0% [0-4]*	-	-	3% [1-6]*	-
Central Latin America	0% [0-4]	-	0% [0-3]*	0% [0-3]	0% [0-3]*	-
Southern Latin America	-	0% [0-1]	-	0% [0-2]	-	-
Tropical Latin America	10% [2-22]*	6% [1-15]	0% [0-1]*	1% [0-4]	-	-
Caribbean	-	-	-	35% [0-100]	-	-
High-income N. America	-	0% [0-1]	-	-	-	-
Oceania	-	-	-	-	0% [0-4]*	-
High-income Asia Pacific	-	-	26% [9-49]*	-	-	-
Central Asia	-	-	1% [0-9]	-	-	-
East Asia	13% [0-38]	-	98% [95-100]	74% [50-92]	94% [84-99]	-
South Asia	22% [12-36]	20% [11-32]	41% [31-52]	65% [57-73]	58% [40-76]	82% [53-99]
Southeast Asia	0% [0-1]	1% [0-5]	4% [0-12]	37% [12-66]	94% [88-98]	97% [92-100]
N. Africa Middle East	0% [0-0]	1% [0-3]	6% [4-9]	9% [4-15]	21% [11-32]	-
Eastern SSA	24% [6-48]	11% [2-25]	41% [3-88]	0% [0-1]	6% [0-16]	-
C. SSA	-	-	-	0% [0-1]	-	-
South SSA	1% [0-2]*	0% [0-1]*	16% [7-28]*	3% [0-15]	-	-
W. SSA	0% [0-10]*	-	16% [1-42]	13% [0-48]	8% [0-40]	-
Studies (Isolates)	97 (20,077)	105 (9,470)	155 (16,319)	179 (34,672)	80 (5,858)	8 (433)
Nalidixic acid- *S.sonnei*						
Central Latin America	0% [0-6]*	-	-	-	-	-
Southern Latin America	-	0% [0-2]	-	0% [0-2]*	-	-
Tropical Latin America	-	2% [0-10]*	-	0% [0-11]*	-	-
Caribbean	-	-	-	79% [60-93]*	-	-
High-income N. America	-	0% [0-2]*	-	-	-	-
High-income Asia Pacific	-	-	26% [9-49]*	-	-	-
Central Asia	-	-	5% [0-19]*	-	-	-
East Asia	13% [0-50]	-	95% [79-100]	79% [51-97]	99% [96-100]	-
South Asia	6% [2-12]	13% [2-29]	45% [16-76]	85% [81-88]	22% [0-64]	98% [92-100]*
Southeast Asia	-	0% [0-5]	3% [0-12]	34% [1-82]	-	-
N. Africa Middle East	0% [0-0]	0% [0-1]	3% [0-8]	7% [1-16]	19% [0-65]	-
Central SSA	-	-	-	0% [0-15]*	-	-
Eastern SSA	0% [0-0]	-	-	-	-	-
Western SSA	-	-	-	1% [0-6]*	-	-
Studies (Isolates)	17 (4,056)	17 (1,347)	37 (2,301)	43 (4,518)	16 (1,328)	1 (55)

Nalidixic acid- *S. flexneri*	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
Central Latin America	0% [0-14]*	-	0% [0-3]*	-	-	-
Southern Latin America	-	0% [0-1]	-	1% [0-8]	-	-
Tropical Latin America	10% [2-22]*	10% [3-18]*	-	-	-	-
High-income N. America	-	0% [0-1]*	-	-	-	-
Central Asia	-	-	0% [0-5]*	-	-	-
East Asia	15% [11-20]*	-	99% [97-100]	66% [31-94]	88% [75-96]	-
South Asia	5% [4-6]	5% [3-7]	44% [30-58]	71% [52-87]	63% [24-95]	88% [72-98]
Southeast Asia	-	5% [0-31]	6% [0-40]	36% [0-90]	-	-
N. Africa Middle East	0% [0-1]	1% [0-4]	6% [2-11]	21% [10-34]	35% [15-57]	-
Eastern SSA	7% [0-39]	18% [0-68]	30% [0-97]	0% [0-1]	0% [0-15]*	-
Central SSA	-	-	-	0% [0-2]*	-	-
Western SSA	0% [0-10]*	-	16% [5-31]*	25% [0-100]	-	-
Studies (Isolates)	10 (278)	18 (384)	28 (1,181)	30 (1,239)	11 (361)	3 (111)
Nalidixic acid- *S. dysenteriae*						
South Asia	66% [40-88]	57% [30-83]	66% [27-96]	40% [22-59]	39% [3-85]	-
Southeast Asia	-	-	0% [0-12]*	-	-	-
N. Africa Middle East	-	0% [0-5]	6% [0-18]	41% [19-66]*	-	-
Central SSA	-	-	-	0% [0-4]*	-	-
Eastern SSA	58% [28-84]	25% [0-78]	50% [0-100]	-	-	-
South SSA	1% [0-2]*	0% [0-1]*	-	-	-	-
Western SSA	-	-	11% [0-46]	42% [15-71]*	-	-
Studies (Isolates)	14 (437)	12 (388)	17 (401)	10 (278)	6 (136)	-
Nalidixic acid- *S. boydii*						
South Asia	2% [1-3]	3% [1-7]	13% [1-34]	54% [49-58]	7% [0-40]	-
N. Africa Middle East	0% [0-2]	0% [0-4]*	0% [0-4]	33% [11-59]*	-	-
Central SSA	-	-	-	0% [0-9]*	-	-
Eastern SSA	-	-	98% [92-100]*	-	-	-
South SSA	-	-	-	0% [0-6]*	-	-
Western SSA	-	-	9% [0-35]*	-	-	-
Studies (Isolates)	6 (121)	6 (288)	8 (157)	6 (87)	3 (80)	-

*Table 2.3: The pooled prevalence of isolates resistant to Nalidixic Acid. Meta-analysis results and 95% confidence intervals are presented by: five-year time periods across the top and GBD regions listed along the left column. The Shigella species the listed in the green bar. The interquartile range is listed in [ ] next to the proportion resistance. The total number of studies and isolates is listed along the bottom of each pathogen-antimicrobial category. *Indicates subgroups with only one study, for which prevalence and calculated 95% confidence intervals are not displayed.*

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
Azithromycin - *Shigella*						
Andean Latin America	-	-	-	2% [0-8]	5% [0-18]	-
Central Latin America	-	-	-	0% [0-1]	0% [0-3]*	-
Southern Latin America	-	-	-	71% [2-100]	-	-
N. Africa Middle East	-	-	-	-	71% [51-88]*	15% [6-26]
South Asia	-	0% [0-5]*	8% [0-22]	22% [2-54]	3% [0-13]	-
Southeast Asia	-	96% [89-99]*	25% [0-90]	19% [0-78]	97% [92-99]	22% [14-32]*
Eastern SSA	-	86% [74-96]	-	2% [0-7]*	-	-
Southern SSA	0% [0-0]*	-	-	-	-	-
Studies (Isolates)	1 (354)	7 (197)	13 (951)	31 (4,984)	24 (1,551)	4 (135)
Ceftriaxone - *Shigella*	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
Andean Latin America	-	0% [0-4]*	-	-	-	-
Central Latin America	0% [0-4]	-	0% [0-3]*	0% [0-1]	0% [0-3]*	-
Tropical Latin America	-	33% [4-71]	0% [0-1]	2% [0-9]	-	-
Eastern Europe	-	-	-	-	-	-
Caribbean	-	-	-	0% [0-7]*	-	-
High-income Asia Pacific	-	-	0% [0-9]*	-	-	-
High-income N. America	-	-	-	-	-	-
N. Africa Middle East	1% [0-3]	0% [0-0]	2% [0-4]	2% [0-7]	2% [0-5]	28% [0-85]
Oceania	-	-	-	-	-	-
Central Asia	-	-	-	-	-	-
East Asia	0% [0-0]	-	3% [0-9]	31% [23-41]	38% [21-57]	-
South Asia	-	2% [0-9]	1% [0-4]	6% [2-11]	7% [3-13]	16% [2-36]*
Southeast Asia	-	0% [0-0]	0% [0-0]	5% [1-12]	57% [19-91]	57% [46-67]*
Southern Latin America	-	-	-	0% [0-1]	-	-
Eastern SSA	0% [0-1]	0% [0-2]*	0% [0-2]	0% [0-3]*	4% [0-19]	-
Central SSA	-	-	-	-	-	-
Southern SSA	0% [0-0]*	0% [0-1]*	4% [0-12]*	0% [0-6]*	-	-
Western SSA	0% [0-2]*	-	0% [0-5]	37% [25-51]*	-	-
Studies (Isolates)	30 (1,808)	64 (4,335)	102 (10,110)	88 (8,832)	52 (2,587)	6 (164)

*Table 2.4: The pooled prevalence of isolates resistant to Azithromycin and Ceftriaxone. Meta-analysis results and 95% confidence intervals are presented by: five-year time periods across the top and GBD regions listed along the left column. The Shigella species the listed in the green bar. The interquartile range is listed in [ ] next to the proportion resistance. The total number of studies and isolates is listed along the bottom of each pathogen-antimicrobial category. *Indicates subgroups with only one study, for which prevalence and calculated 95% confidence intervals are not displayed. SSA = sub-Saharan Africa.*

Data was collected on 9,699 *S. dysenteriae* isolates tested for nalidixic acid resistance. Resistance in South Asia has been high throughout the study period, reporting 92% in 1990 to 46% in 2014. Resistance in Eastern sub-Saharan Africa has also been high throughout the study period reporting 71% resistance in 1990 and 99% resistance 2000. Resistance has risen with time in North Africa and the Middle East, going from 0% in 1995 to 41% in 2014. Western sub-Saharan Africa has also increased over the study period moving from

5% in 2000 to 42% in 2005. Central and Southern sub-Saharan Africa had 0% resistance from 1990-2014.

There were 30,458 *S. flexneri* isolates collected that were tested for nalidixic acid resistance. Overall, resistance in Asia has increased from 5-15% in 1990 to 83-% in 2014. Southern and Central Latin America reported less than 5% resistance throughout the study period. However, Tropical Latin America reported 10% resistance during this same time frame. Resistance in Eastern sub-Saharan Africa decreased over time, whereas resistance in Western sub-Saharan Africa increased. Resistance in North Africa and the Middle East has also increased, from 0% in 1990 to 26% in 2014.

Data collected from *S. boydii* (3,860 isolates) was very scarce, and most time periods contain data from just one study. Resistance in North Africa and the Middle East, and South Asia experienced the same low resistance from 1990 to 2000 and then sharply increased in 2005. Resistance in Central, Southern, and Western sub-Saharan Africa was low, reporting 0-9% throughout the study period. In contrast, Eastern sub-Saharan Africa has 98% in 2000.

There were 13,834 *S. sonnei* isolates collected that were tested for Nalidixic acid resistance. Nalidixic acid resistance was reported to be low in Central and Western Sub-Saharan Africa throughout the study period. Resistance in Asia increased from 4-8% in 1990 up to 98% resistance in 2018. Latin America had low resistance with only 0-2% from 1990-2005, Southern Latin America experienced a sharp increase to 50% in 2005. North Africa and the Middle East experienced a gradual increase in resistance as time went on starting at 0% from 1990-2000 up to 26% in 2014.

Overall, *S.sonnei* has the most resistant isolates recorded and *S.boydii* had the most susceptible isolates throughout the study time period. Resistance tends to increase over time for all three species with the exception of the decline of resistance in *S. dysenteriae*, which was most resistant in 1990-1994.

2.3.3 PREVALENCE OF AZITHROMYCIN RESISTANCE

Forty-one studies tested for resistance to azithromycin on a total of 8,285 *Shigella* isolates. The studies came from 24 different countries in Andean, Central and Southern Latin America, Eastern and Southern sub-Saharan Africa, North Africa Middle East, and South and Southeast Asia. Resistance is highest in Southeast Asia with 96% resistance in 1995 and 97% in 2014. Eastern sub-Saharan Africa also reported high resistance with 86% in 1995. Andean and Central Latin America reported less than 5% resistance throughout the study period, in contrast, Southern Latin America reported 64% resistance in the mid-2000s. Resistance in South Asia has slowly increased over time, whereas the rest of Asia, Africa, and the Middle East had very variable resistance throughout the study period. The heterogeneity could be due to the smaller amount of data available. Thirty-seven studies reported using disc diffusion as the AST method (0 studies used E test), and most used CLSI/NNCLS guidelines. Please note that the number of studies will not add up to the 41 studies, as some studies reported resistance rates for each *Shigella* species, therefore, reporting multiple resistance rates for azithromycin in a single study.

2.3.4 PREVALENCE OF CEFTRIAXONE RESISTANCE

Ceftriaxone resistance was tested in 166 studies on 28,519 *Shigella* isolates. The studies came from 48 countries in Latin America, the Caribbean, Asia, North Africa Middle East,

and Eastern, Southern, and Western sub-Saharan Africa. One hundred twenty-five studies (82.7%) reported using disc diffusion as the AST method (5 studies used E-test), and most followed CLSI/NCCLS guidelines. Latin America reported low resistance throughout the study period. Resistance in Asia increased with time from 0% resistance in the 1990s to a high of 57% in 2018. North Africa and the Middle East followed a similar pattern with 0% resistance in 1990 and increased to 31% in 2018. Overall, sub-Saharan Africa has slowly increased resistance over time, however, many time periods contain data from only one study making it difficult to interpret these trends. Please note that the number of studies will not add up to the 166 studies, as some studies reported resistance rates for each *Shigella* species, therefore, reporting multiple resistance rates for ceftriaxone in a single study.

2.4 DISCUSSION

This systematic review provides an overview of the global situation regarding AMR in *Shigella,* with an in-depth look at nalidixic acid resistance. Data were extracted from 521 studies, comprising 123,202 isolates from 78 countries worldwide. The systematic review builds on previous knowledge by using a comprehensive search strategy, covering all countries, and identifying trends in resistance over 28 years. Locations with a scarcity of susceptibility data have been identified, and efforts in data seeking can be focused on those locations. Antimicrobial susceptibility data for *Shigella* is presented according to country, geographical region, and time period.

Initially recommended treatments for *Shigella* infections were sulphonamides, tetracycline, and chloramphenicol. Resistance was first recorded in the 1940s to sulphonamides in Japan, followed by resistance to tetracycline and chloramphenicol in the 1950s.[87] Once resistance was recorded to these antimicrobials, recommendations changed to ampicillin and co-

trimoxazole. Resistance was detected to ampicillin and co-trimoxazole in the early 1980s in Asia and Africa. Subsequently, fluoroquinolones were introduced to clinical practice in 1987, coinciding with the beginning of our study time period. Nalidixic acid was first recommended for treatment due to its lower cost and effectiveness towards *Shigella*. Nalidixic acid has a similar structure to other fluoroquinolones and is very effective against in vitro *Shigella* due to its ability to reach elevated concentrations in feces.[88] Ciprofloxacin resistance was recorded in India in 2001 to *S. dysentreriae* and 2003 to *S. flexneri*, which is also evident in the systematic review dataset. However, in my dataset, resistance appears to begin in the early 1990s, this is due to nalidixic acid being recommended for *Shigella* treatment before ciprofloxacin.[89] WHO now recommends ceftriaxone, pivmecillinam, and azithromycin to treat fluoroquinolone-resistant shigellosis.[86] It is worrisome that the data shows a high prevalence of resistance in India, Vietnam, and Bangladesh to nalidixic acid, azithromycin, and ceftriaxone. China, Uruguay, and Nepal also reported a high prevalence of resistance to nalidixic acid and ceftriaxone. Iran reported a high prevalence of resistance to both azithromycin and ceftriaxone. Currently, China has reported the presence of multidrug resistance (MDR) *Shigella,* which limits the antibiotics available for treatment, and has turned to azithromycin as a drug of choice, as it is safe for both adults and children. Therefore, as expected, resistance to azithromycin is now being reported in China. The rise in resistance to low-cost antibiotics is an enormous problem for low-income countries, where mortality and morbidity are the highest.[90]

The rapid development of resistance seen in India, China, Uruguay, Nepal, Vietnam, and Bangladesh is exacerbated by the lack of regulation in antibiotics sold over the counter in these countries. While most of these countries have laws prohibiting antibiotics sold without a prescription, the absence of enforcement and regulation leads to high rates of

antibiotic abuse and misuse. The global prevalence of selling antibiotics without a prescription is 62.2%.[91] In Vietnam, this number is 88% in urban areas and 91% in rural areas.[92] In China, 70-80% of pharmacies are dispensing antibiotics without a prescription, despite passing a law in 2004 specifying only pharmacies are permitted to sell antibiotics with a prescription by a licensed pharmacist. Abiding by this law is proving to be difficult, by 2017 there were more pharmacies than licensed pharmacists available, and those who are practicing pharmacists often lack specific training on dispensing antibiotics.[91]

The purchase of antibiotics over the counter is also an obstacle for many high-income counties. Online sales of antibiotics have been steadily increasing over time and have amplified access to antibiotics. Evidence shows that antibiotics are available without a prescription online for customers in Canada, the United Kingdom, and the United States of America. This poses an additional threat to antibiotic stewardship. It is reported that 45% (9/20) of online pharmacies in the United Kingdom sell antibiotics to customers without a prescription.[91]

MDR is not currently defined for *Shigella* and is therefore reported with various definitions. The lack of a standard definition makes it difficult to estimate MDR and compare MDR globally. Describing the MDR definition clearly and the reasoning for the definition would be incredibly helpful to readers and researchers.[92]

There are several limitations to this study. Data collected from the systematic review may be subjected to several biases as most of the data collected was from patients presenting at hospitals. Patients seeking healthcare at a hospital will commonly have the most severe disease leading to an underestimation of the prevalence of the disease and, therefore, an

overestimation of the proportion of resistance in the community. These patients may have already attempted to self-treat with antibiotics and, when symptoms persisted, proceeded to seek treatment at a hospital. As shigellosis can be self-limiting, many living in low and middle-income countries have access to antibiotics without a prescription in the community, and their data is never captured at a hospital.

When patients seek healthcare at a hospital in a low or middle-income setting, clinicians may never collect a diagnostic sample from patients and prescribe an antibiotic as empiric treatment. Samples may not be collected for various reasons, including the hospital may not have a microbiology culture facility. If samples are collected, it is also possible that their facility may not be of a high standard. This can lead to no antimicrobial sensitivity testing performed or low accuracy in the test results.

Data from systematic reviews may also be biased by publication bias. Publication bias may occur if the data results reflect poorly on the hospital or country and their appropriate use of antibiotics or lack of infection control. The researcher may choose not to publish this data, or the research is not published in a journal for political reasons. On the other hand, researchers may be more likely to publish "interesting" or novel findings, such as high rates of antimicrobial resistance. Although our search strategy was written to be exhaustive and several databases were searched, it is possible papers written in foreign languages were missed due to papers not being indexed. It is important to note that countries that have no data in this study does not mean there is no *Shigella* or antimicrobial resistance in these countries. Many countries do not have an antimicrobial surveillance system or the necessary laboratory facilities, therefore, it is difficult to assess the scale of this crisis in many countries. Collecting antimicrobial resistance data is vital to alleviating antimicrobial

resistance. The aim is to fill many of these gaps using data through additional data-seeking efforts.

In the systematic review data analysis, studies reporting less than ten isolates, of which antimicrobial sensitivity testing was performed, were removed from the analysis to reduce some bias. Study populations may not always be representative due to variations in available antibiotic testing discs. In the same year, significant differences in resistance were found between neighboring countries and within countries. One example is two studies from Burundi from 1994, one reporting 97% nalidixic acid resistance in Bujumbura and another reporting 8% nalidixic acid resistance in Gasorwe, with comparable sample sizes. Other examples include Japan, India, and China. These variations in resistance are due to many factors, including differences in medical infrastructure and facilities available within the hospital and antimicrobial access and availability.

This systematic review highlights the importance of having quality control indicators published in papers, as a lack of guidelines when publishing microbiology data restricts the ability to assess the quality of the methodology used and rank the overall quality of studies. Adherence to international reporting guidelines, such as Microbiology Investigation Criteria for Reporting Objectively (MICRO) guidelines, would be beneficial in standardizing AMR surveillance and research.[93] Many papers had one or more of the following variables missing: breakpoint guidelines followed, control strain used, diagnostic sample taken, antimicrobial sensitivity tests used, and external quality assessment guidelines. In instances where conflicting data was found from the same country and time period, it was challenging to decipher which study was more credible or why the conflict in resistance was reported. Moving forward, the systematic review data will be combined

with data from other sources, such as large surveillance systems and AMR reports, in hopes of having more data to aid in these assessments and achieving an efficacious estimation of resistance.

Efforts to decrease the transmission of *Shigella* are essential to curb this global crisis. Health education is a crucial tool to bring awareness to behavior change that can have a significant impact. These include hand washing and improved good hygiene practices, access to a clean water supply and learning how to clean water effectively, proper disposal of human waste, understanding food safety practices, and breastfeeding children. Antimicrobial resistance in *Shigella* differs depending on geographic location and time, therefore, continuous monitoring is necessary for specific and effective treatments to be recommended. Lack of access to antimicrobials can result in an increased number of deaths, however, a lack of regulations and an inefficient surveillance system can render the antimicrobials available ineffective.

A comprehensive review of the published literature reveals widespread resistance to fluoroquinolones, azithromycin, and ceftriaxone in Eastern, Southern, and Southeastern Asia, North Africa and the Middle East, and Western sub-Saharan Africa. Further, it has revealed the need for more data on antimicrobial resistance in *Shigella*. Specifically isolate-level microbiology data, clinical outcome data, and data on antimicrobial use and consumption. To produce a complete picture of AMR *Shigella*, this work will be supplemented with additional data from surveillance systems and collaborators to facilitate geospatial disease mapping to estimate the global burden of AMR *Shigella*.

CHAPTER 3

Global Geospatial Modelling of Antimicrobial drug resistance in *Shigella,* 1990-2020

3.1 INTRODUCTION

Shigellosis is the most serious cause of bloody diarrhea in the world with an estimated 264 million episodes and 220,000 deaths annually and is endemic in the majority of LMICs.[36] Children under five are primarily responsible for the bulk of shigellosis-related mortality.[33] Resistant *Shigella* isolates to various antimicrobials are being reported more frequently than ever before. *Shigella* isolates were previously responsive to ampicillin, chloramphenicol, co-trimoxazole, and nalidixic acid, but today there are high rates of resistance to fluoroquinolones, cephalosporins, and azithromycin.[37] To pinpoint disease hotspots, fill knowledge gaps, and influence antibiotic usage policy, it is crucial to establish the regional and temporal changes in the frequency of drug-resistant *Shigella*.

Shigella data were obtained from multiple sources, including a systematic review (described in Chapter 2), published studies, collaborators on the GRAM project[94], members of the GBD Collaborator Network, surveillance systems, academic institutions, pharmaceutical companies, and individual hospitals. The prevalence of resistance was modeled for key pathogen-antibiotic combinations across 204 countries

and 182 territories from 1990 to 2020. Although data was collected for additional pathogen-antibacterial combinations, due to the lack of data available, only the fluoroquinolone resistance was data rich enough to be modeled at this stage. This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations[95].

3.2 DATA SOURCES DESCRIPTION

Line level and aggregate microbiological data from several sources were combined to provide a comprehensive data set for each pathogen and antimicrobial combination. These data were linked to the country and year in which the infection was acquired. In total, 159,885 test results were gathered for various important pathogen-antibiotic combinations in this envelope. A detailed description of available data for *Shigella* and fluoroquinolone resistance can be found in the appendix, table B.2. For antibiotics with <5% country-year coverage for the 204 countries and 30 years (1990-2020) data input matric and with two or more regions with no data, we excluded these from the modeling for this pathogen due to concerns of data coverage and representativeness.

Microbiological data was supplemented with systematic reviews following the PRISMA guidelines[80]. The published resistance data were collected from countries and territories where surveillance systems do not routinely collect data, to ensure extensive coverage of the pathogen-antibiotic combinations of interest. Data on the prevalence of AMR were extracted from published literature and compiled into comprehensive datasets. The systematic review completed PRISMA checklists, PROSPERO registration, and detailed descriptions can be found in the appendix. Extraction forms were created, and screening and data extraction were completed using DistillerSR.

Region	Data Source	Data Points	Isolates
Andean Latin America	Dataset	1	152
	Surveillance Report	30	7,332
	Systematic Review	3	660
Australasia	Surveillance Report	17	1,173
Caribbean	Surveillance Report	11	1,116
	Systematic Review	1	37
Central Asia	Systematic Review	1	52
Central Latin America	Surveillance Report	77	15,073
	Systematic Review	3	218
Central Sub-Saharan Africa	Dataset	1	5
	Systematic Review	2	170
East Asia	Systematic Review	44	5,255
Eastern Europe	Dataset	3	19
	Systematic Review	2	191
Eastern Sub-Saharan Africa	Dataset	16	932
	Systematic Review	41	4,569
High-income Asia Pacific	Dataset	1	156
	Systematic Review	8	423
High-income North America	Dataset	25	7,484
North Africa & Middle East	Dataset	5	182
	Systematic Review	85	16,033
Oceania	Systematic Review	2	60
South Asia	Dataset	1	68
	Surveillance Report	4	473
	Systematic Review	146	37,352
Southeast Asia	Dataset	2	37
	Surveillance Report	3	124
	Systematic Review	51	4,430
Southern Latin America	Dataset	1	2,810
	Surveillance Report	30	23,722
	Systematic Review	5	435
Southern Sub-Saharan Africa	Dataset	1	759
	Systematic Review	8	759
Tropical Latin America	Surveillance Report	22	4,501
	Systematic Review	7	626
Western Europe	Dataset	10	1,301
Western Sub-Saharan Africa	Dataset	1	6
	Systematic Review	19	878

Table 3.1: Table of data points and isolates collected by data source and geographical region. Number of data points refers to the number of estimates for each country/year.

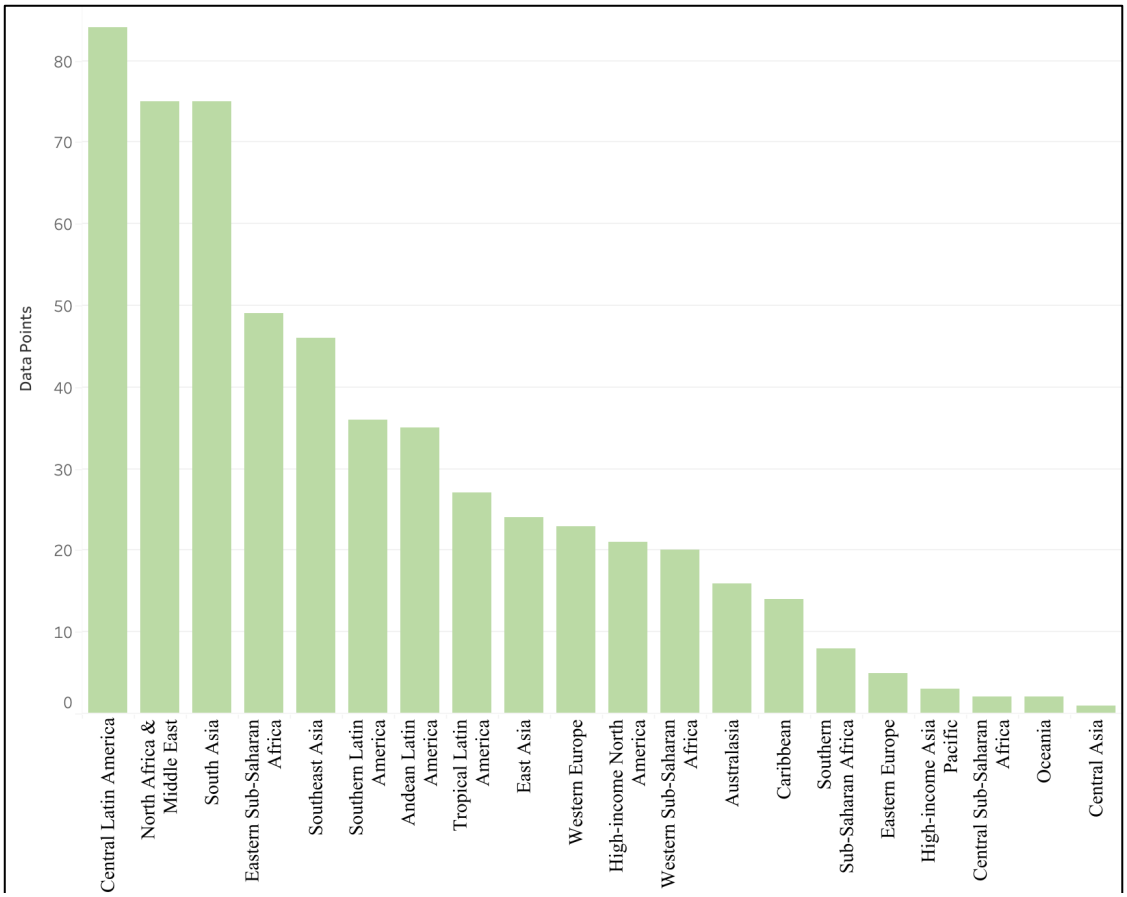

Figure 3.1: Shigella and fluoroquinolones input data of data points by region.

3.3 LIMITATIONS OF DATA

Several limitations arose when collecting and working with AMR data. In particular, the *Shigella* data was very heterogenous, with small numbers of data available for many country-years. The most significant data gaps identified in the *Shigella* and fluoroquinolones dataset were in Central sub-Saharan Africa, Central Asia, and Europe. The considerable heterogeneity in the data could be due to a few different factors. In some countries, data was collected from just a few sentinel cities often very far apart from each other geographically. Some of these cities were either rural or urban, leading to differences in their access to resources, such as lab quality, testing accuracy, and antimicrobials available. Some locations serve different populations with varying behaviors of treatment-seeking or antimicrobial use. In addition, data came from

various settings including hospitals, laboratories, and the community. Data from hospitals were also often from particular wards catering to different populations. These factors could all contribute to the vastly different prevalence of resistance within the same country and during the same year.

Another limitation of the data was missing variables of information from the studies or datasets during data collection. This information would have helped adjust for bias within the data. Many details of the methods used to test for antimicrobial sensitivity, laboratory quality, and sampling methodology were missing, thus, evaluating the quality of studies or surveillance networks was not viable. Additionally, many studies or datasets did not include the hospital, lab, or city where the data was collected.

Lastly, when deciding on a methodology for mapping the prevalence of resistance, defining a catchment area for each hospital, where data was available, was important for obtaining a more accurate estimate of the population served. For this to be possible, the address of each hospital needed to be provided, as well as how big the hospital is, what level of hospital it is, the facilities available within the hospital, and whether the hospital was private or public. However, after a substantial amount of time and effort, creating this list of information proved to be too time-consuming as there is no existing list of hospitals in each country, and many times the information details were not available online.

3.4 GEOSPATIAL MODELLING METHODS

Outputs from the above sections are used to model the proportion of *Shigella* exhibiting fluoroquinolone resistance and produced temporal maps at the national level. The prevalence of AMR in each pathogen-antibiotic combination was modeled separately, *S. dysenteriae, S. flexneri, S. boydii, S. sonnei*. Input data were the proportion of isolates resistant to the specified antibiotics linked to the year and location infection was acquired (or hospital where patients presented). Hospital data is reassigned to the pixels where the infection was most likely acquired, using a k-means clustering method and weighted by the pixels population size and the likelihood of attending the hospital. These data were then modeled using the two-stage Bayesian Model Based Geostatistics (MBG) framework.

Due to high heterogeneity in the input datasets, data points found to have the most extreme values for the prevalence of resistance were outliered. Initially, any data points that appeared to be outliers were doubled checked to ensure a human error did not occur during data extraction. Secondly, a generalized linear mixed-effects model (GLMM) was fit to the data, with nested spatial random effects based on the GBD super-region, region, and country, to capture the crude spatial-temporal trends. Datapoints which lay outside of two times the median absolute deviation (MAD) of the input data from the modeled estimate for each country were determined to be an outlier and removed prior to the stacked ensemble modeling step. Approximately 10% of the most extreme data points were classified as outliers.

The datasets excluding significant outliers were used to fit spatial-temporal statistical models for the prevalence of AMR in each pathogen-antibiotic combination; a stacked

ensemble model was fit to leverage covariate effects, followed by an ST-GPR to smooth the data in time and space. A two-stage spatiotemporal modeling framework was employed to estimate the prevalence of resistance in each priority pathogen-antibiotic combination for 204 countries by year from 1990 to 2020. First, a stacked ensemble model was fit between the input data and selected covariates from the list of socio-economic status, health system access, food consumption, climate, and demographic covariates available in the GBD study database (http://ghdx.healthdata.org/). This incorporates the effects of these covariates to better estimate the prevalence of resistance. The goal of using covariates is to improve estimates in locations without resistance data. The input covariate list included 49 covariates that may have an effect on *Shigella* resistance (Table 3.1). This list was narrowed down using a lasso (penalized) regression model for each pathogen-antibiotic combination to help select the most instructive covariates for each combination to be used in the stacked ensemble stage. Of the most instructive covariates, different combinations of covariates were tested to produce the most accurate prediction of prevalence of resistance for each country-year. This process was carried out by adding covariates one by one and testing in combination as they are added. Each combination of covariates was then tested for accuracy by referring to the correlation (R^2) and the root mean squared error (RMSE), and looking to see if the output makes sense. This model was fit between the logit of the *Shigella* resistance data and the covariate data in order to choose the most significant covariates. The final set of covariates chosen differed for each pathogen and antimicrobial combination can be found in table 3.2 below.

Covariate Description	FQ *Shigella*	FQ *S. flexneri*	FQ *S. boydii*	FQ *S. dysenteriae*	FQ *S. sonnei*
Antibiotic usage proportion					
Childhood stunting					
Age-standardized prevalence of diabetes					
No access to handwashing facility					
Proportion with access to improved water source					
Average latitude of country center point					
Oral rehydration therapy					
Outdoor air pollution					
Pharmacists per capita					
Skilled birth attendant coverage					
Total fertility rate					
Zinc treatment for diarrhea					

Table 3.2: Finalized list of covariates for each pathogen and antimicrobial combination. FQ = fluoroquinolones

The stacked ensemble model was fit between the input data and the selected covariates, matched by country and year. This model tested thirteen child models to see which combination fit the data best. These child models were: extreme gradient boosting (xgboost), generalized additive models (GAM), generalized additive model using LOESS (GAMloess), k-nearest neighbors (KNN), neural networks with a principal component step (pcaNNET), lasso and elastic-net regularized generalized linear models (glmnet), extreme gradient boosting tree (xgbTree), neural nets, random forest, cubist, penalized regression (elastic net, ridge, and lasso) models. As each machine child model has different strengths, multiple child models can be combined to merge those strengths into one stacked model.[96] The correlation and RMSE between the data and predictions was checked to aid in selecting the child models used in each model. The child models used for the *Shigella* and fluoroquinolones models were GAM, random forest, and ridge. This was an iterative process where several combinations of child models were experimented with, then a stacking model combined the child models

together. The R^2 and the RMSE of the input data and the out-of-sample estimates determined the predictive power of the stacked child models. A constrained weight mean stacked the child models together. Each child model was fit using five-fold cross-validation to avoid over-fitting. The out-of-sample predictions from the five holdouts were all placed into one complete set of predictions per model, the stage 1 estimates.

The out-of-sample estimates of the stacked ensemble model[96] were then input into an adapted bespoke spatiotemporal Gaussian process regression (ST-GPR)[97] model to smooth the estimates in space and time. This model is an important piece to the modeling process as it takes into account for space–time correlation and smooths where data is sparse, which the stacked ensemble model does not. The ST-GPR model is versatile stochastic model that takes into account both drivers of disease (the included covariates) and unknown spatiotemporal correlations within the data. This model works by smoothing stage one estimates where spatial and temporal weights were applied to the residuals and fitting trends using the Gaussian Process Regression. The Gaussian process is specified by a mean and a covariance function, and the goal is to predict a smoothed prevalence of resistance estimate per country and year.

$$log\left\{\frac{Q_{ikt}}{1-Q_{ikt}}\right\} = \alpha + S_{kt} + Z_{ikt}$$

Q_{ikt} denotes the estimated resistance prevalence from the stage 1 stacked ensemble from the i-th data source for the k-th country (n=204) in year t (n=29), 1990-2020. S_{kt} is a Spatio-temporal Gaussian process and Z_{ikt} is Gaussian noise. S_{kt} is modeled as a Spatio-temporal Gaussian process with mean 0 and covariance function $\Sigma = \sigma^2[R_s \otimes R_T]$ where $\otimes$ is the Kronecker product (operation on two matrices of arbitrary size resulting in a block matrix) while R_S and R_T are the spatial and temporal correlation matrices,

respectively. R_S is modeled using a conditionally autoregressive (CAR) process (using ten nearest neighbors) with correlation parameter rho (ρ). The assumption is that neighboring countries are more likely to be correlated as are estimates in time. R_T is modeled as an autoregressive process of the first order with a parameter of temporal correlation phi (φ). Z_{ikt} represents the additive noise which is assumed to be a set independent of Gaussian variables with mean zero and variance that considers sample size (weight), and data sources. A sample size of 0 is assumed for locations without data, log is used to obtain equally distributed weights and avoid excess overweighting to data points with larger sample sizes. A Bayesian approach was taken to estimate the parameters governing the Gaussian process. Markov Chain Monte Carlo (MCMC) was used to solve the likelihood function and produce smoothed prevalence estimates in space and time. The MCMC algorithm calculated the mean and 95% uncertainty intervals of the prevalence of AMR from 1,000 draws (based on draws at 10 iteration spacing/thinning to reduce autocorrelation) of the GPR for each country-year following 100,000 burn-in iterations to ensure model stabilization. The MCMC techniques were implemented using the NIMBLE R software package.

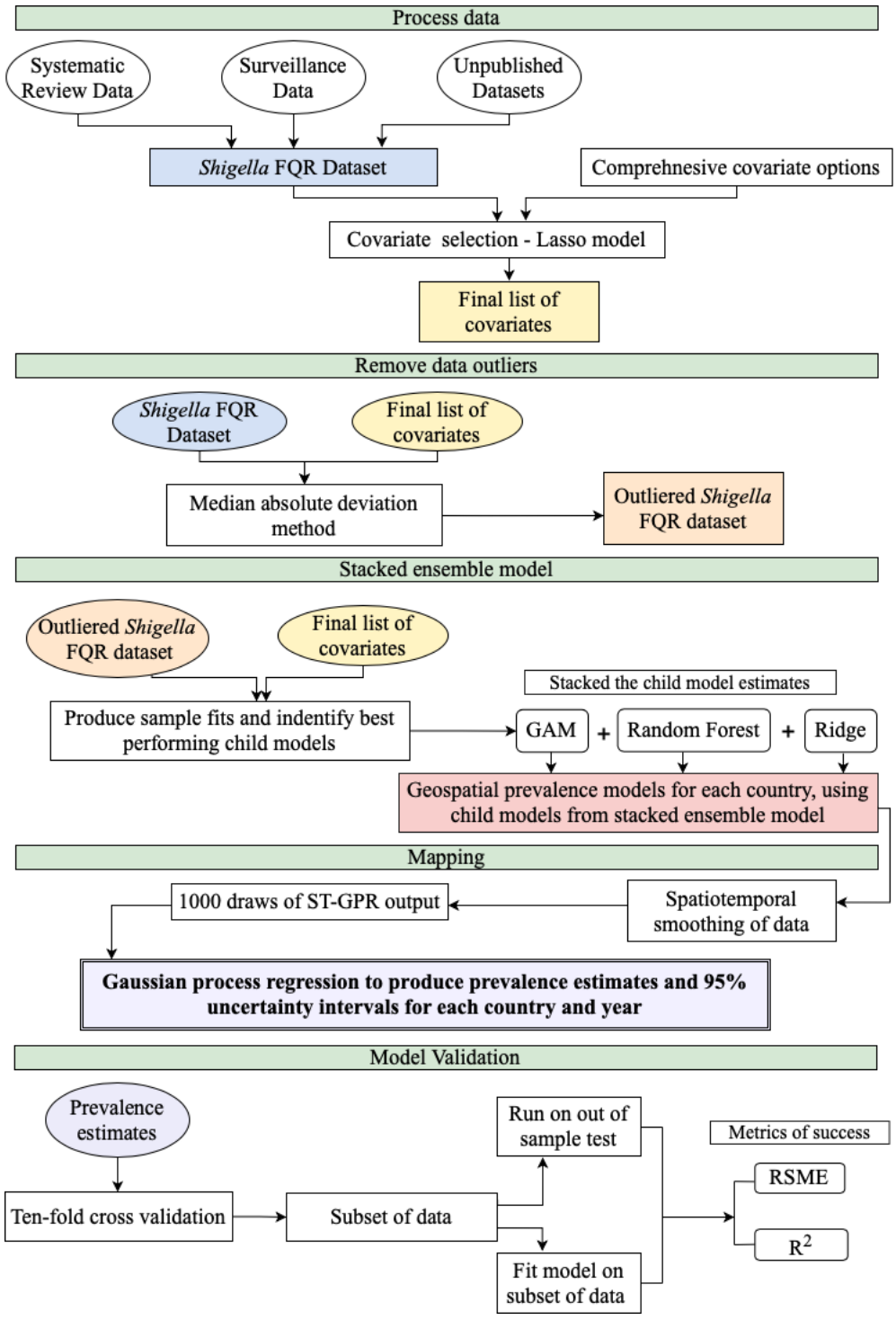

Figure 3.2: Flow chart methods for estimating the prevalence of FQR in Shigella.

The prevalence of AMR in each pathogen–drug combination was modeled separately, except for combinations encompassing sub-species within a given bacterium (e.g. *Shigella: S. dysenteriae, S. flexneri, S. boydii, S. sonnei*) for which a shared component model was utilized. The shared component acts similarly as a covariate for each

Shigella species, in areas where data is missing or sparse for a particular species, the model can draw on information from the other species to help inform/improve the accuracy of the prediction.[98] This model was appropriate for the four *Shigella* species and fluoroquinolones separately as these four species have sparse data and share important AMR determinants. The estimates from the shared component model were then fed into the same bespoke ST-GPR modeling framework. The ST-GPR, stacked ensemble models, shared component model and lasso covariate selection were implemented using R statistical software (Version 4.0.3).

3.5 MODEL VALIDATION

All models were validated using ten-fold cross-validation, and the RMSE and R^2 between the input data and the out-of-sample estimates were calculated to assess the models' predictive performance. Details of the model validation can be found in the appendix, Table B.2.

3.6 RESULTS

Total input data for the FQR *Shigella* model consisted of 208,072 isolates and 2,220 data points from 91 countries for over 30 years (Table 3.3). FQR *S. flexneri* has the most data out of all the *Shigella* species included with 109,875 isolates collected and 1,097 data points from 51 countries over 30 years. For FQR *S. sonnei* 72,022 isolates were collected and 941 data points from 51 countries over 30 years. For FQR *S. dysenteriae* there were 26,681 isolates collected and 699 data points from 38 countries over 30 years. For FQR *S. boydii* there were 10,483 isolates collected and 421 data points from 33 countries over 30 years.

Antimicrobial-pathogen combination	Isolates	Datapoints	Countries
FQR *Shigella*	208,072	2,220	91
FQR *S. flexneri*	109,875	1,097	51
FQR *S. sonnei*	72,022	941	51
FQR *S. dysenteriae*	26,681	699	38
FQR *S. boydii*	10,483	421	33

Table 3.3: Details of input data for FQR Shigella, FQR, S. flexneri, FQR S. sonnei, FQR S. dysenteriae, and FQR S. boydii models. The number of isolates, the number of data points input in the model, and the coverage of countries for each combination are presented.

3.6.1 FQR *SHIGELLA*

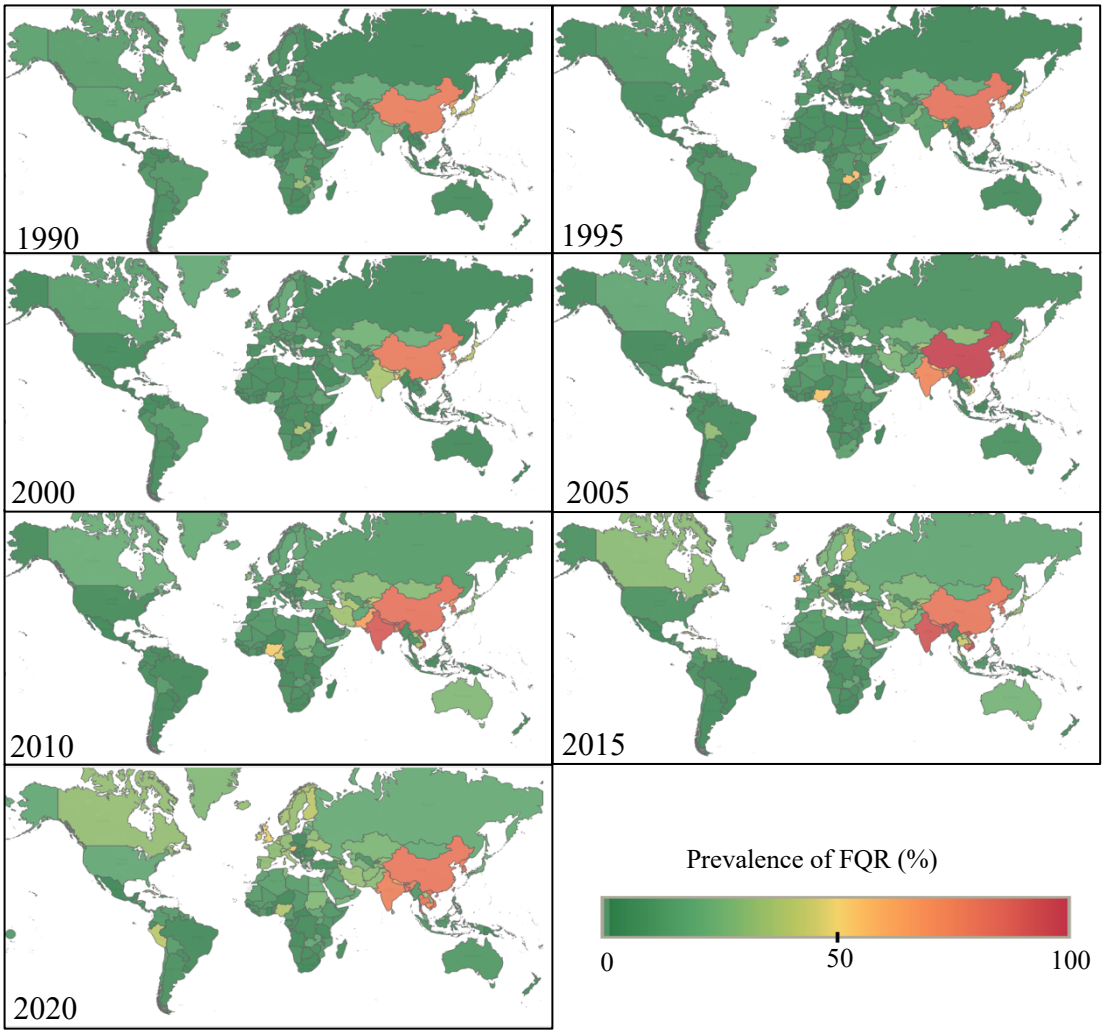

Figure 3.3: Model estimates for the prevalence of resistance for FQR Shigella. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

Shigella has been resistant to fluoroquinolones since the beginning of the study period in 1990. China reports over 90% resistance from 1990 to 2018. Additionally, in 1990, Kyrgyzstan, Bulgaria, Macedonia, Singapore, Bangladesh, Bhutan, Nepal, Zambia, Armenia, Japan, South Korea, Burundi, China and Taiwan all had over 20% resistance. South Korea experienced a steady increase in resistance with 47% in 1990 and 85% in 202**0**. Resistance in India developed rapidly, in 2000 with a reported resistance prevalence of 36% resistance, 74% resistance in 2005, and 90% in 2010. Resistance in Nigeria also increased rapidly, with less than 20% in the 1990s, 20% in 2000, and peaking at 56% in 2012 with a slight decrease to 38% in 2018. Austria gained resistance steadily from 4% in 1990 to 52% in 2020.

3.6.2 *SHIGELLA* SPECIES

Each *Shigella* species was modeled to produce national estimates worldwide, presented in five-year time periods. FQR is the highest in *S. sonnei*, with *S. flexneri* close behind, then *S. dysenteriae* and *S. boydii* with the lowest resistance. In all four species, resistance has increased with time. FQR was already present in 1990 in South, East and Central Asia and Eastern Europe in *S. dysenteriae.* Resistance was highest in South, East and Central Asia, Eastern Europe, and parts of the Middle East in 2020.

3.6.2.1 *S.* FLEXNERI

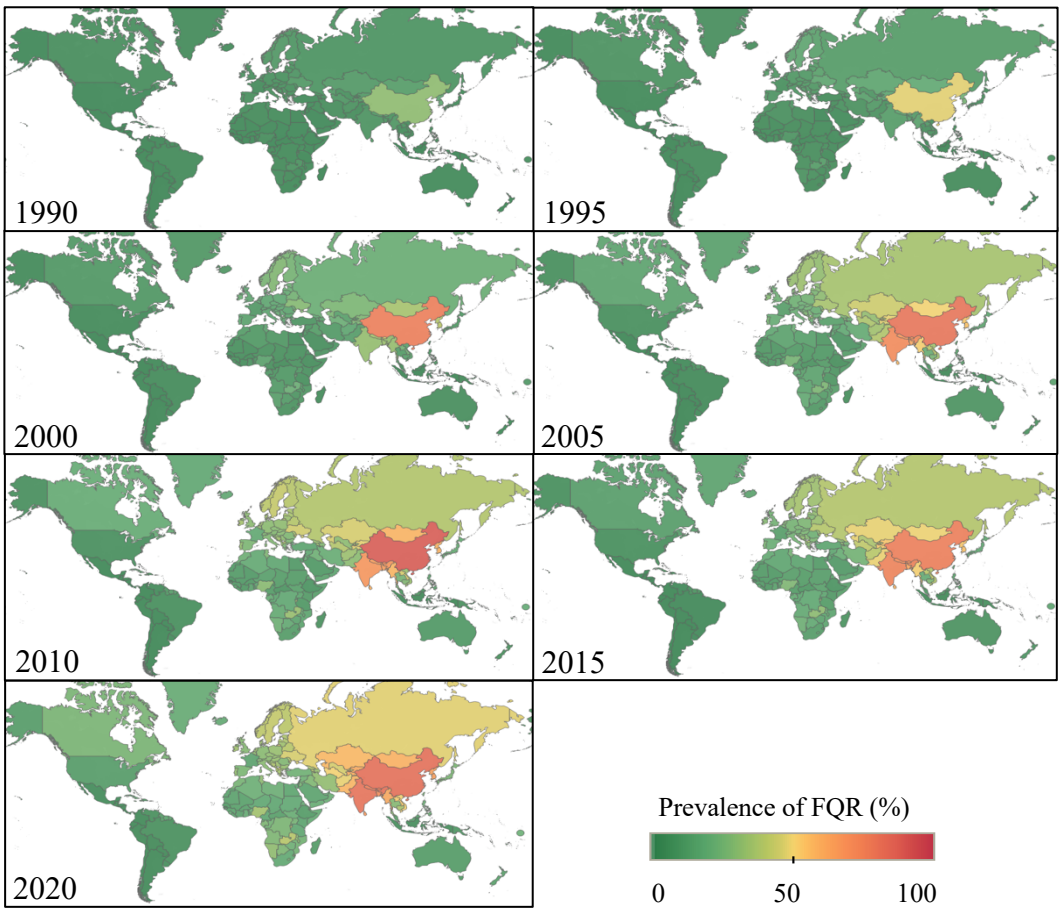

Figure 3.4: Model estimates for the prevalence of resistance for FQR S. flexneri. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

Fluoroquinolone resistance in *S. flexneri* appeared initially in China as early as 1990. Resistance continued to rise in China and spread to Ukraine, Russia, Mongolia, Kazakhstan, India, Nepal, Bangladesh, Myanmar and Laos in 2005. By 2015, resistance can be seen throughout Eastern and Western Europe, South, Central and East Asia, Zambia and Nigeria. In 2020, resistance increased in all these regions and countries and can now be seen in Canada, Central and Southern sub-Saharan Africa and Central Europe. In 20**20**, resistance was highest in China, India, Nepal, Bhutan, and Bangladesh and lowest in Central and South America and Australasia.

3.6.2.2 *S.* SONNEI

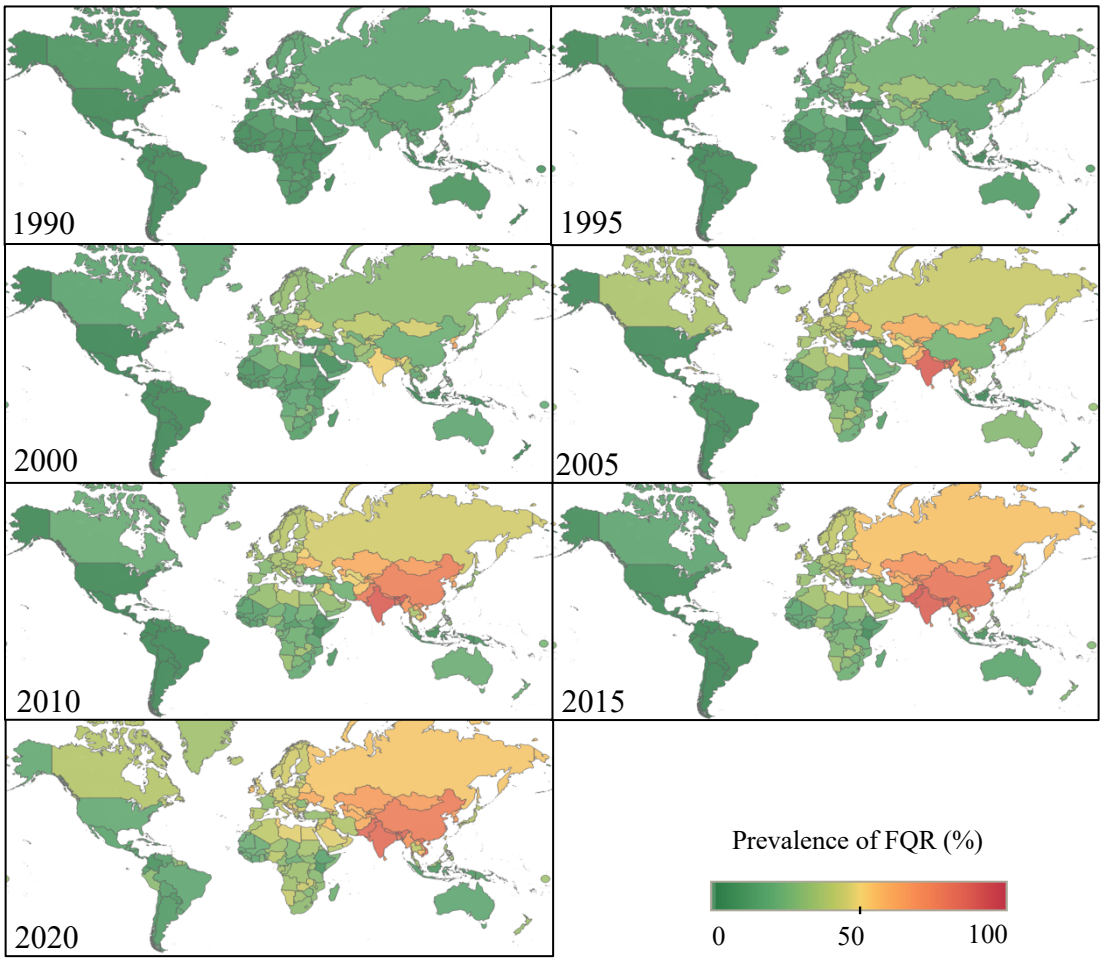

Figure 3.5: Model estimates for the prevalence of resistance for FQR S. sonnei. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

Fluoroquinolone resistance in *S. sonnei* was first seen in 1995 in Mongolia, Kazakhstan, Ukraine, and Nepal. Resistance continued to rise in these locations and spread to India, Korea and Eastern and Central Europe. In 2005, resistance was reported in Canada, Europe, and parts of North Africa and sub-Saharan Africa. Resistance was not reported in China until 2010. By 2020, resistance was highest in India, Pakistan, Nepal, Bangladesh and China and lowest in North, Central and South America, Australasia and the Western tip of Western sub-Saharan Africa.

3.6.2.3 S. DYSENTERIAE

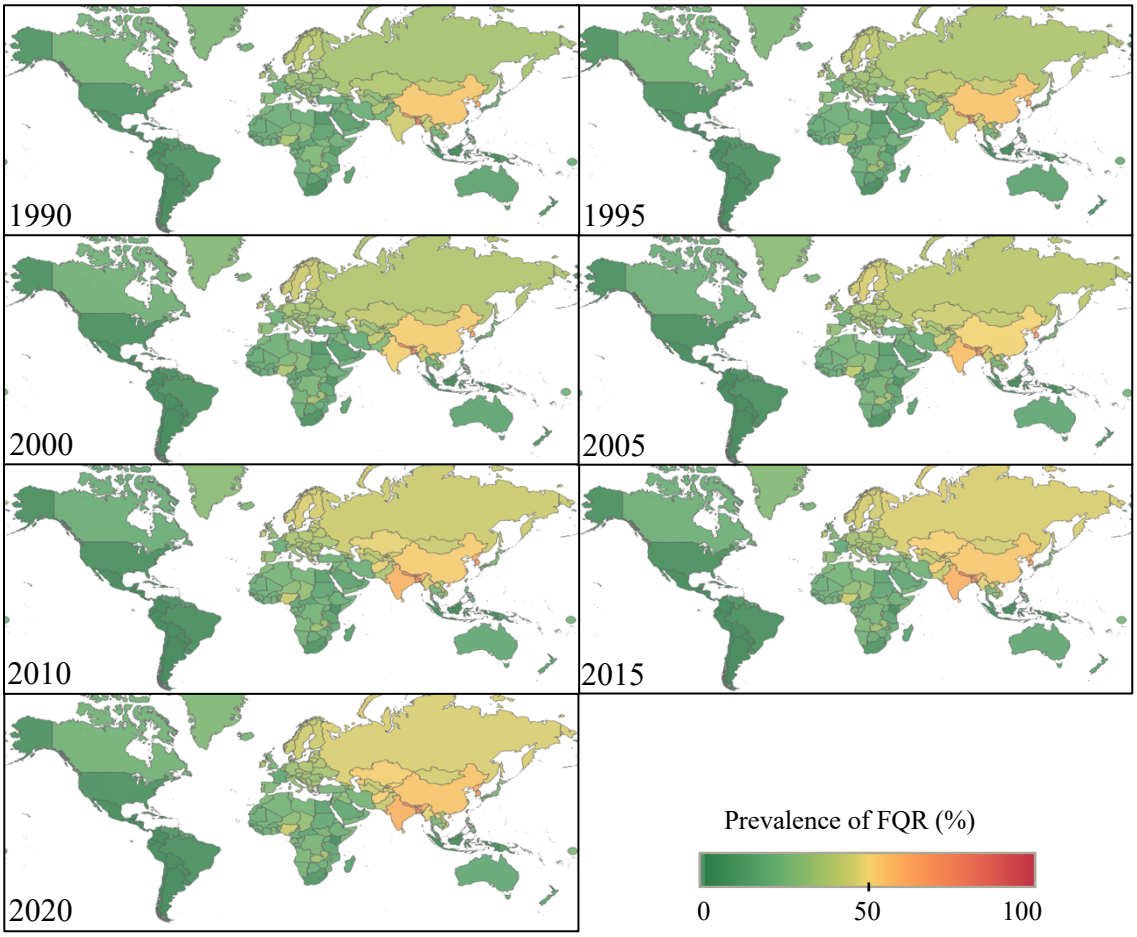

Figure 3.6: Model estimates for the prevalence of resistance for FQR S. dysenteriae. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

In 1990, fluoroquinolone resistance in *S. dysenteriae* was already widely reported throughout Europe, East Asia, Nepal, Bhutan, Bangladesh and Burundi. Over the next ten years, resistance slowly increased in these regions and countries, with India increasing at the fastest rate. By 2020, resistance was the highest in India, Nepal, Bangladesh, Burundi, Korea and China and lowest in North, Central and South America, most of sub-Saharan Africa and Australasia.

3.6.2.4 *S.* BOYDII

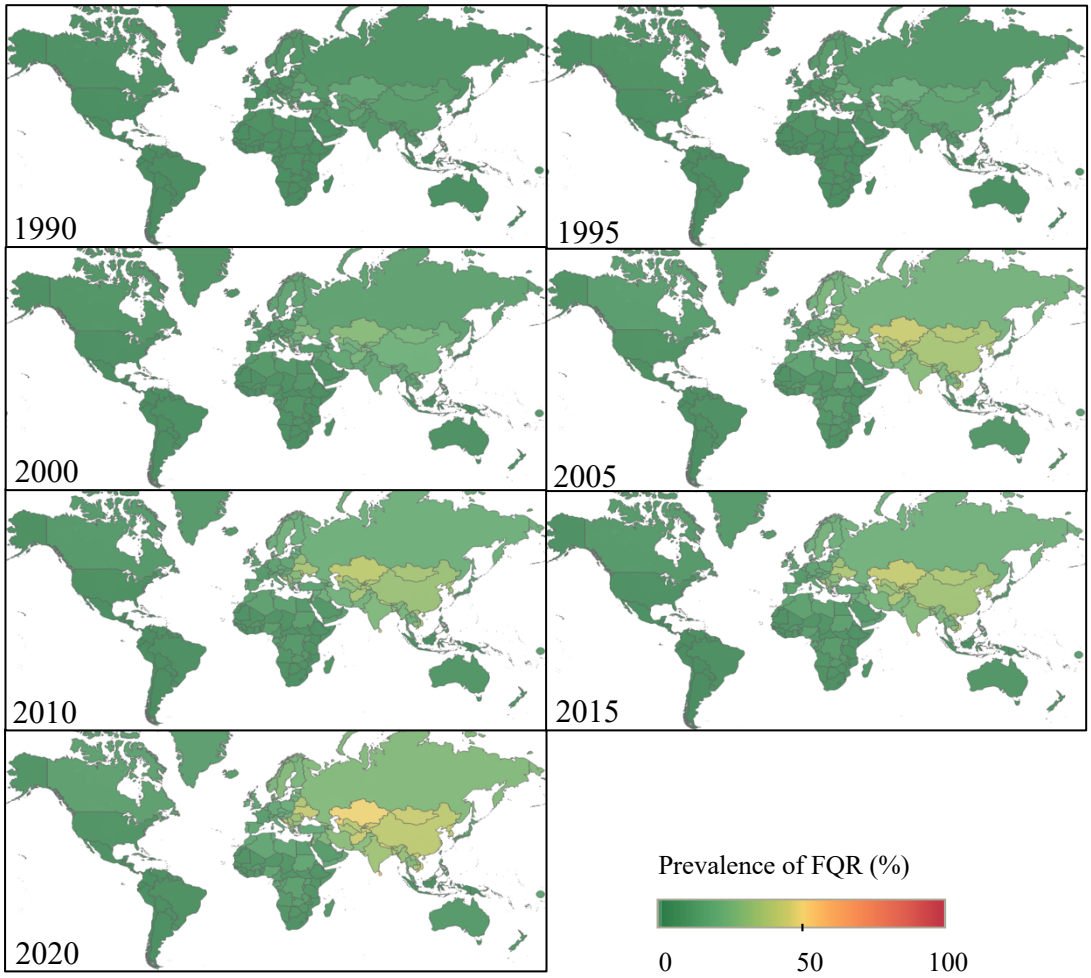

Figure 3.7: Model estimates for the prevalence of resistance for FQR S. boydii. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

Fluoroquinolone resistance in *S. boydii* was first reported in 2005 in Kazakhstan, Mongolia, China, Ukraine, Belarus and Afghanistan. From 2005 to 2020, resistance increased in these countries and spread throughout the Middle East and Southeast, South, and Central Asia regions.

3.7 MODEL UNCERTAINTY

The relative uncertainty of estimates for FQR *Shigella* prevalence was calculated for 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data

were shaded according to the quartile of the proportion of AMR and the quartile of relative uncertainty to which they resided. There are varying degrees of uncertainty in the modeled estimates due to the large data gaps in my *Shigella* dataset. The higher the relative uncertainty indicates a lack of data and a need for more information to produce a more accurate estimate. The estimates of high resistance are accompanied by low relative uncertainty for FQR *Shigella*. Estimates of low resistance are often accompanied by high relative uncertainty, with the exception of Guatemala, Mexico, Paraguay, Lesotho, and Madagascar.

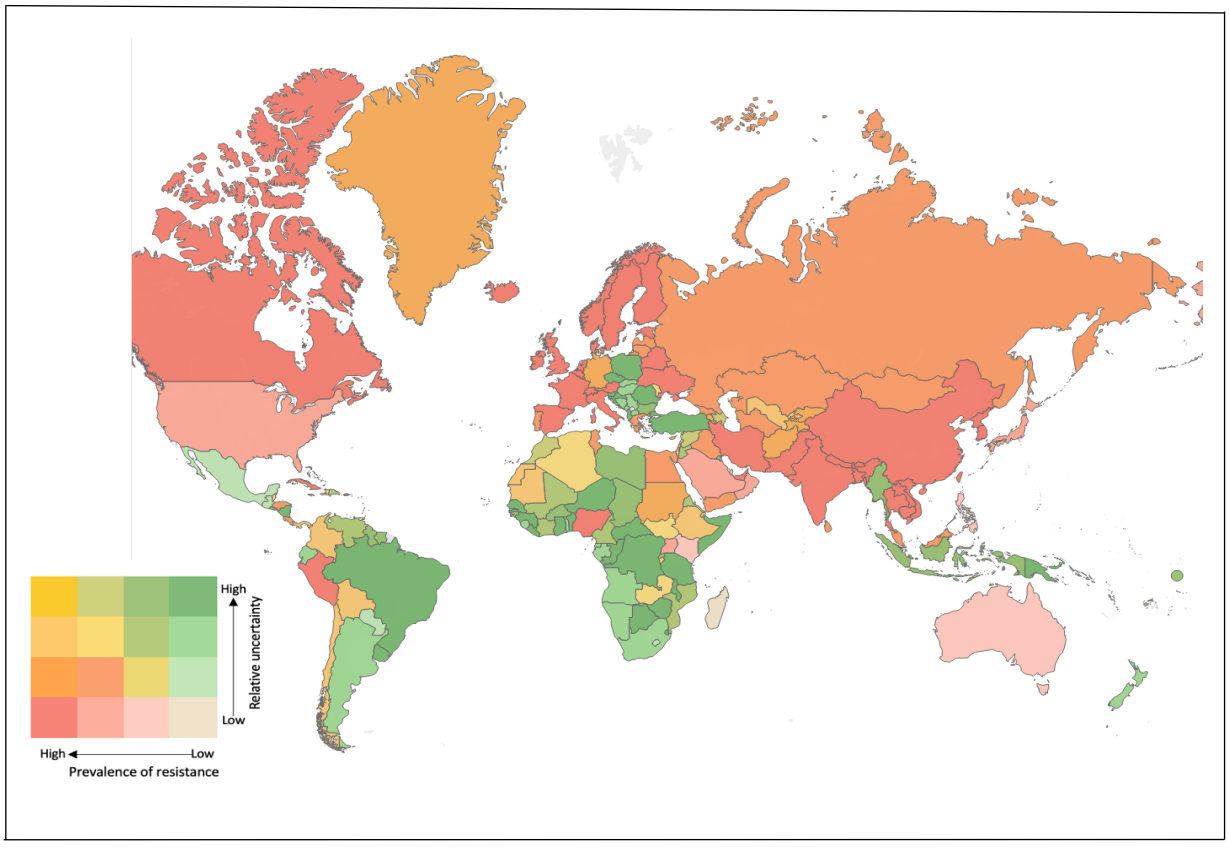

Figure 3.8: Relative uncertainty of estimates for FQR Shigella prevalence in 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data were shaded according to the quartile of the proportion of AMR and relative uncertainty to which they resided.

3.8 CONCLUSION

The most concerning results identified in this study are the >90% fluoroquinolone resistance in China and India. In addition, the high resistance in Thailand, Cambodia and Vietnam and the rising resistance seen in the UK, the USA and Canada.

In India, high FQR has occurred since the early 2000s and continues to the present day. Ciprofloxacin was first suggested for *Shigella* treatment in the 1990s and was efficacious with over-the-county availability. These two factors contribute to the high resistance seen in India, leading to a change in antibiotic treatment from ciprofloxacin to ceftriaxone, pivmecillinam, or azithromycin.[99] High FQR in the 1990s in China has also resulted from the efficacy of fluoroquinolones and their vast availability.

It is worrisome that ciprofloxacin is the current first-line treatment, listed in national and international guidelines and has not been updated recently. The results from this study show that treatment guidelines need to be updated as susceptibility changes and they need to be country or region specific. A global recommendation for antibiotic treatment is difficult to issue today as resistance does differ depending on the country. Countries have different prescribing habits, different views on antimicrobials and use habits, varied availability of antimicrobial classes, and different environments. This can all lead to differences in resistance to the same pathogens and results in having one general treatment recommendation inappropriate. The World Health Organization (WHO) recommends ciprofloxacin as a first-line treatment, which was last updated in 2005.[100] The British National Formulary also recommends ciprofloxacin as a first-line treatment despite 50% fluoroquinolone resistance in the UK, this guideline was last updated in 2016.[101] Additionally, the Infectious Diseases Society of America

(IDSA)[102], Therapeutic Guidelines[103], the American Academy of Pediatrics (AAP)[104], and BMJ Clinical Evidence[105] all recommend ciprofloxacin as a first-line treatment. There were no other treatment guidelines found from other countries. Currently, there is no defined threshold that calls for a change in treatment for fluoroquinolone-resistant *Shigella*. The threshold set for fluoroquinolone resistance in uropathogens is 10%, and if resistance supersedes this number, then an alternative therapy is recommended for that community.[106] The threshold set for methicillin-resistant Staphylococcus aureus is 10-20% and for macrolide resistance in Streptococcus pneumoniae is 25%.[107,108] Figure 3.3 shows that in 2020 North America, Europe, Asia, most of the Middle East and North Africa, Peru, Nigeria, Namibia, and Zambia have >10% fluoroquinolone resistance. That is more than 50% of the world with over 10% fluoroquinolone resistance and the current treatment guidelines for illness caused by *Shigella* do not reflect prevention of further exasperating this resistance.

3.8.1 IMPLICATIONS FOR CLINICAL PRACTICE

High fluoroquinolone resistance has many implications in clinical practice. Patients will begin to experience treatment failure with this first-line drug. In low-income settings, empirical treatment is commonly used as a treatment plan as many healthcare settings may not have access to a laboratory or test supplies. Empirical treatment is often based on antimicrobial treatment guidelines and, in most cases, not on the local prevalence of resistance. An inappropriate empirical treatment increases the healthcare costs to the patient as they will need to purchase another medication, which may lead to a hospital stay or lengthen of their hospital stay due to the severity of their illness. High resistance and treatment failure results in limited treatment options for patients and healthcare providers. Access to antimicrobials may be limited in many countries,

and when first-line drugs do not work, there may not be access to a second option. Availability of antimicrobials is subject to cost, the demand for the antimicrobial and accessibility of the antimicrobial. First-line drugs may be easier to access than second-line drugs, leaving healthcare providers with few alternatives for treatment. This is especially a problem for low-income settings with high resistance and little access to many resources.

CHAPTER 4

Systematic Review of Antimicrobial Drug Resistance in *E. coli* from 1990-2018

4.1 INTRODUCTION

Escherichia coli is a Gram-negative enteric organism and a ubiquitous colonizer of the human gastrointestinal tract. *E. coli* is commonly found in the environment around the world and is often in contact with humans and animals daily. It is common for humans to consume different pathotypes of *E. coli* throughout their lifetime, some of which cause disease and some do not. Diarrhea-causing pathotypes such as Enteropathogenic *E. coli* (EPEC) and enterotoxigenic *E. coli* (ETEC) are prevalent in low and middle-income countries, with ETEC causing travelers diarrhea.[109] High-income countries often suffer from Enterohemorrhagic *E. coli* (EHEC) outbreaks, causing diarrhea and more severe illnesses such as hemorrhagic colitis and hemolytic uremic syndrome.[109] Illness caused by *E. coli* is a global public health threat, resulting in large numbers of deaths, particularly in children under the age of five in developing countries.

The large population of bacteria that make up the genus *E. coli* demonstrates vast genetic and phenotypic variation. Only 20% of the genes in the typical *E. coli* genome are common to all strains, making *E. coli* one of the most diverse bacterial species.[110] Healthy people, regardless of age, are at risk of serious repercussions that may come as a result of being infected with *E. coli*. Some of these illnesses include wound infections,

urinary tract infections, peritonitis, pneumonia, hepatobiliary infections, diarrhea, meningitis, and septicemia.[23] Young children are more prone to developing severe illnesses.[20,25]

The Global Burden of Disease (GBD) study in 2019 estimates that *E. coli* caused 800,000 deaths worldwide associated with antimicrobial resistance, and 200,000 deaths were attributable to antimicrobial-resistant *E. coli.*[4] Third-generation cephalosporin and fluoroquinolone *E. coli* resistance were attributable to the highest number of deaths in 2019, which was estimated to be 59,900 and 56,000 deaths, respectively, worldwide. Carbapenem-resistant *E. coli* was attributable to an estimated 29,500 deaths, aminoglycoside-resistant *E. coli* was attributable to 11,700 deaths, and aminopenicillin-resistant *E. coli* was attributable to 10,500 deaths worldwide.[4]

4.1.1 LABORATORY METHODS TO CHARACTERIZE *E. COLI* INFECTIONS

As *E. coli* can cause a wide array of illnesses, the diagnostic sample collected and tested for *E. coli* depends on the site of infection. For diarrheal diseases, a stool sample or rectal swab will be collected, for urinary tract infections, a urine sample is collected, for a wound infection, a pus sample is collected, for a meningitis infection, a CSF sample is collected, and for sepsis, a blood sample is collected. Once *E. coli* is identified, antimicrobial sensitivity testing (AST) is performed to help inform which antimicrobials will be most effective to prescribe. There are various AST methods, including agar dilution, broth dilution, or disc diffusion.

4.1.2 CURRENT TREATMENT

General current treatment recommendations for community and hospital infections due to *E. coli* are β-lactams, fluoroquinolones, cephalosporins, aminoglycosides, and trimethoprim-sulfamethoxazole.[111] Treatment for Enteroinvasive *E. coli is* azithromycin, fluoroquinolones, and cephalosporins.[111] Fluoroquinolones are also recommended to treat travelers diarrhea, if treatment is required. Studies show that the consumption of last-line antimicrobials, such as colistin and carbapenems, is increasing, leading to an increase in resistance and even fewer treatment options.[112,113] Building a database of *E. coli* resistance to relevant antimicrobials worldwide is essential to create a whole picture of the current state of resistance in countries respective to each other, identify where resistance is highest, and to monitor trends over time to see how quickly resistance develops once an antimicrobial is used regularly. To begin building this database, a global systematic review, described in this chapter, was the first step in collecting this information.

This systematic review aims to compile data from around the world to provide a complete picture of antimicrobial resistance in *E. coli* from 1990 to 2018 worldwide. Data were collected to analyze the temporal and spatial trends to understand better how antimicrobial resistance in *E. coli* has changed over the years. Results from the systematic review are discussed, and a meta-analysis of the data is presented by five-year time periods and GBD region. This systematic review was designed to be comprehensive, filling an existing gap and complementing the current data and research.

4.2 MATERIALS AND METHODS

4.2.1 SEARCH STRATEGY AND SELECTION CRITERIA

A systematic review was conducted of published literature between 1990 and 2018 following PRISMA guidelines. The protocol was registered with the international prospective register of systematic reviews, PROSPERO 2019 CRD42019145148. This review was part of a larger, global systematic review of antimicrobial resistance in *E. coli, Klebsiella pneumoniae, Streptococcus pneumoniae,* and *Staphylococcus aureus.* These four pathogens were included in one systematic review, as much of the literature covers two or more of the pathogens in the same publication. Additionally, all four pathogens are included on the WHO antibiotic-resistant priority pathogen list of bacteria that pose the greatest threat to human health.[30] The systematic search combined Medical Subject Heading terms with free text terms in the title and abstract fields for *E. coli, K. pneumoniae, S. pneumoniae, and S. aureus* with the terms for antimicrobial drug resistance. The search was limited to publications from 1990 to 2018. The search was undertaken using the following online bibliographic databases: MEDLINE, Ovid Embase, Global Health, and Cochrane. There were no language restrictions, and reference lists of relevant studies were checked to identify secondary references.

The focus was on specific syndromes caused by the respective pathogen:

• *E. coli* that causes pneumonia, urinary tract and bloodstream infections, neonatal infection, post-surgical sepsis, and intra-abdominal sepsis

• *K. pneumoniae* that cause pneumonia, urinary tract and bloodstream infections, neonatal infection, post-surgical sepsis, and intra-abdominal sepsis

• *S. pneumoniae* that cause pneumonia, otitis media, meningitis, and bloodstream infections

• *S. aureus* that causes wound and bloodstream infections

Included studies reported quantifiable in vitro antimicrobial susceptibility data for *E. coli, K. pneumoniae, S. pneumoniae, and S. aureus*.

Inclusion criteria included the following:

• Reports published from 1990 to 2018

• *E. coli, K. pneumoniae, S. pneumoniae, S. aureus* strains isolated from consecutive patients

• The minimum number of strains isolated is 10

Exclusion criteria:

• Studies that do not report quantifiable resistance data

• Pooled resistance data, where it is not possible to assign a separate susceptibility profile

• Failure to report the study location

• Studies that show inconsistencies that cannot be resolved by information from the authors

The general methods used in this systematic review followed the same format as the *Shigella* systematic review described in Chapter 2. The Endnote library was deduplicated and imported using the proprietary software DistillerSR. Considering the scale of the systematic review, data extraction was targeted at countries where data was challenging to obtain from other sources. All 70,229 papers were first screened at the title/abstract level in DistillerSR and geotagged during this stage. Geotagging refers to assigning each reference to a location where the study was conducted. As shown below in figure 4.1, each included paper was geotagged to assist with identifying the regions

of priority. Africa was chosen as the first priority region as there was a significant data gap in the data already collected from other sources. This can be seen when comparing the coverage of Africa in figure 4.1 to the coverage in the data sets shown in figure 4.2.

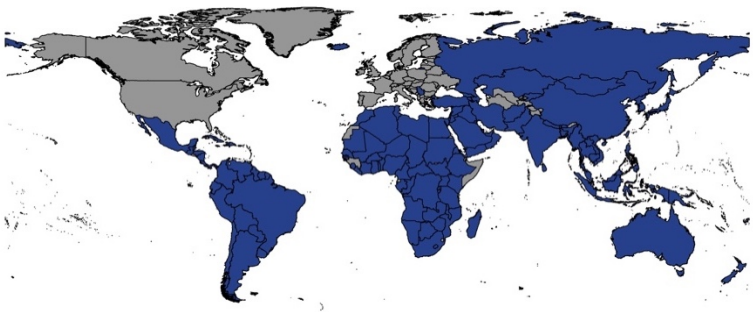

Figure 4.1: Map showing the location of all geotagged references in the systematic review.

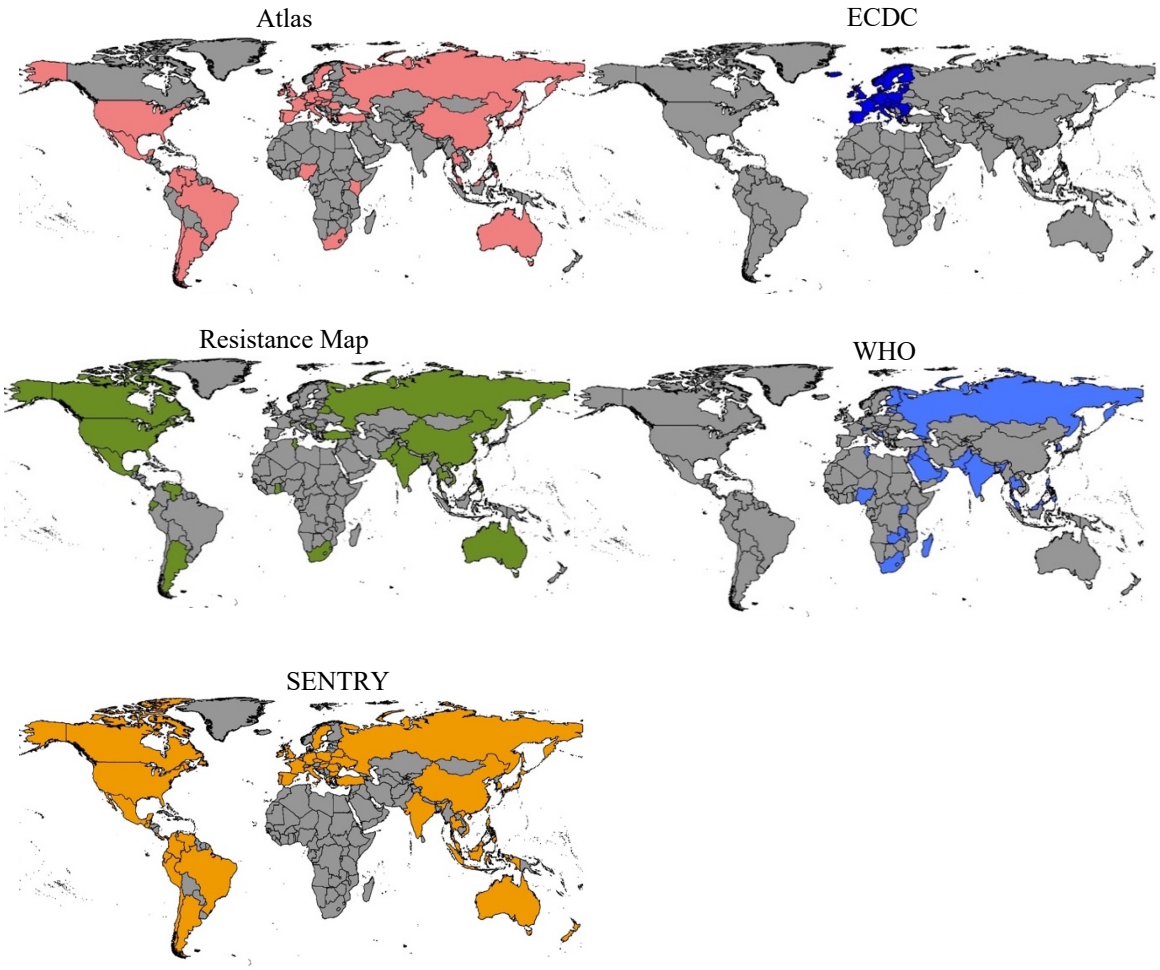

Figure 4.2:The maps above show where data was obtained from researchers, surveillance networks, or other sources. This information informs which countries/regions will be of priority for a systematic review to gather data.

From the screened and geotagged references, 1,642 references were identified as geographically from Africa. These references were screened again at the full-text level to confirm they reported the resistance profile of *E. coli, K. pneumoniae, S. pneumoniae* or *S. aureus* isolates to clinically relevant antimicrobials. There were 34,902 studies excluded during the full-text screening as they were geotagged as being outside of Africa. Data from full-text articles identified as being from Africa (N=1,571) were then extracted. Once all the systematic review Africa data was collected, there were further data gaps to fill. Figure 4.2 shows large data gaps in the Middle East, South America, and Asia. Large studies from these regions were identified from the geotagged references and were extracted to fill this gap in data. This resulted in extracting an additional 85 studies from 19 countries outside of Africa in order to obtain global coverage of data.

All reasons for excluding studies can be found in the PRISMA flow chart (Figure 4.3). Two authors screened papers independently and reviewed them against the inclusion and exclusion criteria. A short description of the reason for exclusion was recorded. The two authors extracted the data independently and discrepancies were resolved by discussion. Any disagreements were resolved through discussion with the senior author.

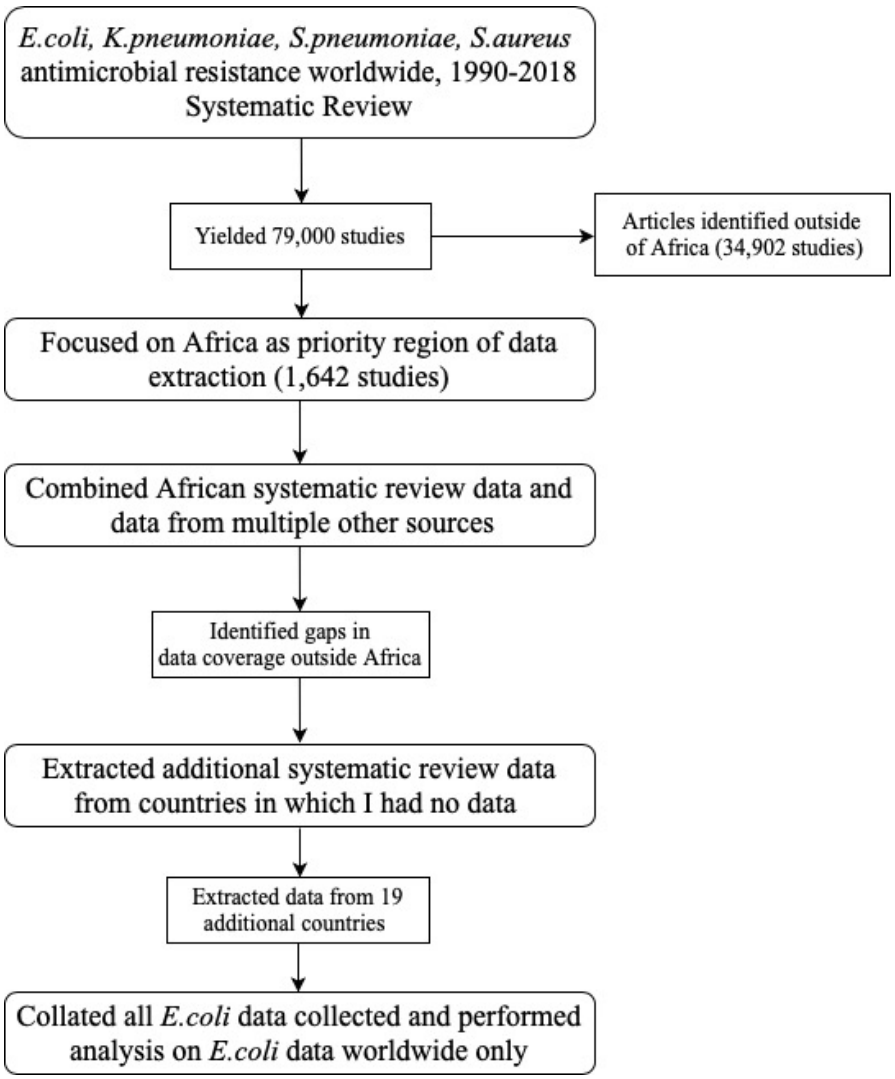

Figure 4.3: Systematic review methods flow chart.

The prevalence of antimicrobial resistance amongst *E. coli* was defined as the percentage of isolates being resistant out of the total number of isolates tested for the specific drug. Antimicrobial susceptibility data is presented according to country, geographical region, and time period.

4.2.2 DATA EXTRACTION

Data were extracted directly into DistillerSR, and the variables extracted included:

- corresponding author information
- start and end date of the study
- study site (country, region and city information, including geolocated facility information)
- study setting (hospital-, community- or referral laboratory-based)
- whether it was part of a more extensive surveillance network
- patient demographics (age, percent male, inpatient or outpatients)
- clinical information such as comorbidities, outcomes, pre-admission antibiotics, infectious syndrome, and hospital-acquired/community-acquired
- pathogen information, including the number of positive cultures, outbreak infections, and clinical sample type
- lab information (antimicrobial susceptibility testing method used, control strains used, antimicrobial susceptibility testing guidelines and breakpoints used)
- antimicrobial susceptibility information by pathogen and antimicrobial

Studies that reported the results aggregated in a way that could not be used in the analysis were excluded. Examples include where the results were aggregated for several countries together, where antimicrobial susceptibility was reported for drug classes rather than single drugs, and where pathogens were not defined at the species level. Contact author information was collected to try and acquire the data broken down in a way that was usable.

Bias was primarily controlled by the use of the inclusion criteria, which specify at least 10 consecutive isolates are required. Duplicate publications were excluded; if the same author/institution has published several studies during overlapping periods, the author/institution was contacted. Quality assessment tools were not used as an exclusion criterion.

4.3 DATA ANALYSIS

A meta-analysis was performed for each pathogen-antimicrobial combination by taking the total number of isolates tested and the number of resistant isolates to generate effect size and standard error. The 95% confidence intervals were estimated using the Agresti-Coull method.[81] The effect size and standard error were then used to pool the estimates of AMR. Freeman-Tukey double arcsine transformation was used to stabilize variance and a random-effects meta-analysis was performed to pool the estimates to allow for heterogeneity in the data. The meta-analysis was calculated using R statistical software (Version 4.0.3) using the statistical software package "metafor". This analysis is presented by region and 5-year time periods (1990-1994; 1995-1999; 2000-2004; 2005-2009; 2010-2014; 2015-2018) based on the midyear of the study. If study dates were not provided, the mid-year was imputed as the median difference between the publication date and mid-year for the remaining studies in the dataset. As the data is presented by region and five-year time periods, in some areas data is very limited and results in wide 95% confidence intervals. Geographical regions are defined according to the Global Burden Disease (GBD) regional classification system.[82] Analysis was done by time period and on GBD region separately. The percentage of isolates from

each study with antimicrobial-resistant strains of *E. coli* identified and intermediate resistant strains were classified as resistant.

4.3.1 RISK OF BIAS ASSESSMENT FOR EXTRACTED DATA

According to the conducted sensitivity analysis, none of the conditions that were looked into had a significant impact on the combined prevalence of resistance (Figure 4.4). The pooled prevalence of fluoroquinolone resistance *E. coli* was calculated for each location and time period using data from all studies, and these findings confirmed the choice not to omit any studies based on the risk of bias assessment.

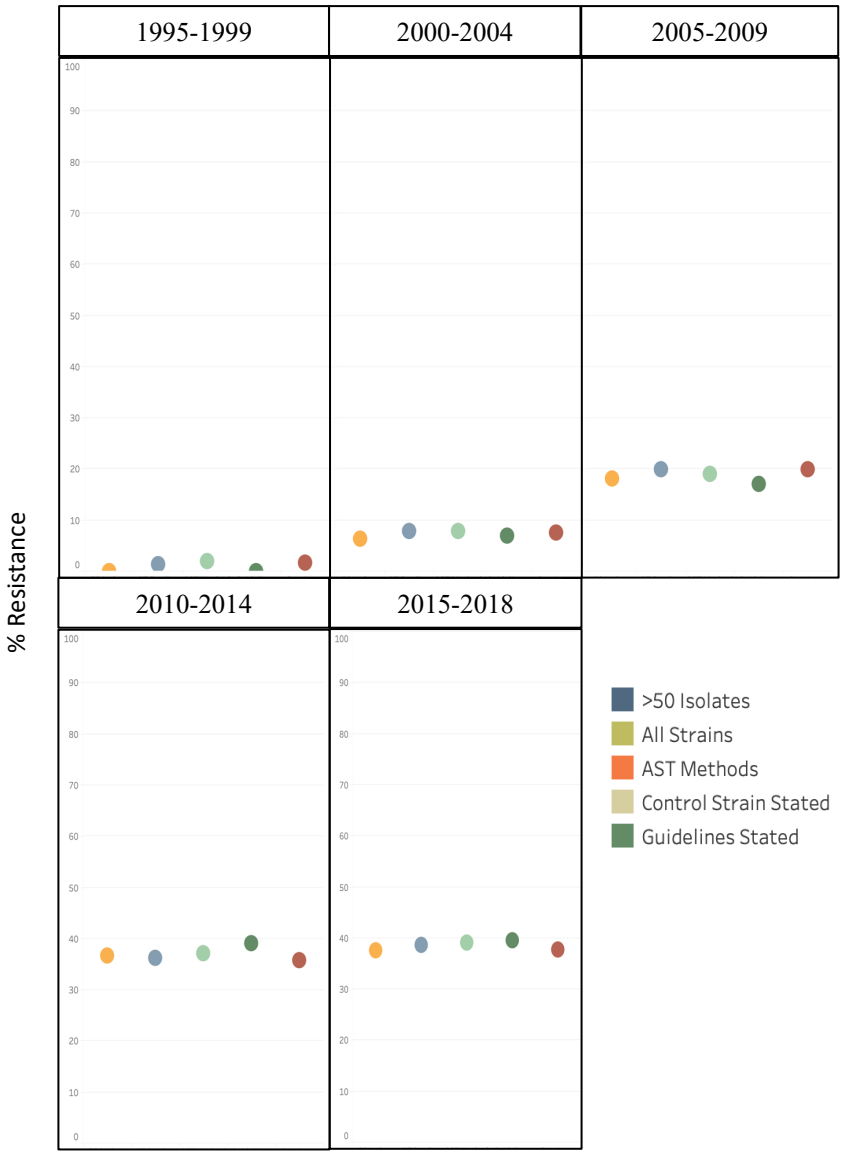

Figure 4.4: Sensitivity analysis for risk of bias assessment for extracted data. Random effects meta-analysis results for studies on E. coli *and fluoroquinolones by five-year time periods. Each plot compares the pooled prevalence of resistance for: all studies, less than 50 isolates, a control strain stated, AST breakpoint guidelines stated, and AST methods.*

4.4 RESULTS

4.4.1 SUMMARY OF STUDIES

The literature search identified 79,158 studies and after the title and abstract screening was performed, there were 70,229 studies included. All 70,229 studies were geotagged, and studies from Africa were targeted to be extracted first. There were 1,642 studies from Africa, and 456 of those studies had *E. coli* data. Additionally, 44 studies from

outside of Africa with *E. coli* data were extracted and included in the systematic review. This is a total of 500 studies, with a total of 4,304,273 isolates extracted in the systematic review.

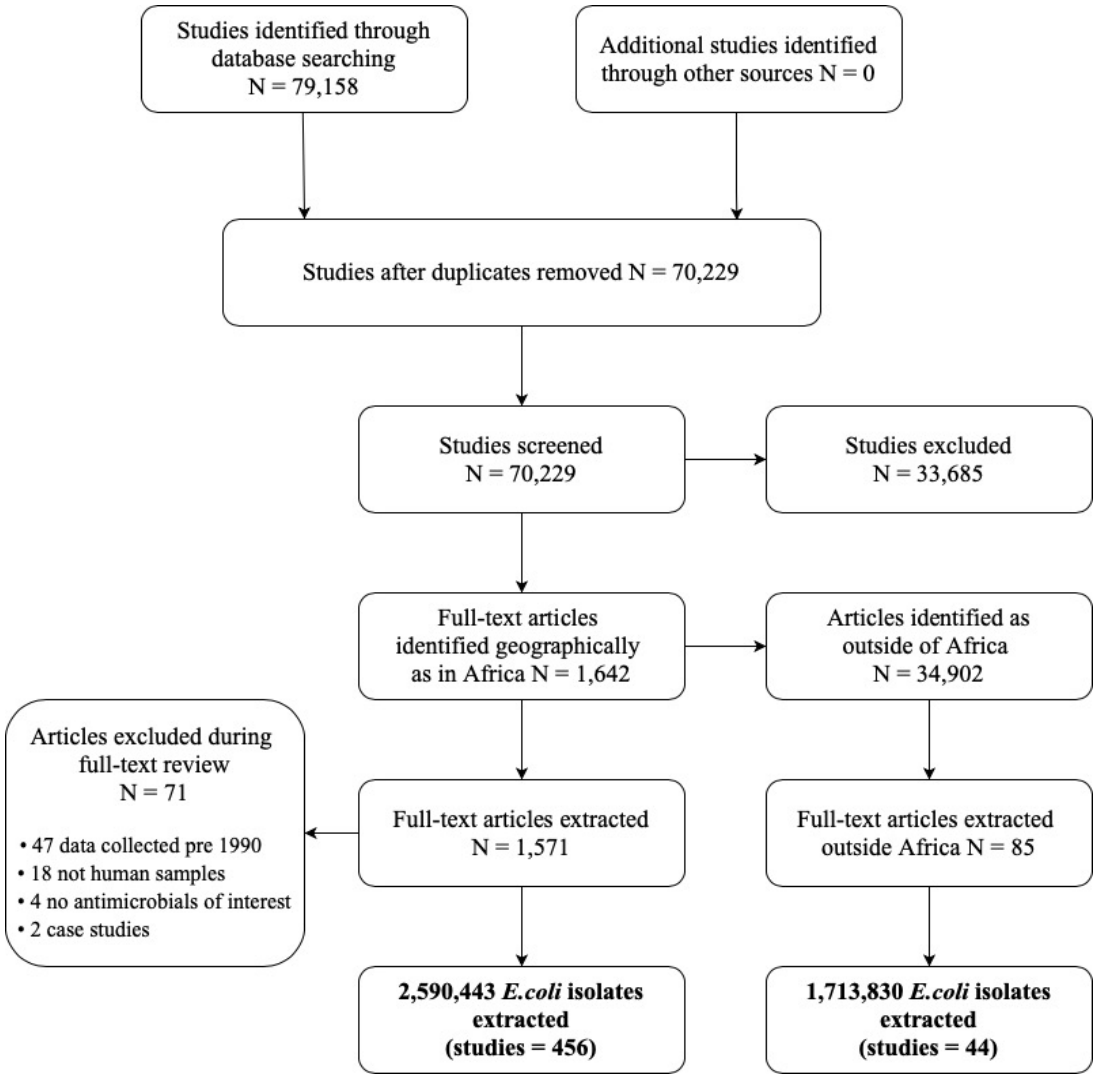

Figure 4.5: PRISMA Flow chart depicting study screening and selection.

4.4.2 DATA COVERAGE



Figure 4.6: E.coli data availability by year and country. All included data are plotted by country (y-axis) and year (x-axis), grouped by GBD region. The size of the point depicts the number of studies for each country-year.

4.4.3 STUDY CHARACTERISTICS

Study Characteristics		Number of studies
Study Setting		
	Hospital	406
	Community	14
	Referral lab	46
	Unknown	34
Source of Infection		
	Hospital (nosocomial)	60
	Community	108
	Both	28
	Not stated	304
Specimen Type		
	Blood	67
	Stool	29
	Urine	171
	Wound	29
	Other sterile site	13
	Other non-sterile site	304
	Not stated	128
Method of antimicrobial susceptibility testing		
	Disk-diffusion	399
	E-test	5
	Microdilution Assay	12
	Automated methods	20
	Combination of methods	20
	Not stated	44
Breakpoints for antimicrobial resistance		
	BSAC/EUCAST	19
	CLSI/NCCLS	314
	Other	44
	Not stated	123
Specific age groups		
	Adults only	70
	Children only	82
	No specified age /Adults and children	348
Reported pre-healthcare attendance antibiotic use		
	0%	101
	1-25%	11
	26-50%	10
	51-75%	6
	76-100%	6
	Not stated	355
Syndrome		
	Bloodstream Infections	35
	Urinary tract infections	160
	Wound infection	35
	Otitis media	20
	Other	76
	Multiple syndromes	56
	Not stated	118

Table 4.1: Study characteristics

Study Distribution		Number of Studies
Time Period	1995-1999	13
	2000-2004	28
	2005-2009	61
	2010-2014	213
	2015-2018	193
GBD Super Region		
Latin America & Caribbean		**2**
	Brazil	1
	Colombia	1
Central Europe, Eastern Europe & Central Asia		**8**
	Russia	6
	Kazakhstan	2
High Income		**1**
	Sweden	1
South Asia		**13**
	India	12
	Pakistan	1
Southeast Asia, East Asia and Oceania		**9**
	China	7
	Vietnam	2
North Africa & Middle East		**113**
	Egypt	44
	Iraq	9
	Algeria	6
	Oman	5
	Morocco	7
	Syria	3
	Tunisia	14
	Turkey	1
	Sudan	10
	Libya	8
	Iran	1
	Israel	1
	Jordan	1
	Lebanon	1
	Saudi Arabia	1
	Yemen	1
Sub-Saharan Africa		**336**
	Benin	2
	Botswana	1
	Burkina Faso	6
	Cameroon	7
	Chad	2
	Democratic Republic of the Congo	3
	Ethiopia	51
	Gambia	3
	Ghana	13
	Kenya	20
	Lesotho	1
	Madagascar	8
	Malawi	3
	Mali	3
	Mauritania	1
	Mozambique	5
	Niger	1
	Nigeria	144
	Rwanda	3
	Senegal	7
	Sierra Leone	1
	South Africa	18
	Tanzania	2
	Togo	1
	Uganda	18
	Zambia	1
	Zimbabwe	3
	Cote d'Ivoire	2
	Central African Republic	1
	Gabon	2
	Guinea-Bissau	1
	Namibia	2

Table 4.2: Study distribution over time and GBD super region.

Syndrome	Source Of Infection	
	Community-acquired	Hospital-acquired
Blood Stream Infections	13 (536)	59 (112,699)
Burns	-	16 (976)
Intra-abdominal Sepsis	58 (10,438)	58 (23,084)
Meningitis	4 (40)	-
Otitis Media	11 (205)	-
Pneumonia	-	5 (175)
Post-surgical Sepsis	-	33 (1,084)
Urinary Tract	478 (162,849)	29 (5,122)
Wound Infections	14 (854)	40 (1,895)

Table 4.3: Number of studies (number of isolates). Number of studies reporting each syndrome per source of infection.

The studies collected in the systematic review took place in three different settings, 81% of studies took place in a hospital setting (406/500 studies), 3% took place in the community setting (14/500 studies), 9% took place in a referral lab (46/500 studies) and 7% did not disclose where the study took place (34/500 studies). The age of the patients included in the studies was not specified in 70% of studies (348/500 studies), 16% of studies included only children in the study population (82/500 studies) and 14% of studies included only adults (70/500 studies). Most studies did not state if the infections reported were community or hospital-acquired (61%, 304/500 studies). Of those studies that did state this information, 22% of studies had data on community-acquired infections (108/500 studies), 12% of studies had data on hospital-acquired infections (60/500 studies) and 6% of studies had data on both community and hospital-acquired infections (28/500 studies). Many specimen types were collected for diagnosis of an infection caused by *E. coli*; 34% of studies tested urine samples (171/500 studies), 13% of studies tested blood samples (67/500 studies), 6% of studies tested stool samples (29/500 studies) and 6% of studies tested wound samples (29/500 studies). Specimen type was not recorded in 26% of studies (128/500 studies). Urinary tract infection was a reported syndrome in 32% of studies (160/500 studies), bloodstream infections were reported in 7% of studies (35/500 studies), wound infection was

reported in 4% of studies (20/500 studies) and otitis media was reported in 4% of studies (20/500 studies).

There are several methods for antimicrobial susceptibility testing, 80% of studies reported using the disk diffusion method (399/500 studies), 1% of studies used E-test (5/500 studies), 2% of studies used microdilution assay (12/500 studies), 4% of studies used automated methods (20/500 studies), 4% of studies used a combination of 2 or more of these methods (20/500 studies) and 9% of studies did not state which testing methods used (44/500 studies). Most studies used CLSI/NCCLS breakpoint guidelines (63%, 314/500 studies) for determining antimicrobial resistance, 4% of studies used EUCAST guidelines (19/500 studies), and 25% did not state which breakpoint guidelines they used (123/500 studies). Reporting of patients who took pre-healthcare attendance antibiotics was rarely done, with this information being stated in only 27% of studies (134/500 studies).

4.5 RESULTS: PREVALENCE OF RESISTANCE META-ANALYSIS

Prevalence of resistance is presented for *E. coli* resistance to fluoroquinolones, carbapenems, third-generation cephalosporins, fourth-generation cephalosporins, piperacillin-tazobactam, aminopenicillins, and aminoglycosides. The proportion of resistance for each *E. coli* and antimicrobial combination was calculated for each study in the systematic review using the Agresti-Coull interval method.[81] Intermediate resistant strains were classified as resistant. To stabilize the variance of each study's proportion, a double arcsine transformation was used, and a random-effects meta-analysis quantified the pooled prevalence for each GBD region where the infection was

acquired and the five-year time period in the analysis. Five-year time periods were calculated based on the mid-year of each study and were placed into one of the following: 1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2014, and 2015-2018. The heterogeneity of the data can be seen in the forest plots presented in the appendix (figure A1) and are quantitatively assessed using the I^2 statistic and the corresponding p-value. The statistical analysis was calculated with a 5% significance level using the R statistical software package called "metafor".

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Third generation cephalosporins**						
Central Latin America	-	-	0% [0-9]	-	-	-
Tropical Latin America	-	-	-	-	1% [0-4]	-
Eastern Europe	-	-	4% [3-6]	-	8% [7-10]	54% [47-61]*
Western Europe	-	-	-	-	1% [0-4]	-
East Asia	-	4% [2-5]	22% [15-30]	42% [34-50]	52% [40-65]	41% [11-75]
South Asia	-	-	-	63% [57-69]	69% [57-80]	80% [62-94]*
Southeast Asia	-	-	-	-	7% [1-17]*	-
N. Africa Middle East	-	0% [0-1]	4% [0-16]	29% [17-42]	35% [28-42]	40% [26-56]
C. Sub-Saharan Africa	-	-	0% [0-1]	-	27% [10-48]	-
E. Sub-Saharan Africa	2% [1-4]*	-	27% [14-43]	9% [5-14]	40% [31-49]	39% [27-52]
S. Sub-Saharan Africa	5% [0-20]*	8% [3-16]*	-	7% [0-20]*	18% [5-35]	35% [1-82]
W. Sub-Saharan Africa	0% [0-7]	16% [3-35]	16% [8-26]	18% [13-23]	34% [27-41]	37% [24-51]
Total Studies (Isolates)	**4 (500)**	**13 (48,916)**	**28 (25,019)**	**82 (131,862)**	**189 (202,515)**	**52 (28,679)**
GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Piperacillin-tazobactam**						
Central Latin America	-	-	0% [0-15]*	-	-	-
Eastern Europe	-	-	-	-	11% [6-18]*	8% [4-12]*
East Asia	-	-	6% [2-11]	7% [5-9]	6% [4-7]	3% [3-4]*
South Asia	-	-	-	18% [9-30]	59% [41-75]	68% [48-85]*
N. Africa Middle East	-	-	-	10% [1-26]	10% [4-17]	13% [1-34]
C. Sub-Saharan Africa	-	-	-	-	22% [11-35]*	-
E. Sub-Saharan Africa	-	-	21% [19-23]*	16% [8-26]*	21% [6-41]	-
S. Sub-Saharan Africa	0% [0-8]*	-	-	0% [0-6]*	11% [6-16]	20% [19-22]*
W. Sub-Saharan Africa	-	-	-	12% [8-17]	11% [4-20]	48% [38-58]*
Total Studies (Isolates)	**1 (20)**	**0 (0)**	**4 (5,896)**	**18 (57,871)**	**36 (72,701)**	**13 (12,101)**
GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* Aminopenicillin**						
Central Latin America	-	-	64% [42-84]	-	-	-
Tropical Latin America	-	-	-	-	9% [0-50]	-
Eastern Europe	-	-	53% [48-58]*	-	41% [33-49]	-
Western Europe	-	-	-	-	15% [7-25]	-
East Asia	-	55% [26-82]	-	-	4% [1-11]	48% [0-100]
South Asia	-	-	-	72% [54-87]	78% [73-82]	80% [62-94]*
Southeast Asia	-	-	-	-	54% [6-97]	-
N. Africa Middle East	34% [24-45]	76% [62-88]	52% [20-83]	56% [46-66]	62% [56-68]	51% [32-70]

C. Sub-Saharan Africa	-	-	-	-	87% [77-95]	-
E. Sub-Saharan Africa	57% [20-90]	73% [33-98]	60% [49-70]	61% [49-72]	69% [61-76]	60% [43-76]
S. Sub-Saharan Africa	38% [0-94]	79% [53-97]	-	51% [32-70]	55% [42-69]	30% [28-32]*
W. Sub-Saharan Africa	-	72% [42-94]	68% [58-77]	62% [54-68]	69% [63-75]	48% [31-65]
Total Studies (Isolates)	**8 (1,038)**	**21 (90,554)**	**46 (12,758)**	**113(431,600)**	**211(392,453)**	**48 (26,860)**

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Fourth generation cephalosporins**						
Eastern Europe	-	-	4% [2-6]*	-	7% [5-10]	54% [47-61]*
East Asia	-	-	21% [12-32]	41% [33-49]	45% [35-55]	40% [39-41]*
South Asia	-	-	-	55% [35-73]	71% [62-79]	-
N. Africa Middle East	-	0% [0-0]	0% [0-1]*	35% [4-76]	28% [18-39]	63% [42-81]
C. Sub-Saharan Africa	-	-	-	-	17% [8-30]*	-
E. Sub-Saharan Africa	-	-	9% [7-11]*	15% [9-22]	26% [0-98]	26% [2-63]
S. Sub-Saharan Africa	0% [0-8]*	-	-	-	6% [4-9]*	18% [16-19]*
W. Sub-Saharan Africa	-	-	-	-	12% [0-43]	7% [3-13]*
Total Studies (Isolates)	**1 (20)**	**1 (2,974)**	**6 (9,645)**	**17 (57,447)**	**43 (88,625)**	**15 (12,339)**

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Fluoroquinolones**						
Central Latin America	-	-	27% [4-58]*	-	-	-
Tropical Latin America	-	-	-	-	6% [2-12]	-
Eastern Europe	-	-	4% [2-6]*	-	13% [7-21]	12% [5-21]
Western Europe	-	-	-	-	6% [2-12]	-
East Asia	-	13% [12-14]	57% [31-82]	65% [58-71]	62% [57-67]	44% [42-46]
South Asia	-	-	-	69% [55-82]	70% [65-76]	96% [84-100]*
Southeast Asia	-	-	-	-	33% [20-48]*	-
N. Africa Middle East	-	15% [0-54]	14% [2-35]	37% [28-47]	39% [33-45]	40% [29-52]
C. Sub-Saharan Africa	-	-	8% [4-13]*	-	45% [30-60]	-
E. Sub-Saharan Africa	10% [7-13]*	0% [0-1]*	1% [0-3]	10% [5-15]	32% [25-39]	21% [9-35]
S. Sub-Saharan Africa	0% [0-8]*	0% [0-2]	3% [1-4]	18% [16-21]	21% [16-27]	19% [6-37]
W. Sub-Saharan Africa	0% [0-7]	5% [1-12]	19% [13-26]	26% [21-31]	36% [30-43]	28% [20-37]
Total Studies (Isolates)	**4 (500)**	**14 (48,530)**	**50 (18,071)**	**120(450,781)**	**207(411,171)**	**53(30,001)**

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Carbapenems**						
Central Latin America	-	-	0% [0-15]*	-	-	-
Eastern Europe	-	-	0% [0-1]*	-	0% [0-0]	7% [5-10]
East Asia	-	0% [0-1]	0% [0-1]	1% [1-1]	1% [1-2]	1% [1-1]
South Asia	-	-	-	2% [0-4]	13% [3-27]*	52% [38-66]
N. Africa Middle East	-	0% [0-0]	0% [0-0]	7% [0-18]	3% [1-5]	18% [7-33]
C. Sub-Saharan Africa	-	-	-	-	1% [0-8]	-
E. Sub-Saharan Africa	-	-	-	1% [0-4]	1% [0-4]	2% [0-6]
S. Sub-Saharan Africa	0% [0-8]*	-	-	1% [0-7]	0% [0-1]	0% [0-0]
W. Sub-Saharan Africa	-	1% [0-4]*	0% [0-1]	-	5% [1-11]	22% [2-54]
Total Studies (Isolates)	**1 (20)**	**3 (43,155)**	**11 (13,534)**	**33 (115,844)**	**133 (248,402)**	**34 (30,045)**

GBD Region	Pooled prevalence of resistance (%) [95% confidence interval]					
	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
***E. coli* - Aminoglycosides**						
Central Latin America	-	-	9% [1-23]	-	-	-
Tropical Latin America	-	-	-	-	2% [0-9]*	-
Eastern Europe	-	-	5% [0-18]	-	5% [1-12]	47% [15-81]
Western Europe	-	-	-	-	3% [0-8]	-
East Asia	-	15% [2-36]	8% [5-12]	21% [10-35]	19% [8-34]	19% [2-48]
South Asia	-	-	-	19% [11-30]	65% [57-73]	60% [40-79]*
Southeast Asia	-	-	-	-	21% [10-35]*	-
N. Africa Middle East	0% [0-3]	2% [0-8]	25% [5-52]	19% [12-27]	14% [10-17]	29% [16-44]

C. Sub-Saharan Africa	-	-	1% [0-5]	-	26% [16-37]	-
E. Sub-Saharan Africa	8% [6-11]*	3% [0-10]	16% [14-18]	14% [9-19]	19% [13-26]	22% [11-36]
S. Sub-Saharan Africa	12% [3-25]	11% [6-16]	12% [10-14]	6% [4-9]	10% [6-16]	20% [2-49]
W. Sub-Saharan Africa	0% [0-12]*	42% [0-93]	18% [8-32]	28% [21-35]	31% [24-39]	24% [14-36]
Total Studies (Isolates)	**6 (586)**	**22 (93,658)**	**43 (14,627)**	**118 (493,359)**	**205 (518,575)**	**49 (40,351)**

*Table 4.4: Pooled prevalence of resistance in fluoroquinolones, aminoglycosides, aminopenicillin, piperacillin-tazobactam, fourth generation cephalosporin, third generation cephalosporin and carbapenem resistance in E. coli. The pathogen and antimicrobial combination are listed in the green bar, with the GBD region listed underneath. Follow the meta-analysis numbers across to follow the antimicrobial resistance in that region over time. The interquartile range is listed in [ ] next to the proportion resistance. The total number of studies and isolates is listed at the bottom of each species category. *Indicates subgroups with only one study, for which prevalence and calculated 95% confidence intervals are displayed.*

4.5.1 *E. COLI* – FLUOROQUINOLONES

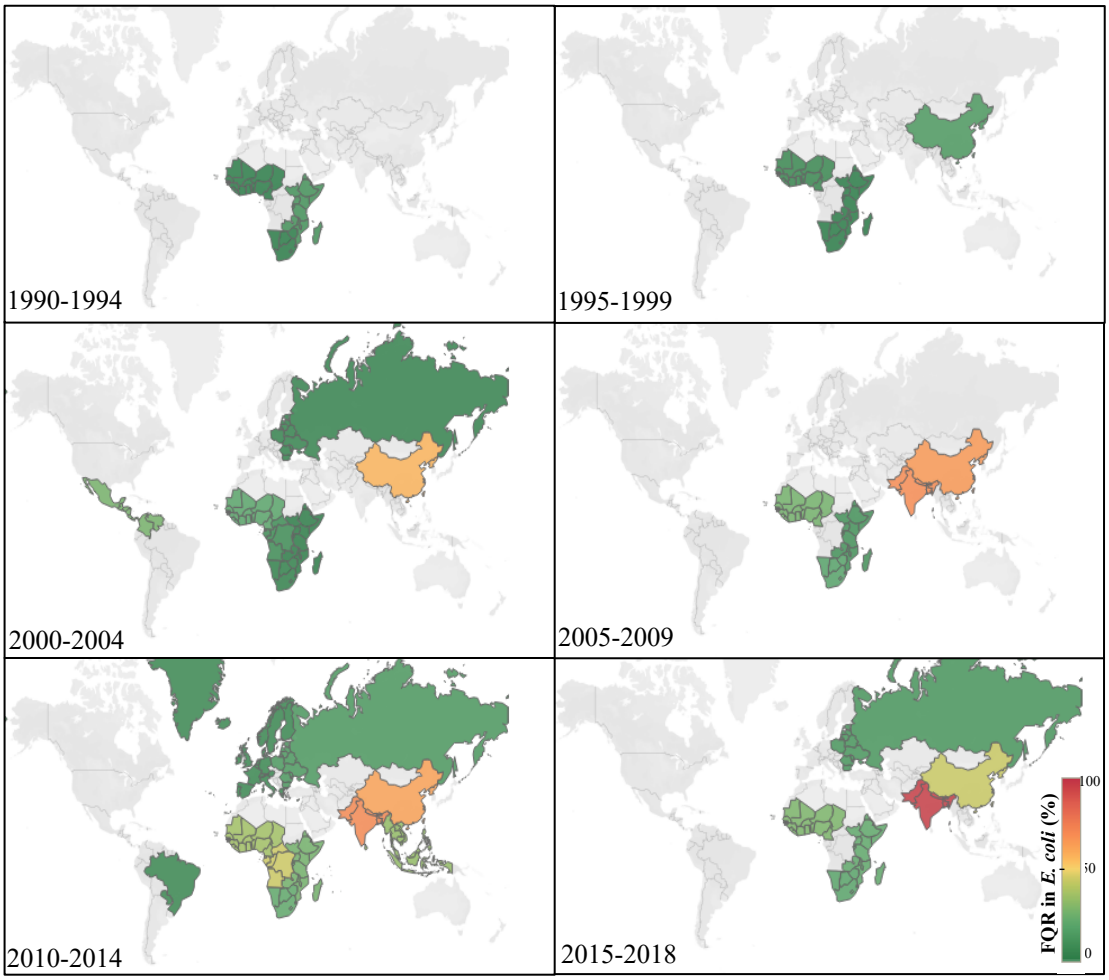

Figure 4.7: Prevalence of FQR in E. coli by GBD region and time period. Grey shading indicates no data.

FQR in *E. coli* is widespread and increasing. The systematic review collected 959,054 *E. coli* isolates tested for FQR. Figure 4.7 shows the highest prevalence of resistance in South Asia in 2005, where FQR was 69% and increased to 96% in 2018. East Asia also

reported high resistance, with 13% in 1995, 65% in 2005, and 44% in 2015. North Africa and the Middle East had similar resistance as East Asia, with 13-15% in 1995 which increased to 40-44% in 2018. Central and Tropical Latin America had lower resistance, with 27% in 2000 in Central Latin America and only 6% resistance in Tropical Latin America. Europe also had lower resistance with 4% resistance in 2000 in Eastern Europe, which only raised to 12% in 2018 and Western Europe found 6% resistance in 2010. Eastern, Southern and Western sub-Saharan Africa all had similar trends of resistance over the study period reporting 0-10% resistance in 1990 and increasing up to 19-28% in 2018.

4.5.2 *E. COLI* – CARBAPENEMS

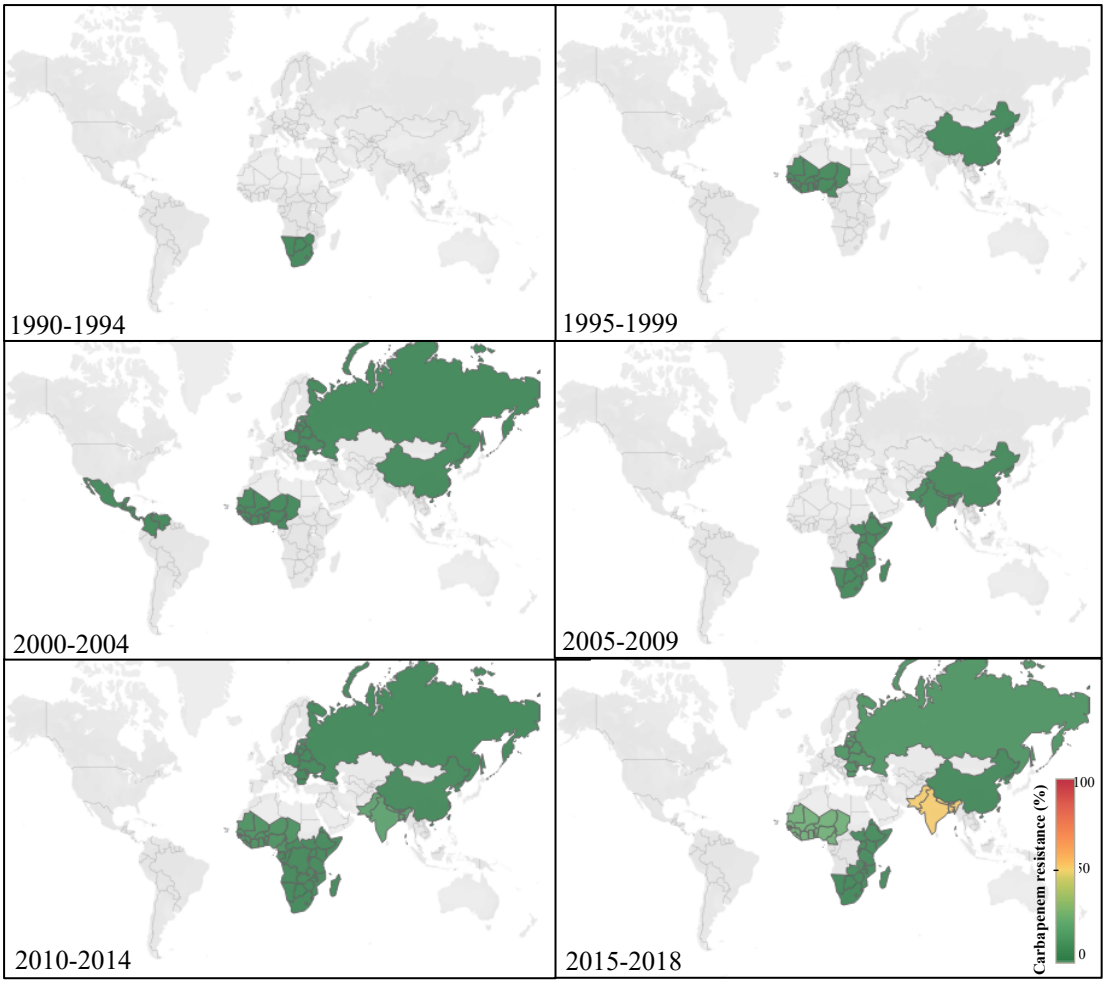

Figure 4.8: Prevalence of carbapenems resistance in E. coli by GBD region and time-period. Grey shading indicates no data.

There were 451,000 *E. coli* isolates tested for carbapenem resistance collected in the systematic review. Overall, *E. coli* has the least resistance to carbapenems out of the antimicrobials discussed in this chapter, with the highest rate recorded in South Asia at 52% in 2018. East Asia only reported 0% in 1995 with a slight increase to 1% throughout 2005-2018. Both Central Latin America and Southern sub-Saharan Africa reported 0-1% resistance to carbapenems. Eastern sub-Saharan Africa had 1% resistance from 2005-2014 and raised to 2% in 2018. Western sub-Saharan Africa reported 1% resistance in 1995, a much higher increase to 22% in 2015. North Africa and the Middle East had similar trends to Western sub-Saharan Africa, with 0-1% resistance in 1995 with a rise to 19-22% in 2015. Eastern Europe has gradually increased resistance from 0% to 7% in 2018.

4.5.3 *E. COLI* - THIRD-GENERATION CEPHALOSPORIN

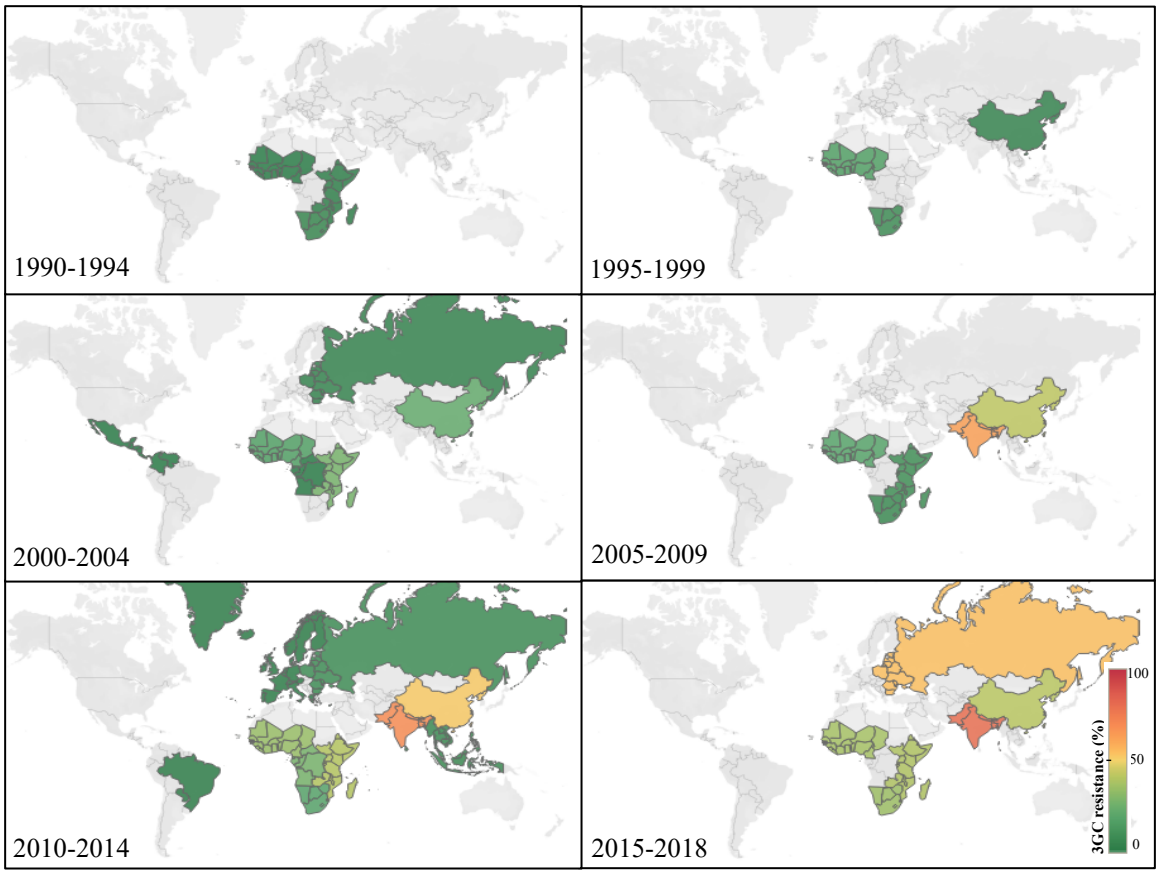

Figure 4.9: Prevalence of third-generation cephalosporin resistance in E. coli by GBD region and time-period. Grey shading indicates no data. 3GC = third-generation cephalosporin.

A total of 437,491 *E. coli* isolates were tested for third-generation cephalosporin resistance collected in the systematic review. *E. coli* resistance to third-generation cephalosporins has increased over the study period. Eastern Europe recorded 4% resistance in 2004, 8% in 2010 and 54% in 2018. East Asia also had an increase in resistance over time, reporting 4% resistance in 1995, 42% in 2005, and 41% in 2018. North Africa and the Middle East experienced a similar trend, with 0% resistance in 1995, 29% in 2005, and 40% in 2015. Eastern, Southern, and Western sub-Saharan Africa had a similar pattern of carbapenem resistance with 2%, 5%, and 0% resistance, respectively, in 1990 and increased to 39%, 35%, and 37% resistance, respectively, in 2018. Less data was available for Central sub-Saharan Africa, but a similar trend can be seen with 0% in 2000 and then increased to 27% in 2007. Central Latin America reported the lowest resistance at 0% in 2000.

4.5.4 *E. COLI* - FOURTH-GENERATION CEPHALOSPORIN

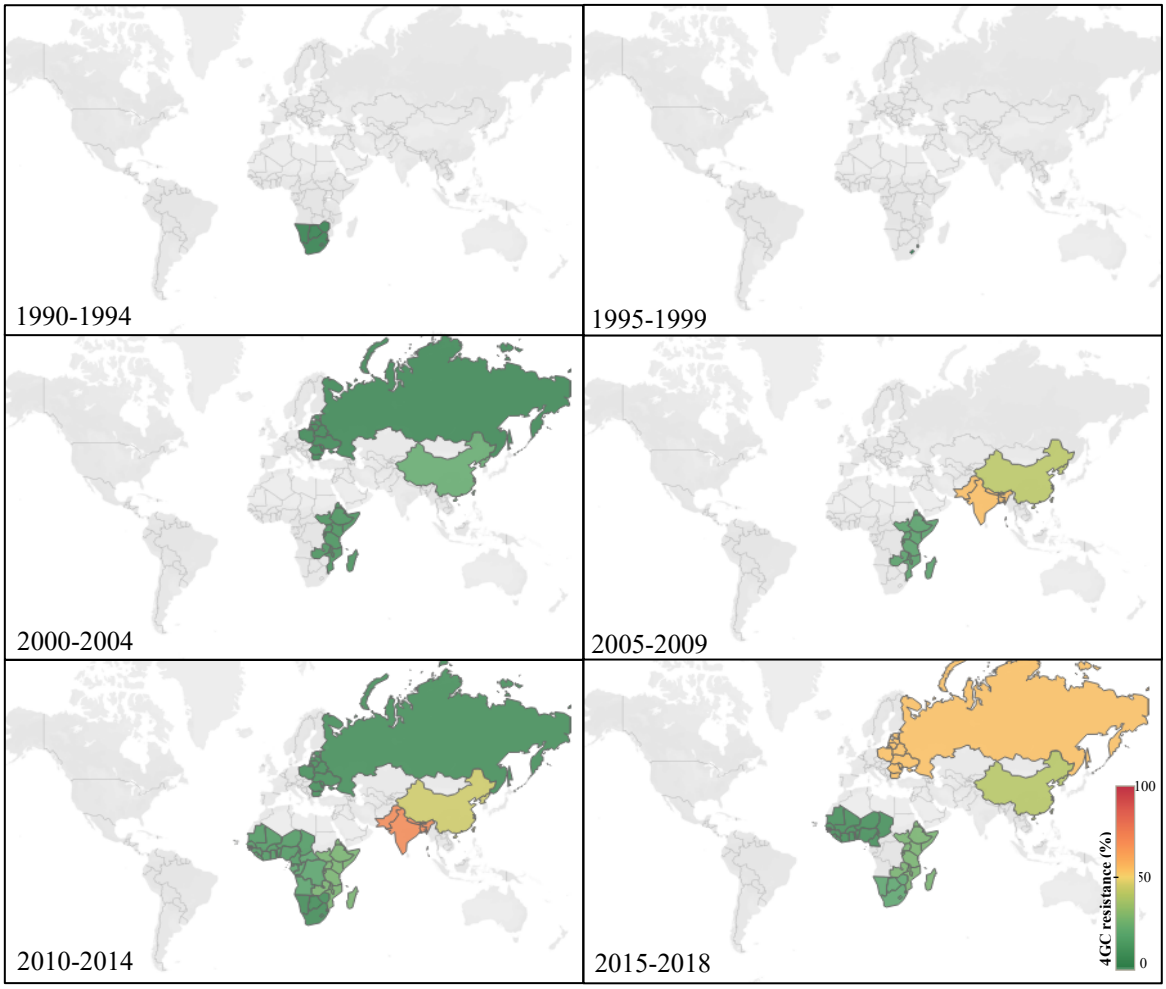

Figure 4.10: Prevalence of fourth-generation cephalosporin resistance in E. coli by GBD region and time-period. Grey shading indicates no data. 4GC = fourth-generation cephalosporin.

There were 171,023 *E. coli* tested for fourth-generation cephalosporin resistance in the systematic review. South Asia reported the highest resistance at 71% in 2010. Behind South Asia with the highest resistance were Eastern Europe, East Asia, and North Africa and the Middle East in 2018 at 54%, 40%, and 63% resistance, respectively. Eastern sub-Saharan Africa reported 9% resistance in 2000, increasing to 26% in 2018. Southern sub-Saharan Africa had slightly lower resistance with 0% in 1990 and increased up to 18% in 2018. Less data was available for Central sub-Saharan Africa,

which reported 17% resistance in 2010, and Western sub-Saharan Africa reported 12% in 2010 and 7% resistance in 2018.

4.5.5 *E. COLI* - PIPERACILLIN-TAZOBACTAM

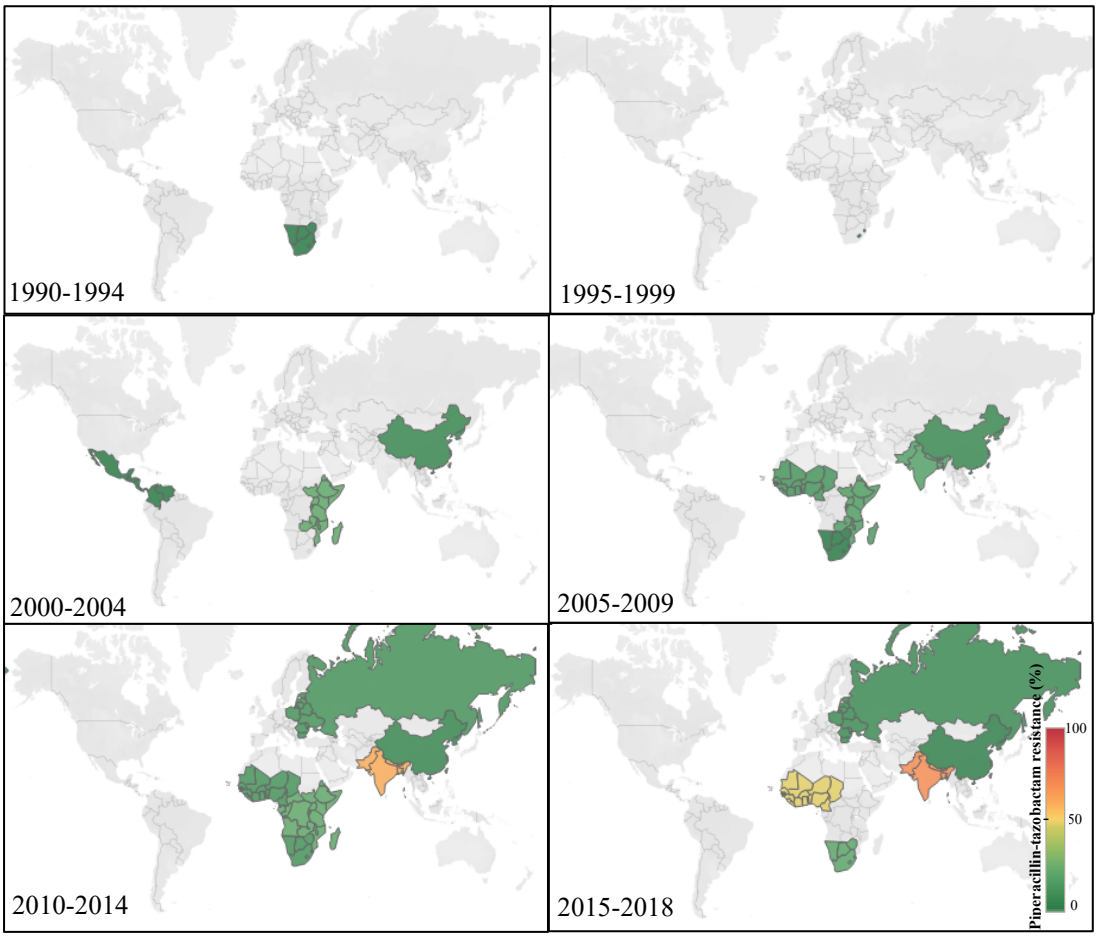

Figure 4.11: Prevalence of piperacillin-tazobactam resistance in E. coli by GBD region and time-period. Grey shading indicates no data.

The systematic review tested 171,023 *E. coli* isolates for piperacillin-tazobactam resistance. South Asia saw a steady increase in resistance over the years, reporting 18% in 2005, 59% in 2012, and 68% in 2018. Central Latin America, Eastern Europe, East Asia and North Africa and the Middle East have the lowest resistance. Central Latin America reported 0% resistance in 2000, Eastern Europe reported 8-11% resistance in 2010-2018, East Asia reported 3-6% in 2000-2018, North Africa and the Middle East

reported 10-13% from 2005-2018. Eastern sub-Saharan Africa had 21% resistance from 2000-2018, Southern sub-Saharan Africa had an increase in resistance from 0% in 1990 to 20% in 2018, and Western sub-Saharan Africa also saw a rise from 12% in 2005 to 48% in 2018.

4.5.6 *E. COLI* – AMINOPENICILLIN

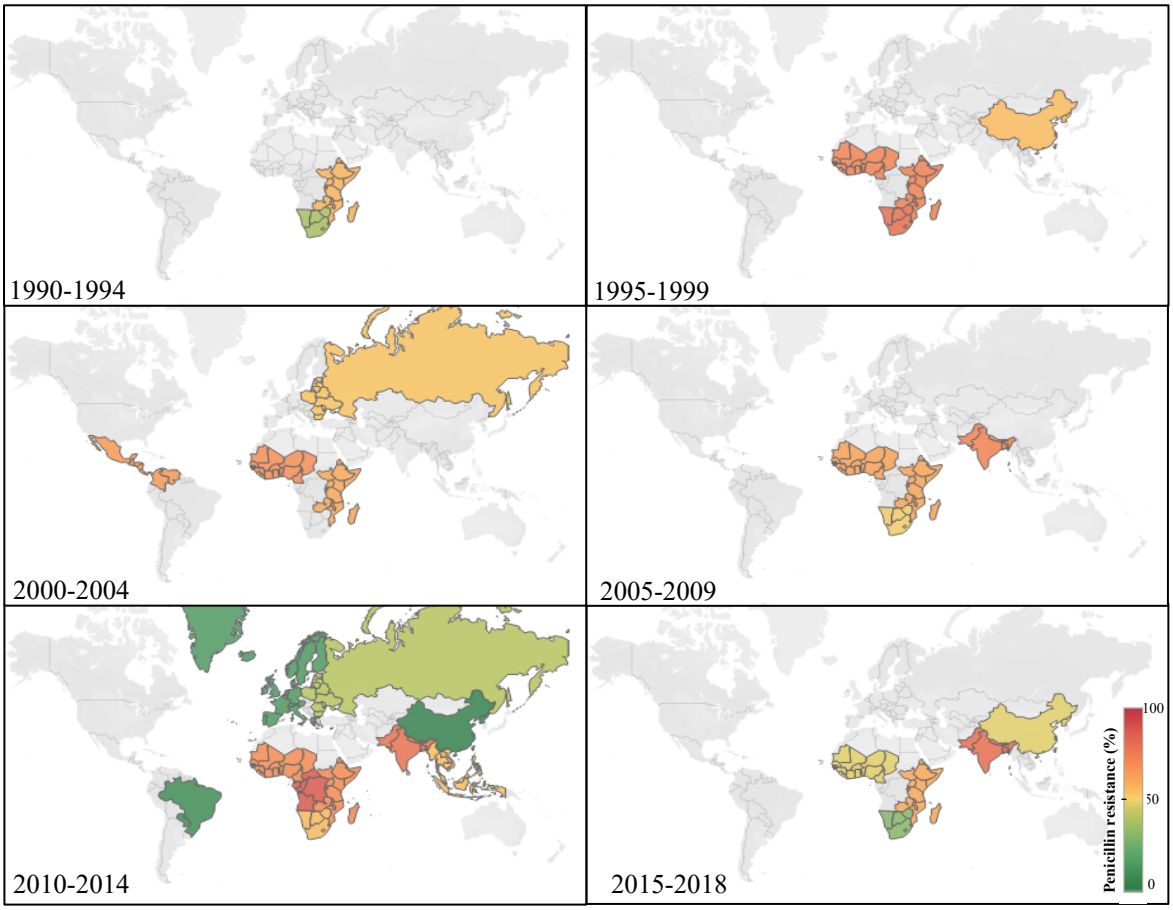

Figure 4.12: Prevalence of aminopenicillins resistance in E. coli by GBD region and time-period. Grey shading indicates no data.

E. coli resistance to aminopenicillins is widespread and has remained relatively high throughout the study. The systematic review tested 148,591 *E. coli* isolates for aminopenicillin resistance. In Eastern and Southern sub-Saharan Africa, resistance was recorded to have 57% and 38% resistance, respectively, in 1990, and in 2010 both had 69% resistance. East Asia reported 55% resistance in 1995 and slightly declined to 48%

in 2018. South Asia reported 72-80% from 2005-2018, and Southeast Asia reported lower resistance with 54% in 2010. North Africa and the Middle East were consistently high, with 34% resistance in 1990, 56% in 2005, and 51% in 2018. Less data was available for Latin America across the study period, Central Latin America had 64% resistance from 2000-2004, and Tropical Latin America had 9% resistance from 2010-2014.

4.5.7 *E. COLI* – AMINOGLYCOSIDES

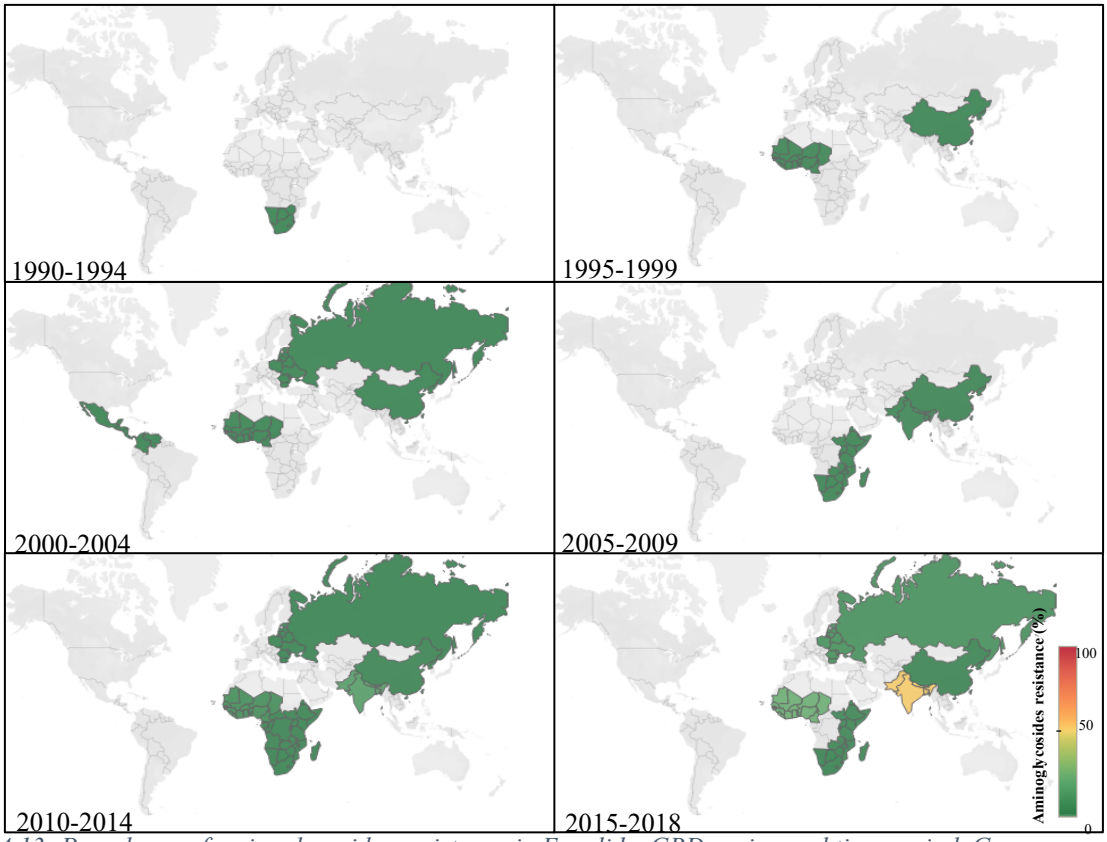

Figure 4.13: Prevalence of aminoglycosides resistance in E. coli by GBD region and time-period. Grey shading indicates no data.

There were 1,190,156 *E. coli* isolates tested for aminoglycoside resistance. Resistance gradually increased in sub-Saharan Africa, Eastern sub-Saharan Africa reported 8% in 1990, 16% in 2004, and 22% in 2018, Southern sub-Saharan Africa reported 12% in 1990, 12% in 2004, and 20% in 2018, and Western sub-Saharan Africa reported 0% in

1990, 18% in 2004 and 24% in 2018 and Central sub-Saharan Africa reported 1% in 2004 and 26% in 2014. East Asia had a minimal increase with 15% resistance in 1994 and 19% in 2018, whereas South Asia increased more drastically with 19% resistance in 2005 and 60% in 2018. Eastern Europe also saw a dramatic increase, with 5% resistance in 2000 and 47% in 2018. Latin America and Western Europe had low resistance, with only 2% in 2014 in Tropical Latin America, 9% in 2000 in Central Latin America, and 3% in 2014 in Western Europe. North Africa and the Middle East reported 0% resistance in 1990, 25% in 2000, and 29% in 2018.

4.6 DISCUSSION

This systematic review provides an in-depth overview of the global situation regarding AMR in human isolates of *E. coli*. Data were extracted from 500 studies, comprising of 4,304,273 isolates from 57 countries around the world. The systematic review builds on previous knowledge by using a comprehensive search strategy, including all countries, and identifying trends in resistance over 28 years. Locations with a scarcity of susceptibility data have been identified, and efforts in data seeking can be focused on those locations. Antimicrobial susceptibility data for *E. coli* is presented according to country, geographical region, and period. Geographical regions are defined according to the GBD regional classification system.

E. coli resistance varies greatly depending on the region and antimicrobial of interest. In the 1990s, *E. coli* was the most resistant to aminopenicillins, with high resistance in North Africa, the Middle East, East Asia, and sub-Saharan Africa. In 1995, high resistance to aminoglycosides was reported in Western sub-Saharan Africa. High resistance to fluoroquinolones began in the early 2000s in East Asia. The mid to late

2000s is when resistance became more widespread across the globe and across antimicrobial classes. High fluoroquinolone resistance was seen in Asia, North Africa, and the Middle East. High resistance to third-generation and fourth-generation cephalosporins was seen throughout South and East Asia. From 2010-2018 resistance was the highest overall in all antimicrobials. Resistance to fluoroquinolones was high throughout Asia, North Africa, the Middle East, and sub-Saharan Africa. Resistance to third-generation cephalosporins was high in Eastern Europe, South and East Asia, and sub-Saharan Africa. Resistance to fourth-generation cephalosporins was high in Eastern Europe, East, and South Asia, North Africa, and the Middle East. Resistance to piperacillin-tazobactam was high in South Asia and Western sub-Saharan Africa. Resistance to aminoglycosides was high in Eastern Europe and South Asia. Resistance to aminopenicillins was high throughout the study period from 1990-2018 around the globe, and resistance to carbapenems remained low from 1990-2018 across the world except in South Asia (52% resistance) from 2015-2018.

There are several limitations to this study. Although data was collected on several antimicrobials, most of the data available was on fluoroquinolone resistance and therefore there was too little data to model other pathogen-antibiotic combinations at this stage. Minimum Inhibitory Concentration (MIC) values were only reported in 7/500 studies included in the systematic review, therefore, it was not possible to harmonize breakpoint changes over time and between different breakpoint guidelines. Analysis and further discussion of the potential bias in data from breakpoint changes can be found in Chapter 6. Data collected from the systematic review may be subjected to several other biases as most of the data collected was from patients presenting at hospitals. Patients seeking healthcare at a hospital will most commonly have the most

severe disease leading to an underestimation of the prevalence of the disease and, therefore, an overestimation of the proportion of resistance in the community. These patients may have already attempted to self-treat with antibiotics and, when symptoms persisted, proceeded to seek treatment at a hospital. As many *E. coli* caused diarrheal illnesses can be self-limiting, many living in low and middle-income countries have access to antibiotics without a prescription in the community, and their data is never captured at a hospital.

Many limitations in this systematic review are similar to those discussed in Chapter 2 regarding the *Shigella* systematic review and are summarized here. Diagnostic samples may not be collected or tested for antimicrobial resistance at the physicians' discretion or are dependent on access to necessary resources to perform tests. If tests are performed, the availability of testing methods may be limited, or the lab may not be of a high standard resulting in low accuracy of test results. Data from systematic reviews may be biased by publication bias. Although the search strategy was written to be exhaustive and several databases were searched, it is possible papers written in foreign languages was missed due to papers not being indexed. Studies reporting less than 50 isolates, of which antimicrobial sensitivity testing was performed, were removed from the analysis to reduce some bias. Study populations may not always be representative due to variations in available antibiotic testing discs.

This systematic review was not fully completed as many papers that met the inclusion criteria are not yet extracted. The *Shigella* systematic review took four months to complete, which started with 3,663 studies, and data from 521 studies was extracted. Based on this information, it was concluded that it would take over four years to

complete this systematic review in its entirety with a starting library of 79,000 studies. To make completing the systematic review more feasible without compromising on the validity checks within the methods, data extraction was done by region of priority. The first region of focus was Africa due to the lack of data from Africa from other data sources, which can be seen in Figures 4.1 and 4.2. Once the systematic review data from Africa was combined with data obtained through other sources, any remaining gaps in the data set became the next region of priority in the systematic review. Additional data was extracted from East Asia, Central Asia, South Asia, Eastern Europe, the Middle East, and Central and Tropical Latin America.

Efforts to decrease the transmission of *E. coli* are essential to curb this global crisis. Health education is a vital tool to bring awareness to behavior change that can have a significant impact. These include hand washing and improved good hygiene practices, access to a clean water supply and learning how to clean water effectively, proper disposal of human waste, understanding food safety practices, and proper antimicrobial use. It is often the case where an individual will choose to misuse an antimicrobial as the benefit of recovery outweighs the risks. Additionally, infection control within hospitals is an essential tool to decrease the transmission of *E. coli* in the hospital and the community. This includes hand washing and proper sanitary practices and serving properly cooked food. Antimicrobial resistance in *E. coli* differs depending on geographic location and time, therefore, continuous monitoring is necessary for specific and effective treatments to be recommended. Lack of access to antimicrobials can result in an increased amount of deaths, however, a lack of regulations and an inefficient surveillance system can render the antimicrobials available ineffective.

A comprehensive review of the published literature reveals widespread resistance to many antimicrobial classes. To produce a complete picture of AMR in *E. coli*, this work will be supplemented with additional data from surveillance systems and collaborators to facilitate geospatial disease mapping to estimate the global burden of AMR in *E. coli* to several antimicrobial classes.

CHAPTER **5**

Global Geospatial Modelling of Antimicrobial Drug Resistance in *E. coli,* 2000-2020

5.1 INTRODUCTION

The GRAM study reported that 1.27 million deaths were caused by drug-resistant infections, placing AMR as the leading cause of death globally, particularly in LMICs.[4] *E. coli* was found to be responsible for the most deaths attributable to AMR. Resistance to carbapenems, fluroquinolones[114] and cephalosporins is spreading rapidly resulting in a major global health threat.[115] This is worrying as cephalosporins are used most often to treat Gram-negative infections.[115] The prevalence of resistance to carbapenems, fluoroquinolones, and third-generation cephalosporins is important to understand at the national level so countries can take measures to not worsen this issue. Knowing which antimicrobials have the lowest and highest prevalence of resistance within the community is a helpful tool when deciding on treatment recommendations and antimicrobial availability. This data can also aid in shaping laws and regulations regarding antimicrobial accessibility and antimicrobial misuse. These practices can not only save lives but also can help save money, as treatment failure, longer hospital stays, and severe illness can cost a substantial amount.

A global dataset was compiled to model national estimates of the prevalence of resistance in *E.coli* worldwide. Data were obtained from multiple sources, including published studies, directly from collaborators on the GRAM project[94], members of the GBD

Collaborator Network, and other data providers. The prevalence of resistance was modeled for key pathogen-antibiotic combinations across 204 countries and 182 territories from 2000 to 2020. This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting recommendations[95].

5.2 DATA SOURCES DESCRIPTION

Line level and aggregate microbiological data from several sources were combined to provide a comprehensive data set for each pathogen and antimicrobial combination. Data were collected in a systematic review (described in Chapter 4), from surveillance systems, and directly from GRAM project collaborators, GBD collaborators, academic institutions, pharmaceutical companies, and individual hospitals. The data were linked to the country and year the infection was acquired. In total, 16,577,845 test results were gathered for various important pathogen-antibiotic combinations in this envelope. A detailed description of the available data for *E. coli* and fluoroquinolones, *E. coli* and third-generation cephalosporins, and *E. coli* and carbapenems resistance can be found in the appendix. Antibiotics with <5% country year coverage for the 204 countries and 20 years of data input matric and with two or more regions with no data, were excluded from the modeling for this pathogen due to data coverage and representativeness concerns.

Microbiological data was supplemented with systematic reviews following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[80]. This published resistance data were collected from countries and territories where surveillance systems do not routinely collect data to ensure extensive

coverage of the pathogen-antibiotic combination of interest. Data on the prevalence of AMR were extracted from published literature and compiled into comprehensive datasets. The systematic review completed PRISMA checklists, PROSPERO registration, and detailed descriptions can be found in the appendix. Extraction forms were created, and screening and data extraction were completed using DistillerSR.

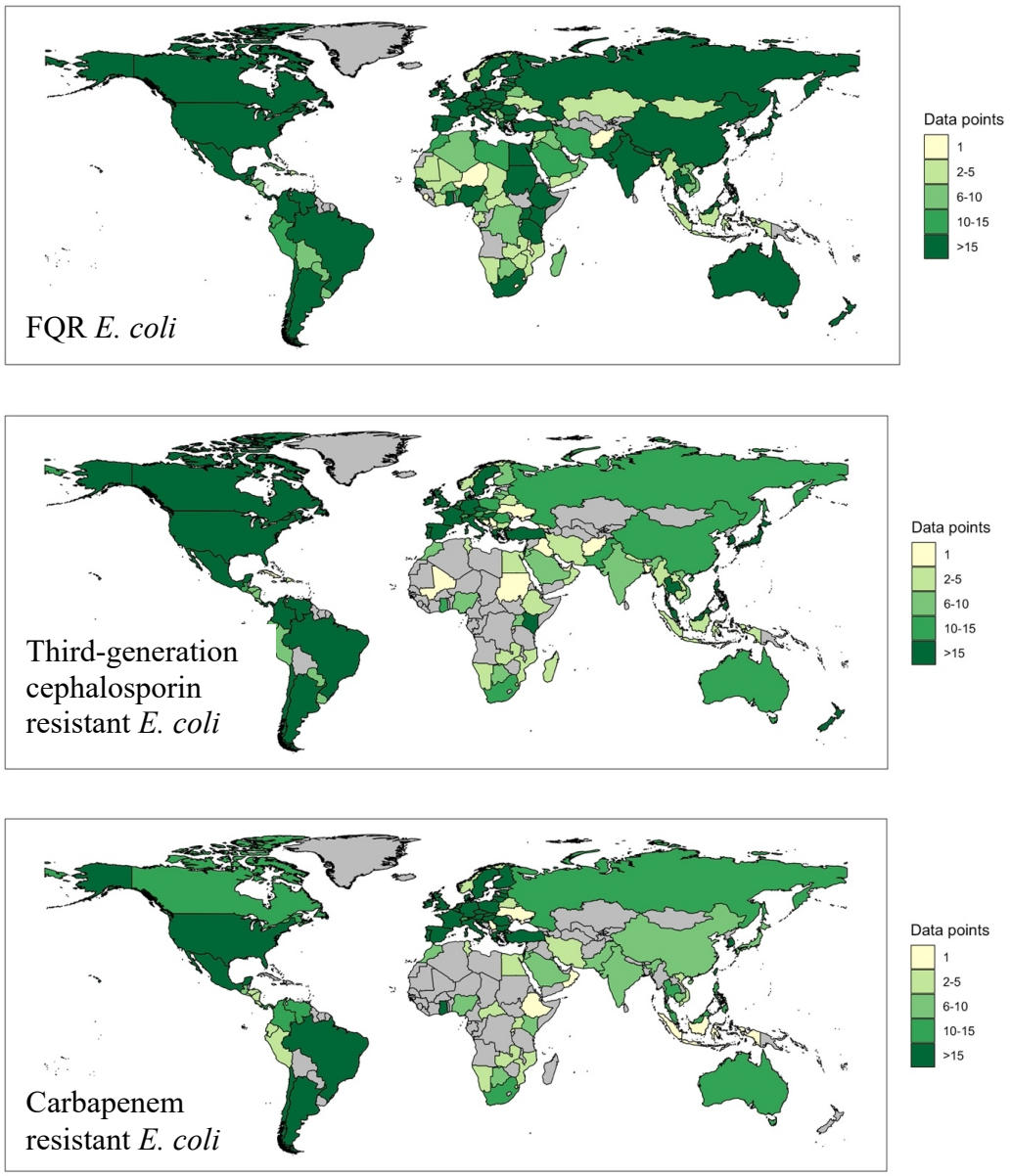

Figure 5.1: Data coverage by data points in each country where data was available.

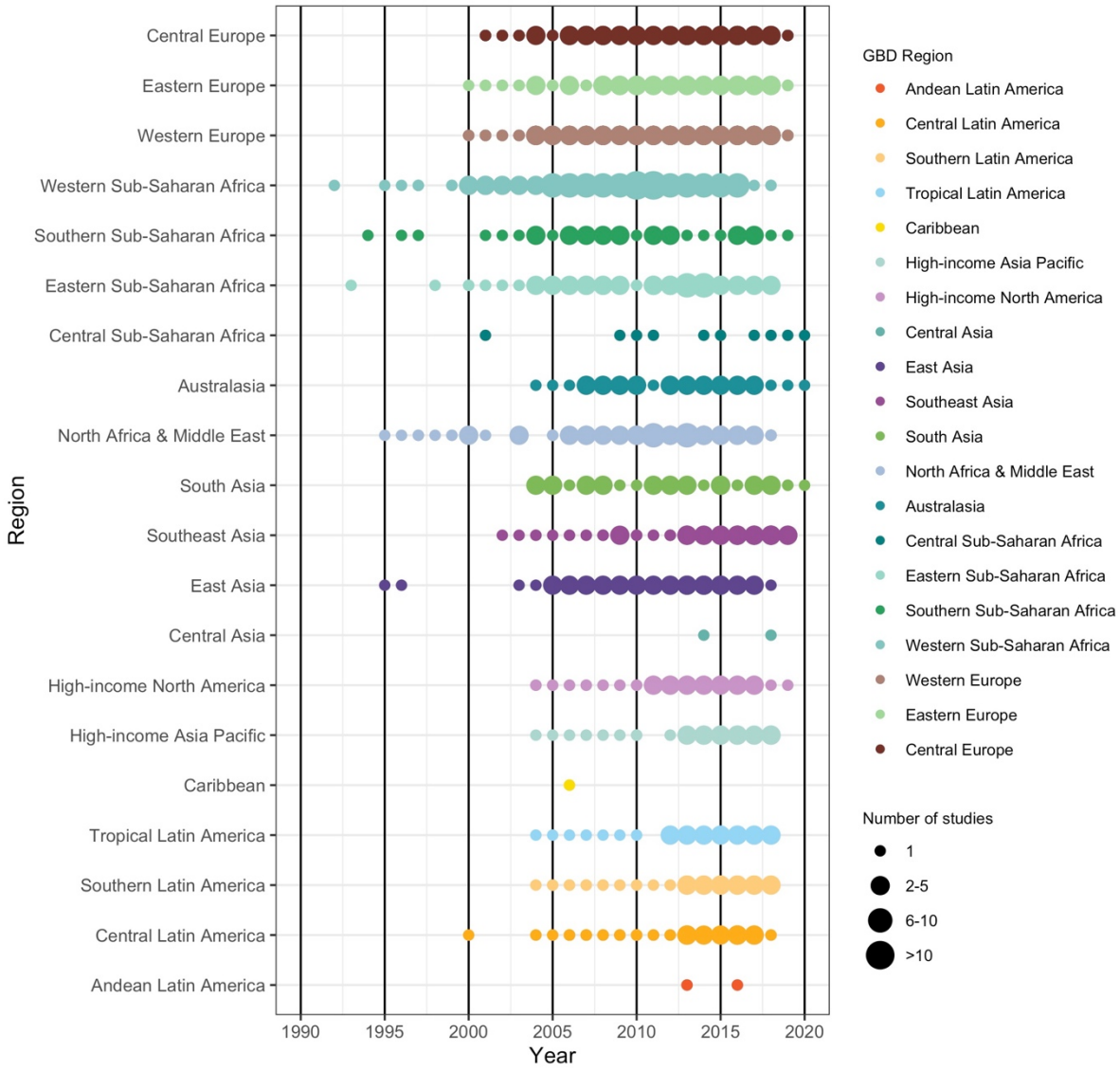

Figure 5.2: FQR E. coli Data availability by year and country. All included data are plotted by country (y-axis) and year (x-axis), grouped by GBD region. The size of the point depicts the number of studies for each country year.

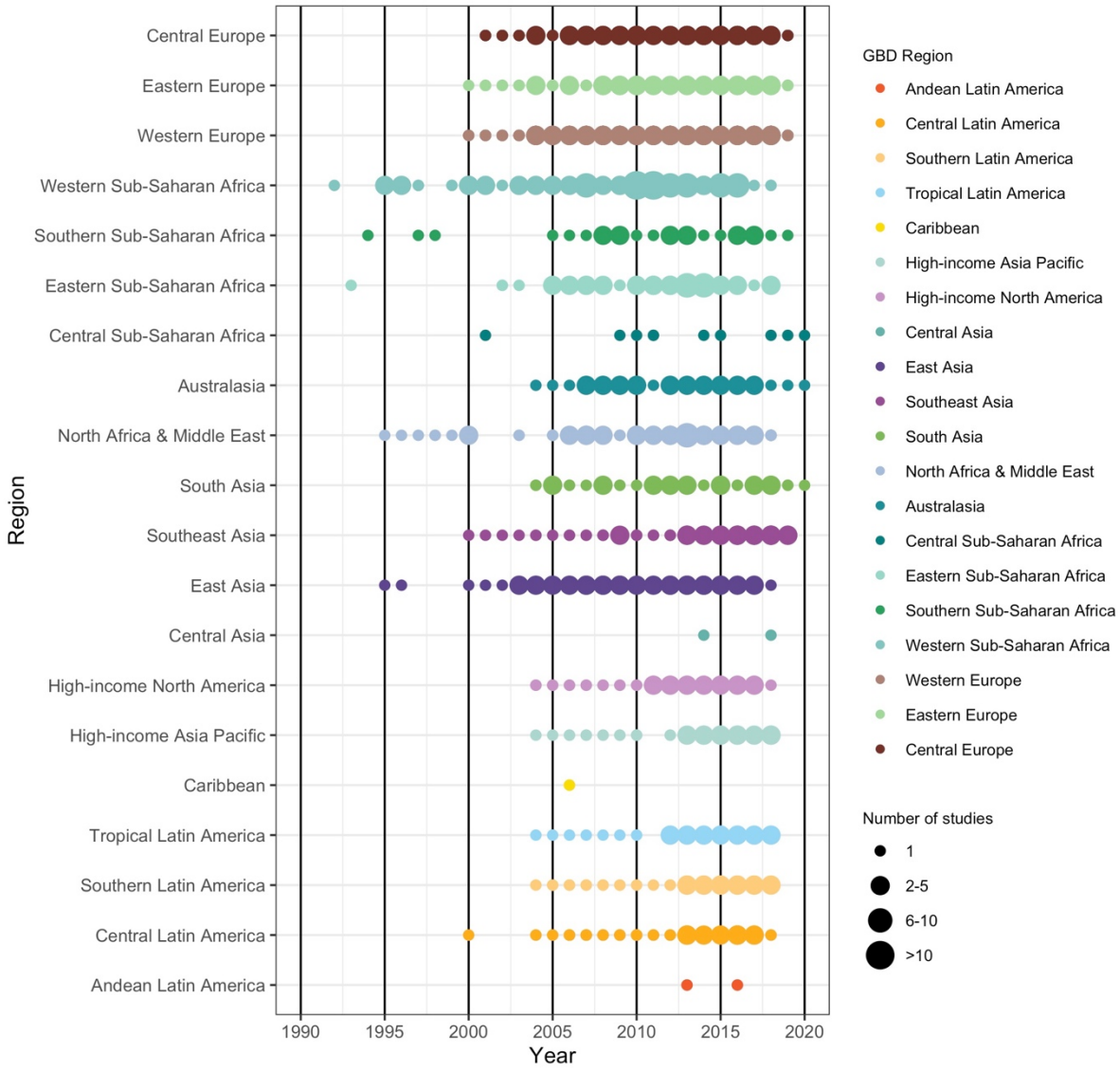

Figure 5.3: Third-generation cephalosporin resistant E. coli data availability by year and country. All included data are plotted by country (y-axis) and year (x-axis), grouped by GBD region. The size of the point depicts the number of studies for each country year.

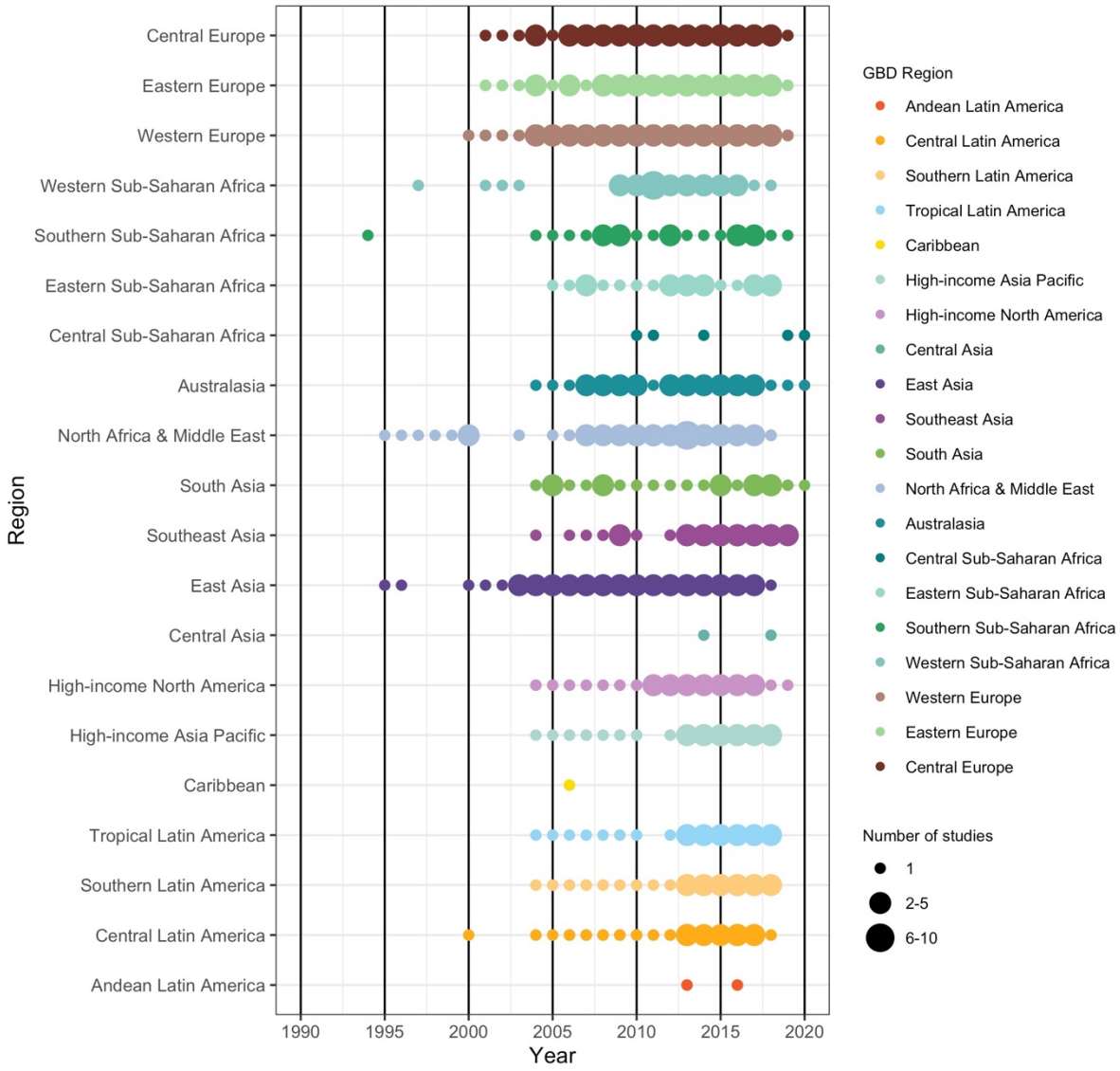

Figure 5.4: Carbapenem resistant E. coli data availability by year and country. All included data are plotted by country (y-axis) and year (x-axis), grouped by GBD region. The size of the point depicts the number of studies for each country year.

5.3 LIMITATIONS OF DATA

Many limitations in the *E. coli* dataset restricted the ability to do several analyses. There is a lack of data on whether the infection was hospital-acquired or community-acquired. Only 12 datasets stated if the infection was community-acquired, and 35 indicated if the infection was hospital-acquired. This led to the inability to model this data separately, and assess the difference in resistance in hospital-acquired or community-

acquired infections. Specimen type was also missing from many datasets, limiting the ability to do an analysis only using isolates that were isolated from sterile specimens. In addition, similar to what was seen in the *Shigella* dataset, many details of the methods used to test for antimicrobial sensitivity, laboratory quality, and sampling methodology were missing. Furthermore, many studies or datasets did not include the hospital, lab, or city in which the data was collected.

Another limitation in the *E. coli* dataset is data availability. Figure 5.1 shows there is still a significant data gap in the majority of Africa, despite having conducted a systematic review with the main focus on data from Africa. The more data to feed into the geospatial model, the more accurate the estimates will be. These data gaps maintain the need to use geospatial modeling to provide estimates of the prevalence of resistance and to best inform the public of the current state of this issue in their country.

Lastly, data was modeled for 2000-2020 as there was a significant gap in data for 1990-1999 when data was broken down by separate antimicrobial combinations.

5.4 GEOSPATIAL MODELLING METHODS

Outputs from the above sections were used to model the proportion of *E. coli* exhibiting fluoroquinolone resistance, carbapenem resistance, and third-generation cephalosporins and produce temporal maps at the national level. The input data is the proportion of isolates resistant to the specified antibiotics linked to the year and location infection was acquired (or hospital where patients presented). Hospital data wa reassigned to the pixels where the infection was most likely acquired, using a k-means

clustering method and weighted by the pixels population size and the likelihood of attending the hospital. This was then be modeled using the two-stage ST-GPR framework.

A two-stage spatiotemporal modeling framework was employed to estimate the prevalence of resistance in each priority pathogen-antibiotic combination for 204 countries by year from 2000 to 2020. First, a stacked ensemble model was fit between the input data and selected covariates within the list of plausible and health-related covariates available in GBD. Furthermore, estimates of antibiotic consumption were tested and incorporated [116]. The input covariate list was narrowed down using a lasso (penalized) regression model for each pathogen-antibiotic combination to help select the most influential covariates for each combination to be used in the stacked ensemble stage. The out-of-sample estimates of the stacked ensemble model[96] were then input into an adapted bespoke ST-GPR[97] model to smooth the estimates in space and time. The prevalence of AMR in each pathogen-antibiotic combination was modeled separately.

Due to high heterogeneity in the input datasets, data points found to have the most extreme values for the prevalence of resistance were outliered. A generalized linear mixed-effects model (GLMM) was fitted to the data, with nested spatial random effects based on the GBD super-region, region, and country, to capture the crude spatial-temporal trends. Datapoints that lay outside of two times the median absolute deviation (MAD) of the input data from the modeled estimate for each country were determined to be an outlier and removed prior to the stacked ensemble modeling step.

Approximately 10% of the most extreme data points were classified as outliers. Further details of the outliering analysis are presented in the appendix.

The datasets excluding significant outliers were used to fit spatial-temporal statistical models for the prevalence of AMR in each pathogen-antibiotic combination; a stacked ensemble model was fit to leverage covariate effects, followed by an ST-GPR to smooth the data in time and space. The selected covariates and child models, as well as the bespoke formulation (and hyper prior assumptions) used for the ST-GPR, are displayed in the appendix. The mean and 95% uncertainty intervals of the prevalence of AMR were calculated from 1,000 draws (based on draws at 10 iteration spacing/thinning to reduce autocorrelation) of the GPR for each country-year following 100,000 burn-in iteration to ensure model stabilization.

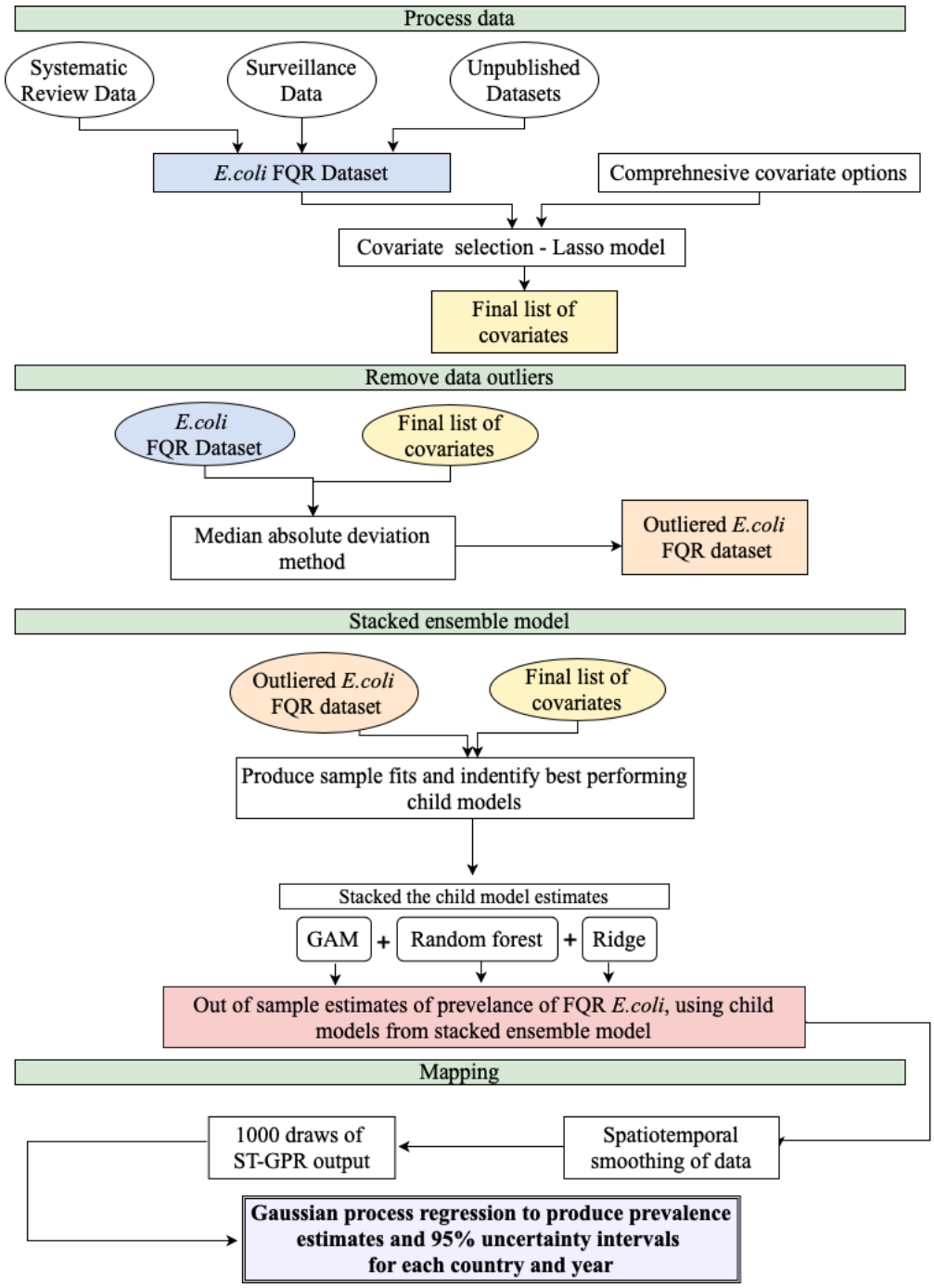

Figure 5.5: Flow chart methods for estimating the prevalence of FQR in E.coli.

5.5 MODEL VALIDATION

All models were validated using ten-fold cross validation, and the RMSE and R^2 between the input data and the out-of-sample estimates were calculated to assess the

models' predictive performance. Details of the model validation can be found in the appendix, Table D.4.

5.6 RESULTS

Input data for the FQR *E.coli* model consists of 9,850,272 isolates collected and 2,599 data points from 140 countries covering 20 years (Table 5.1). The carbapenems resistant *E.coli* model includes 4,250,579 isolates collected and 1,119 datapoints from 109 countries covering 20 years. The third-generation cephalosporin resistant *E.coli* model includes 2,043,110 isolates collected and 1,402 data points from 95 countries covering 20 years.

Antimicrobial-pathogen combination	Isolates	Datapoints	Countries
FQR *E. coli*	9,850,272	2,599	140
Carbapenem-resistant *E. coli*	4,250,579	1,119	109
3GC-resistant *E. coli*	2,043,110	1,402	95

Table 5.1: Details of input data for FQR E. coli, Carbapenem-resistant E. coli, 3GC-resistant E. coli. The number of isolates, the number of data points input in the model, and the coverage of countries for each combination are presented.

5.6.1 PREVALENCE OF *E. COLI* FQR

E. coli resistance to fluoroquinolones began to increase in 2000, with over 50% resistance present in Mexico, Pakistan, India, China, Nepal, Bhutan, Bangladesh and the Democratic Republic of the Congo. Resistance continues to climb in these countries in 2005 and spreads to South America with high resistance now seen in Peru. By 2010, resistance is high in Peru, Venezuela, Bolivia and Argentina. Additionally, North Africa and the Middle East has a rise in resistance. Resistance increases in North Africa and the Middle East and spreads further down into Central sub-Saharan Africa in 2015. Resistance also moves up north into Russia and Belarus in 2015. By 2020, Cambodia,

India, Myanmar and Pakistan report 93%, 83%, 80%, and 81% resistance respectively. Vietnam (72%), Indonesia (68%), Afghanistan (69%), Iran (60%), Iraq (67%), Syria (63%), Egypt (70%), Sudan (68%), Ethiopia (65%), Cameroon (66%), Democratic Republic of the Congo (74%), Mexico (72%), Guatemala (70%), Honduras (64%), Nicaragua (67%), Macedonia (70%) all reported over 70% resistance.

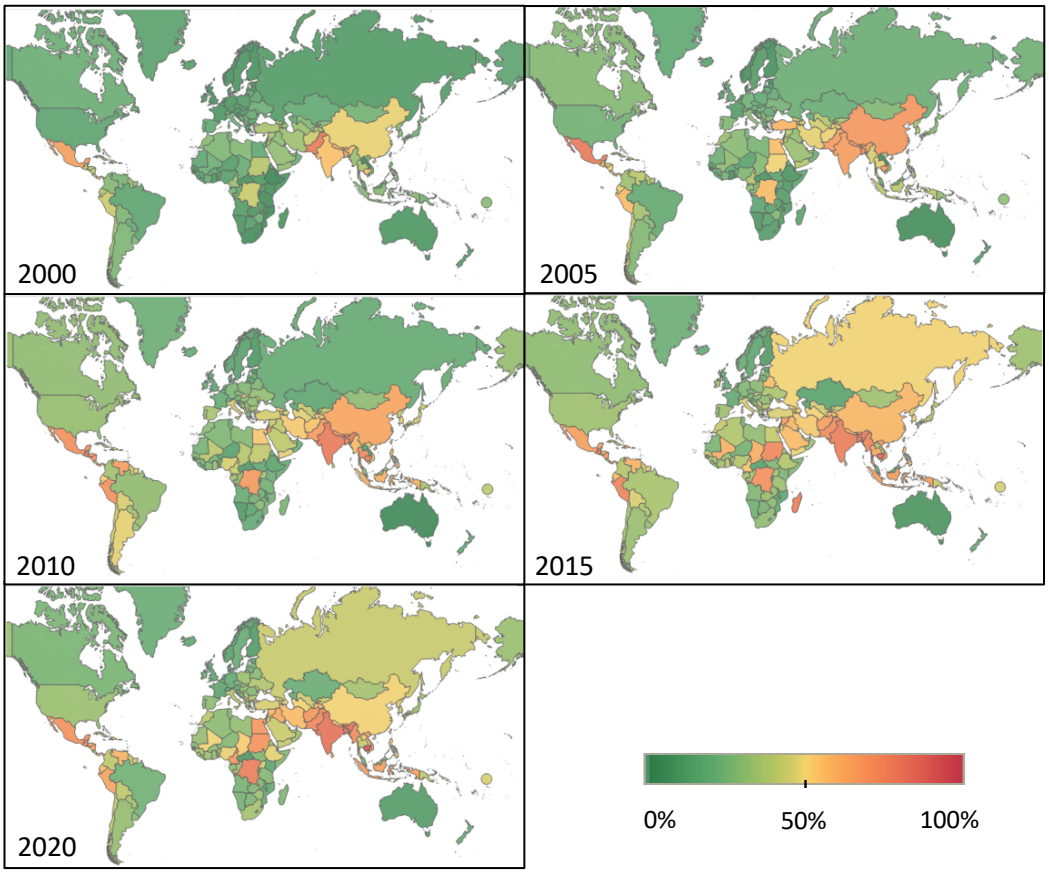

Figure 5.6: Model estimates for the prevalence of resistance for FQR E. coli. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

5.6.2 PREVALENCE OF *E. COLI* RESISTANCE TO CARBAPENEMS

Resistance first appeared in Iran, India and Mexico with 82%, 58% and 48% respectively in 2000. Resistance in these countries worsened in 2005 and spread out to China, Afghanistan, Turkey, Egypt and Sudan. In 2010, resistance is >50% throughout the Middle East and Asia. Resistance had also began to rise in Canada with 44%

resistance, Italy with 40%, Romania with 40%, France with 36% and Spain with 31% resistance. By 2020 resistance began to spread across North and West Africa.

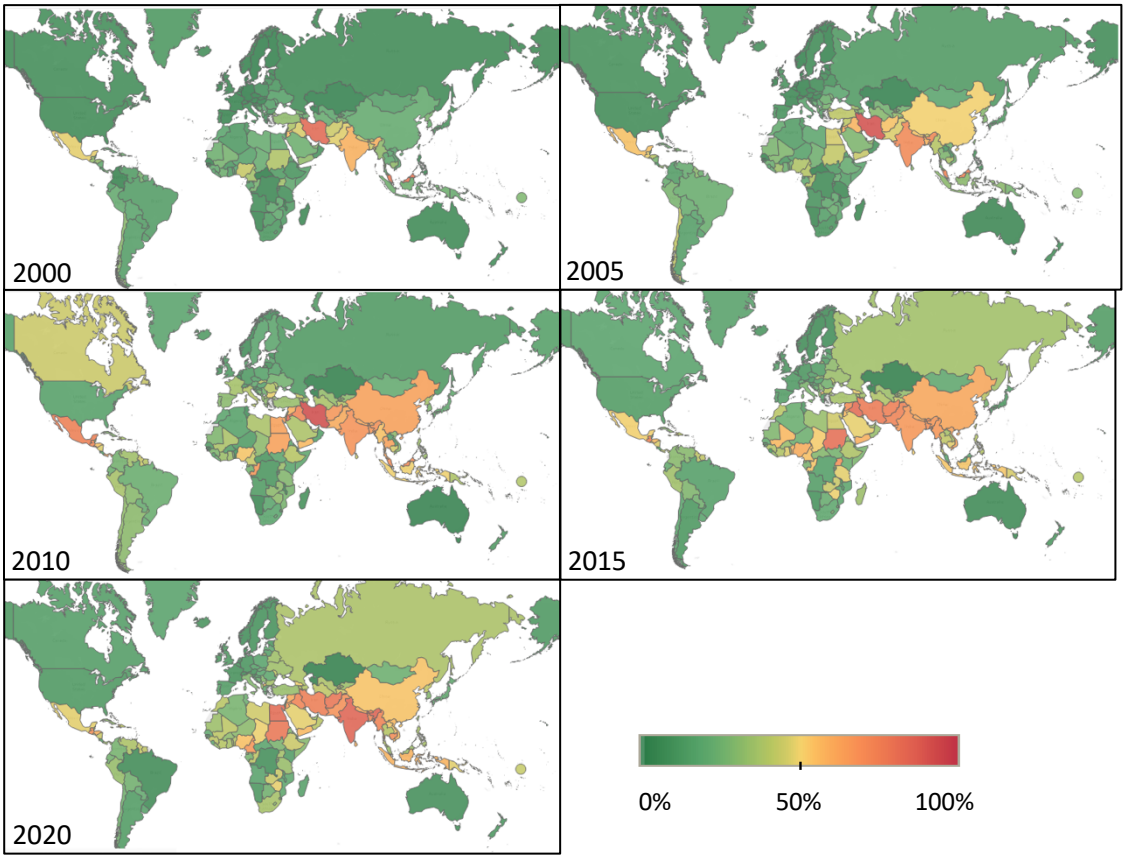

Figure 5.7: Model estimates for the prevalence of resistance for carbapenem-resistant E. coli.. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

5.6.3 PREVALENCE OF *E. COLI* RESISTANCE TO 3RD GENERATION CEPHALOSPORINS

In 2000, resistance was mostly seen in the Middle East and India reported high resistance. India has 72% resistance, Iran has 67%, Pakistan with 60%, Afghanistan has 57%, and Iraq with 50%. Mexico, Nigeria and Sudan also have high resistance with 55%, 50% and 52% respectively. In 2005, resistance increased in these countries and spread to China (50%) and Egypt (52%). In 2010, resistance was additionally reported in Canada (47%) and Nigeria (57%). By 2020, resistance has spread throughout

Northern and Western Africa, Central America, Asia, the Middle East and Eastern Europe.

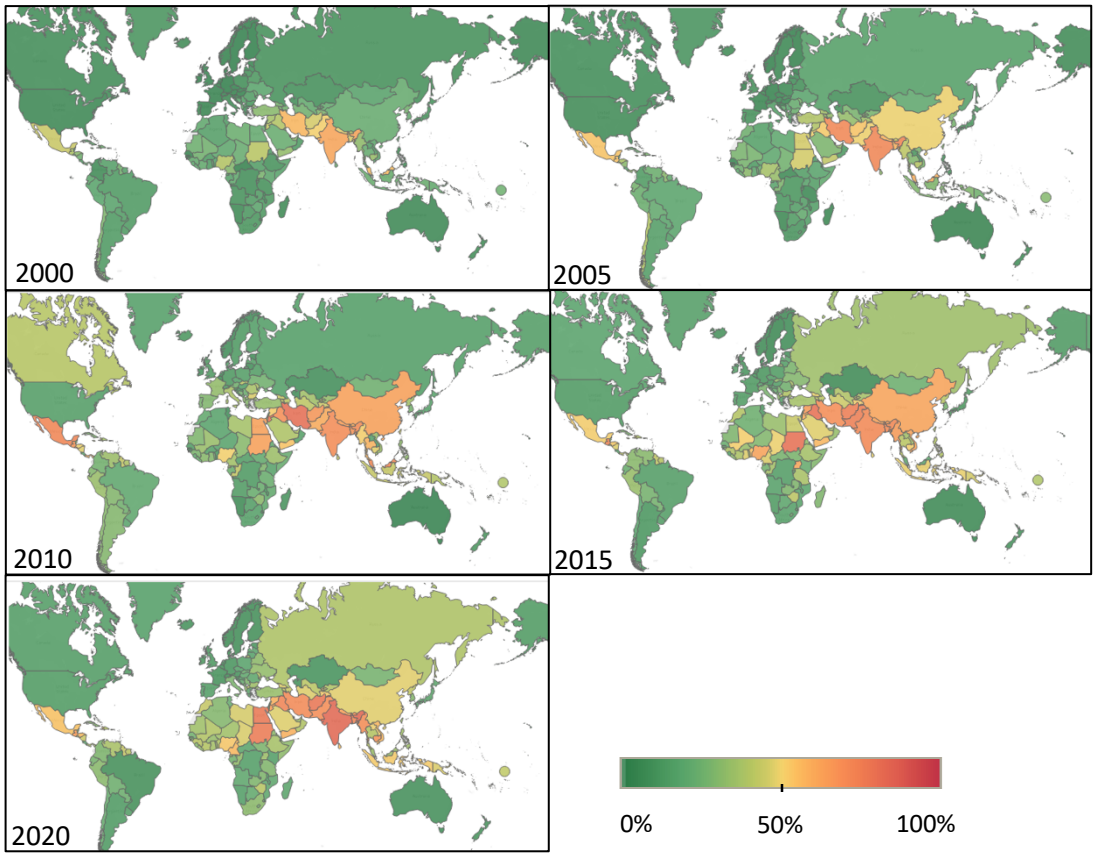

Figure 5.8: Model estimates for the prevalence of resistance for 3rd generation cephalosporins resistant E. coli. Mean 1,000 draws of the stacked ensemble and the ST-GPR model.

5.7 MODEL UNCERTAINTY

The relative uncertainty of estimates of resistance in *E.coli* prevalence was calculated for 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data were shaded according to the quartile of the proportion of AMR and the quartile of relative uncertainty to which they resided. There are varying degrees of uncertainty in the modeled estimates

due to the large data gaps in my *E.coli* dataset. The higher the relative uncertainty is due to a large variation in resistance which indicates a lack of data and a need for more information to produce a more accurate estimate.

5.7.1 FQR *E.COLI*

The estimates of high resistance were most often accompanied by low relative uncertainty for FQR *E.coli*. Countries with the lowest relative uncertainty are the majority of Europe, South and Southeast Asia, the United States of America, Australia, India, Pakistan, Ethiopia, Egypt, Turkey, Mexico, Panama, Venezuela, Argentina, and Brazil. Estimates of low resistance were accompanied by both high relative uncertainty and low relative uncertainty, depending on the geographical location. Figure 5.9 shows that Brazil, parts of Western Europe, Canada, and Australia all have a low prevalence of resistance and low relative uncertainty, whereas, parts of Western Europe, Kazakhstan, Mongolia, Southern, Eastern, and parts of Western sub-Saharan Africa have low resistance and high relative uncertainty.

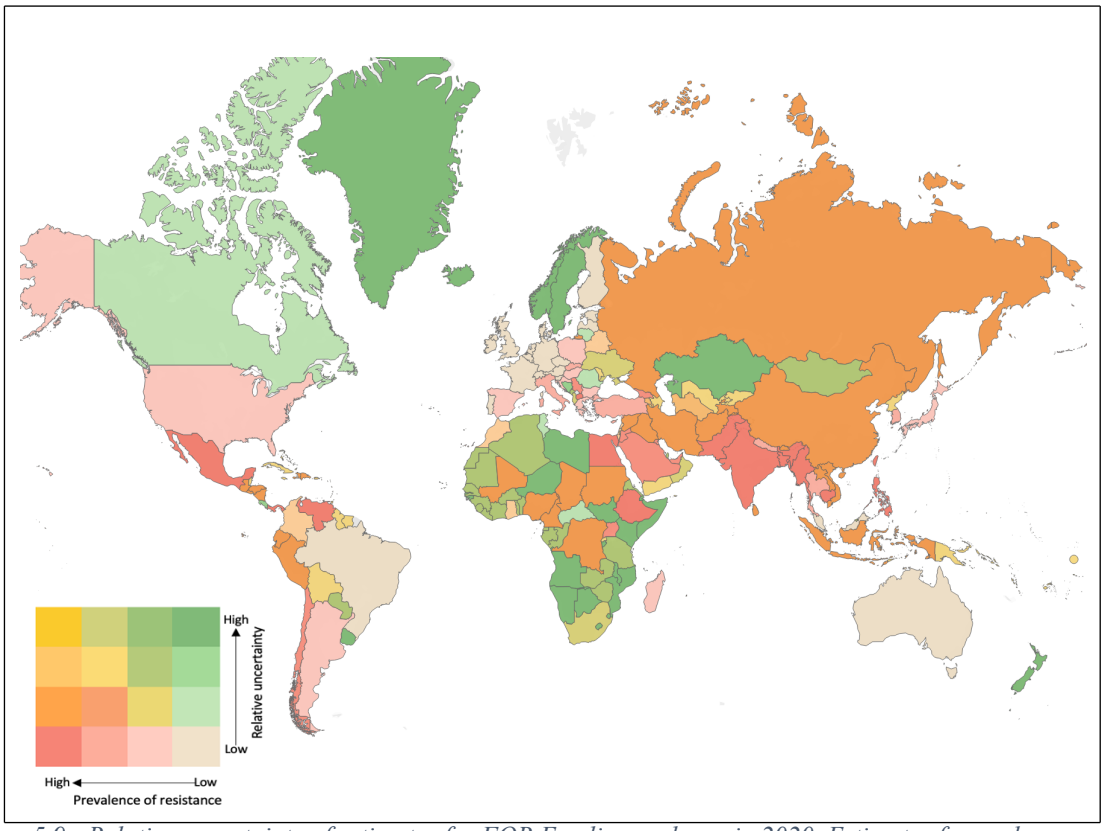

Figure 5.9: Relative uncertainty of estimates for FQR E.coli prevalence in 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data were shaded according to the quartile of the proportion of AMR and relative uncertainty to which they resided.

5.7.2 3GC *E.COLI*

The estimates of high resistance were most often accompanied by low relative uncertainty for 3GC resistance in *E.coli*. Estimates of low resistance were accompanied by both high relative uncertainty and low relative uncertainty, depending on the geographical location. Countries with a low relative uncertainty are most of Europe, Australia, Japan, Argentine, Brazil, Venezuela, Guatemala, Mexico, Egypt, Iraq, Jordan, Syria, Afghanistan, Tunisia, Ethiopia, Sudan, Madagascar, and parts of South and Southeast Asia. Figure 5.10 shows that parts of Europe, Japan, Australia, Brazil, Argentina, and Tunisia all have a low prevalence of resistance and low relative uncertainty, whereas, parts of South and Southeast Asia, Guatemala, Mexico, Egypt, Iran, Iraq, Jordan, Syria, Afghanistan, Ethiopia, and Sudan have low resistance and high relative uncertainty.

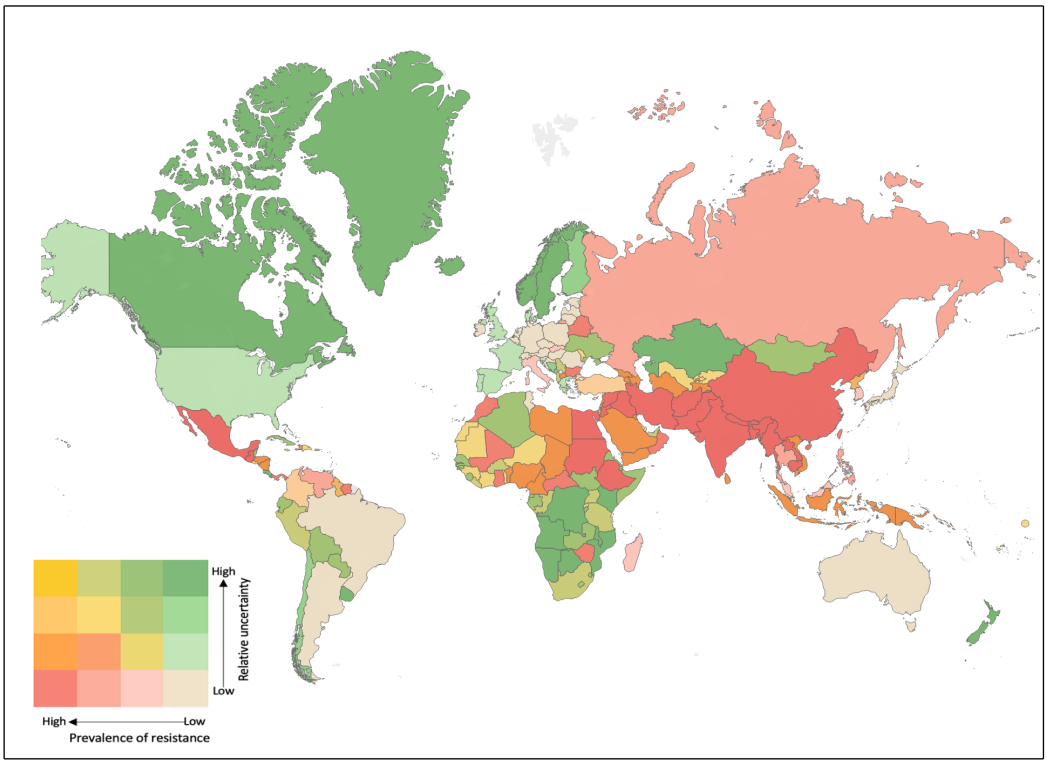

Figure 5.10: Relative uncertainty of estimates for 3GC E.coli prevalence in 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data were shaded according to the quartile of the proportion of AMR and relative uncertainty to which they resided.

5.7.3 CARBAPENEMS *E.COLI*

The estimates of high resistance were most often accompanied by low relative uncertainty for Carbapenem resistance in *E.coli*. Estimates of low resistance were accompanied by both high relative uncertainty and low relative uncertainty, depending on the geographical location. Countries with the lowest uncertainty are most of Europe, South and Southeast Asia, Australia, Egypt, Tunisia, Iran, Iraq, Afghanistan, Mexico, Argentina, Brazil, Ethiopia and Madagascar.

Figure 5.11 shows that parts of Europe, Japan, Argentina, Brazil, Tunisia, and Australia all have a low prevalence of resistance and low relative uncertainty, whereas, parts of Western

Europe, New Zealand, Uruguay, and countries in Southern, Central, Eastern and Western sub-Saharan Africa have low resistance and high relative uncertainty.

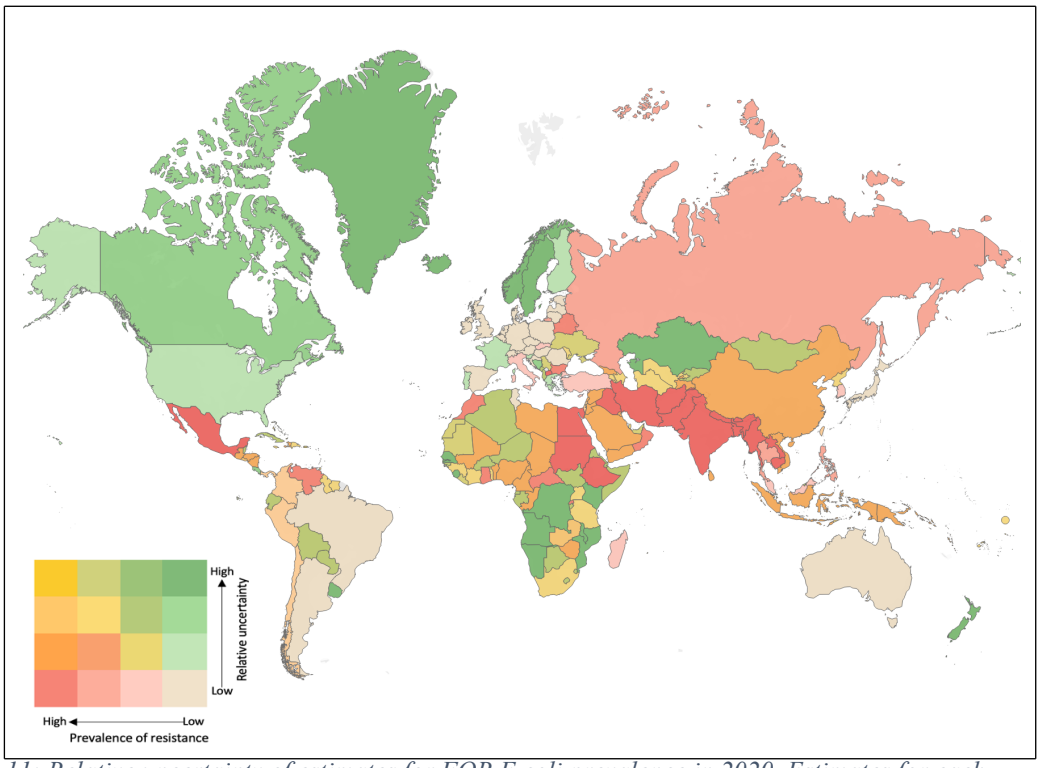

Figure 5.11: Relative uncertainty of estimates for FQR E.coli prevalence in 2020. Estimates for each country are presented. Relative uncertainty was defined as the ratio of the 95% uncertainty intervals to the proportion of AMR. Data were shaded according to the quartile of the proportion of AMR and relative uncertainty to which they resided.

5.8 DISCUSSION

AMR is a global public health crisis and understanding the trends of resistance is important in targeting interventions and policy change where it is most needed. Rates of resistance differ from country to country, making generalized recommendations no longer appropriate and effective. In this study, estimates of the prevalence of resistance in *E. coli* to fluoroquinolones, 3rd generation cephalosporins, and carbapenems worldwide are reported.

High rates of fluoroquinolone resistance were mostly concentrated in South Asia, East Asia, and Mexico in 2000. Resistance quickly spread to neighboring countries over time, with resistance rates rising in the Middle East and North Africa, Oceania, and down Central America by 2005. By 2020, resistance was widespread throughout Western, Central and Eastern sub-Saharan Africa, Asia, Eastern Europe, Andean and Central Latin America. Figure 5.6 show the only countries with <20% fluoroquinolone resistance is Finland, Denmark, Australia, Norway, Switzerland, Netherlands, France, Iceland, Sweden, The Gambia, Estonia, Malawi, United Kingdom, New Zealand, and Mozambique. In 2020, the following regions had >20% resistance, the threshold generally set to indicate the need for change in antimicrobial treatment:

- East Asia
- Southeast Asia
- Central Asia
- South Asia
- Oceania
- Eastern Sub-Saharan Africa
- Central Sub-Saharan Africa
- Southern Sub-Saharan Africa
- Western Sub-Saharan Africa
- Eastern Europe
- Central Europe
- Western Europe – Greenland, Austria, Luxembourg, Germany, Portugal, Ireland, Belgium, Greece, Spain, Andorra, Cyprus, Italy
- High-income Asia Pacific

- High-income North America
- North Africa & Middle East
- Andean Latin America
- Tropical Latin America
- Southern Latin America
- Central Latin America
- Caribbean

As most of the world has >20% fluoroquinolone resistance, the recommended antimicrobial treatment should be updated to reflect an appropriate treatment for today.

In 2000, high third-generation cephalosporin resistance was only prevalent in Mexico, India, Iran, Afghanistan, Pakistan, Sudan and Nigeria. Resistance spread to China and the Middle East by 2005. Resistance continued to rise and spread up into Eastern Europe and across into North Africa, and out into Southeast Asia in 2015. In 2020 resistance rates increased and moved additionally into Western sub-Saharan Africa. Figures 5.7 show the regions with >20% third-generation cephalosporin resistance in 2020 are:

- Caribbean
- Central Europe – Bosnia, Montenegro, Serbia, Slovakia, Albania
- Eastern Europe – Ukraine, Belarus, Bulgaria, Russia, Moldova
- High-income Asia Pacific
- North Africa & Middle East
- Oceania

- Central Asia
- East Asia
- South Asia
- Southeast Asia
- Andean Latin America
- Central Latin America
- Southern Latin America
- Tropical Latin America
- Eastern Sub-Saharan Africa
- Central Sub-Saharan Africa
- Southern Sub-Saharan Africa
- Western Sub-Saharan Africa

In 2000, most of the world was susceptible, with carbapenem resistance only seen in Iran, Afghanistan, Pakistan, India, Mexico, and Nigeria. Resistance spread through the Middle East over to China, and over to North Africa in 2005. By 2015 resistance rates have increased and spread further into sub-Saharan Africa and Southeast Asia. Figures 5.8 show the regions with >20% carbapenem resistance in 2020 are:

- Andean Latin America
- Central Latin America
- Caribbean
- Central Europe – Montenegro, Serbia, Slovakia, Albania
- Eastern Europe – Ukraine, Russia, Bulgaria, Belarus, Moldova
- High-income Asia Pacific – Singapore, S Korea

- North Africa & Middle East
- Oceania
- Central Asia
- East Asia
- South Asia
- Southeast Asia
- Central Sub-Saharan Africa
- Eastern Sub-Saharan Africa
- Southern Sub-Saharan Africa
- Western Sub-Saharan Africa

Many countries also have >20% resistance to third-generation cephalosporins and carbapenems and should adjust the recommended antimicrobial treatment for *E. coli*. Overall, the most concerning results identified are the countries with 50 - 100% resistance in all three antimicrobial classes, fluoroquinolones, third-generation cephalosporins, and carbapenems. India has over 80% resistance to all three antimicrobial classes and Cambodia, Pakistan, Egypt, Myanmar, and Bangladesh have over 70% resistance to all three antimicrobial classes. Fluoroquinolones and cephalosporins are some of the generally recommended first-line treatments for *E. coli*.[111] Carbapenems are generally recommended to be saved as a last-line treatment or treatment for MDR infections.[117]

Providing national estimates is crucial to understanding which countries need targeted resources, policy change, and intervention. The results presented in this study show that resistance does differ between neighboring countries, making regional

recommendations not applicable. For example, Mexico has a higher resistance to fluoroquinolones, 3rd generation cephalosporins, and carbapenems than the United States, Guatemala, and Belize. Mexico shares a border with all three countries and has a very different prevalence of resistance. In Mexico, approximately 18% of people lack access to healthcare, antimicrobials are easily accessed over the counter, and were one of the leading countries in clinical antimicrobial use (about 15 defined daily doses per 1000 inhabitants per day) between 1997 and 2004.[118] This correlates with the results presented in this chapter, as resistance in Mexico seems to peak between 2005-2010. Mexico, the United States, and Guatemala all have similar amounts of data points and came from large sample sizes. Another example is the difference in resistance between China and the countries at the Southeast border, Vietnam, Laos, Myanmar, and Thailand. China reports having a high antimicrobial consumption, which increased by 79% between 2000-2015.[119] China is densely populated and the poor air quality causes many cases of chronic obstructive pulmonary disease leaving residents more susceptible to bacterial infections thus using antimicrobials more often.

In an attempt to slow the rise in resistance to carbapenems in *E. coli,* the ECDC proposed two calls of action in 2019.[120] To prevent the spread of the resistance within the community, the ECDC called for an international ban on any food items containing Carbapenem-resistant Enterobacteriaceae (CRE). There are increasing reports detailing CRE found in the environment, food, and animal sources.[120] As *E. coli* is the cause of many hospital-acquired infections, the limited treatment options currently available are increasing the need for strict infection control within hospitals. To reduce the risks in hospitals and healthcare facilities, the ECDC recommends WHO's guidelines of eight strategies to implement infection prevention and control; 1. hand hygiene compliance,

2. infection surveillance, 3. asymptomatic digestive tract carriage screening, 4. contact precautions, 5. patient isolation, 6. environmental cleaning, 7. environmental surveillance cultures, 8. monitoring, auditing, and feedback. [121] However, many countries with the highest mortality due to *E. coli* infections do not have the resources to practice these eight strategies outlined by the WHO. The ECDC acknowledges this and is additionally calling for new antimicrobials to be created to alleviate the current AMR crisis.[120]

This study provides compelling information displaying trends in *E. coli* resistance to three antimicrobial classes; fluoroquinolones, third-generation cephalosporins, and carbapenems, over 20 years. This information is the first to provide a complete picture of the state of AMR worldwide and provides data to aid in changes necessary to disrupt the continual increase of AMR. The output from this study is important and vital to making informed decisions regarding appropriate treatment on a national level. Additionally, this study identifies where AMR surveillance and interventions need to be implemented.

5.9 IMPLICATIONS FOR CLINICAL PRACTICE

A high prevalence of AMR in *E.coli* has numerous clinical implications. With this first-line drug, patients will begin to experience treatment failure. Empirical treatment is commonly used as a treatment plan in low-income settings as many healthcare settings do not have access to a laboratory or test supplies. An inappropriate empirical treatment can increase the patient's healthcare costs as they will need to purchase additional medication which may result in a longer hospital stay contingent on the severity of the

illness. Patients and healthcare providers face limited treatment options as a result of high resistance and treatment failure.

With the global increase in carbapenem resistance, these carbapenem-resistant strains are recommended to be treated with tigecycline or colistins. However, this treatment is not widely available to patients who need it as both antimicrobials are not as effective in successful treatment or easily accessible. Many countries may have limited access to antimicrobials, and if first-line medications are ineffective, a secondary medication may not be available. Antimicrobial availability is determined by cost, demand for the antimicrobial, and accessibility to the antimicrobial. First-line medications may be more accessible than second-line treatments, potentially leaving healthcare practitioners with fewer treatment options. This is particularly an issue in low-income environments where there is considerable resistance and limited access to many resources.

CHAPTER **6**

Challenges, Bias, and Missing Information in the Collection of Data for Estimating AMR

6.1 INTRODUCTION

Managing and treating bacterial illnesses are increasingly becoming more difficult, negatively impacting populations around the world. Estimates of the prevalence of AMR can be used to inform intervention and policy change, which will aid in the battle against AMR. To determine where assistance is most required, it is crucial to study the spatial and temporal trends in resistance. Estimates of the burden of AMR from the O'Neil report [122], as well as European estimations of the AMR burden [123], have all been published on the state of AMR in the Global Burden of Disease (GBD) [4] research, and it is critical to acknowledge the biases and problems within AMR data and how this influences the estimates.

There are several aspects and difficulties in determining the impact of AMR. The severity of these issues such as data biases, a lack of external quality assessments (EQA), poor laboratory quality, and a lack of reported data, varies across HICs and LMICs. Data used to track AMR is gathered from a variety of sources, including different types of hospitals, studies conducted in the community, surveillance systems, labs, and research institutions, to mention a few. Each source has a unique methodology[124], making use of a variety of AST tests, sample techniques, details

provided, and resources. AMR data reporting is not governed by any national or international standards, therefore even within surveillance systems, highly varied data is generated.[125,126]

Accurately estimating the prevalence of resistance requires an awareness of the challenges and biases present in AMR data. The data gathered for this project were used to explore these important biases, and this chapter covers the constraints and biases in estimating the prevalence of resistance. The constraints resulting from a lack of data and the consequences of not having a laboratory standard for reporting AMR are discussed in this chapter. Also addressed is how to deal with problems that can occur when reporting the prevalence of AMR and what strategies researchers might use to correct for these biases.

6.2 DATA AVAILABILITY

The coverage of AMR surveillance varies significantly by location. In HICs, there are well-established surveillance networks with the ECDC continuously collating data across Europe,[60] and the CDC across the USA[127] as well as numerous other country specific AMR surveillance systems.[128–130] In LMICs data availability is much more sparse. Red Latinoamericana de Vigilancia de la Resistancia a los Antimicroibians (ReLAVRA)[131] and the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR)[132] provide supranational surveillance data for multiple countries across Central/South America and Central Europe/Eastern Asia respectively. Still, few other countries have nationally representative continuous AMR surveillance.

In order to gather and report on AMR data of comparable quality using techniques of a similar standard, the WHO developed GLASS in 2015. [124] According to its quality evaluations and the GLASS recommendations on the types of data to submit, each participating country in GLASS collects AMR data at its own discretion. A country must have local testing and reporting facilities in order to participate in reporting to GLASS, favoring HICs and middle-income nations in terms of participation. Since many nations lack the infrastructure for a surveillance system, the majority of AMR data from LMICs is based on research from academic institutions and pharmaceutical businesses. [133] Only 28 of the 82 countries that took part in GLASS-AMR surveillance in 2020 supplied data on the sample size used to test for resistance, whereas 66 of them gave information on the prevalence of resistance in priority pathogen-antibiotic combinations. [134]

Studies that are long-term and involve multiple centers include Typhoid Surveillance in Africa (TSAP)[135], Strategic Typhoid Alliance across Africa and Asia (STRATAA)[136], Mortality from Bacterial Infections Resistant to Antibiotics (MBIRA) in Africa [137], the Clinically Oriented Antimicrobial Resistance Surveillance Network (ACORN) study in Africa and Asia[138], the Global Antimicrobial Resistance, Prescribing, and Efficacy Among Neonates and Children (GARPEC) [139], the Community-level antibiotic access and use (ABACUS) [140] project, and the Global Antimicrobial Resistance. These investigations can yield high-quality AMR data, but they are frequently expensive and resource-intensive to carry out. Short time periods of data and limited spatial coverage are the outcome, which makes it difficult to examine temporal trends. Understanding the full scope of AMR and its impact on the world requires a thorough report that spans a wide time period and has worldwide coverage.

Data from systematic reviews, as stated in Chapters two and four, data from healthcare facilities or research centers, and collaboration with other researchers are some sources of AMR. The lack of a testing technique, a sampling strategy, and high-quality data further limit this data. The majority of LMICs lack the funding necessary to put in place a surveillance system. Therefore, standardized procedures for testing, reporting, and sample collection are frequently not followed by the data reported by LMICs. [141]

The GRAM project has been compiling a global database of the prevalence of AMR in key pathogens (*Acinetobacter spp., Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae*, *Pseudomonas aeruginosa, Salmonella enterica*, *Shigella* spp., *Staphylococcus aureus,* and *Streptococcus pneumoniae*) from multiple sources since 2017. Analyzing the available data shows variability in the type and quantity of data collected between HICs and LMICs. A paucity of high-quality surveillance data is identified in LMICs, particularly in sub-Saharan Africa (Figure 6.1). The Fleming Fund from the UK Department of Health and Social Care has developed a roadmap for increasing the participation of LMICs in GLASS,[142]along with investing in both retrospective and prospective collection of AMR data in LMICs.[143] An increase in the amount of high-quality AMR data from LMICs would be incredibly beneficial for individual patient management, the development of local and national empiric treatment guidelines, and estimating both the prevalence and burden of AMR.

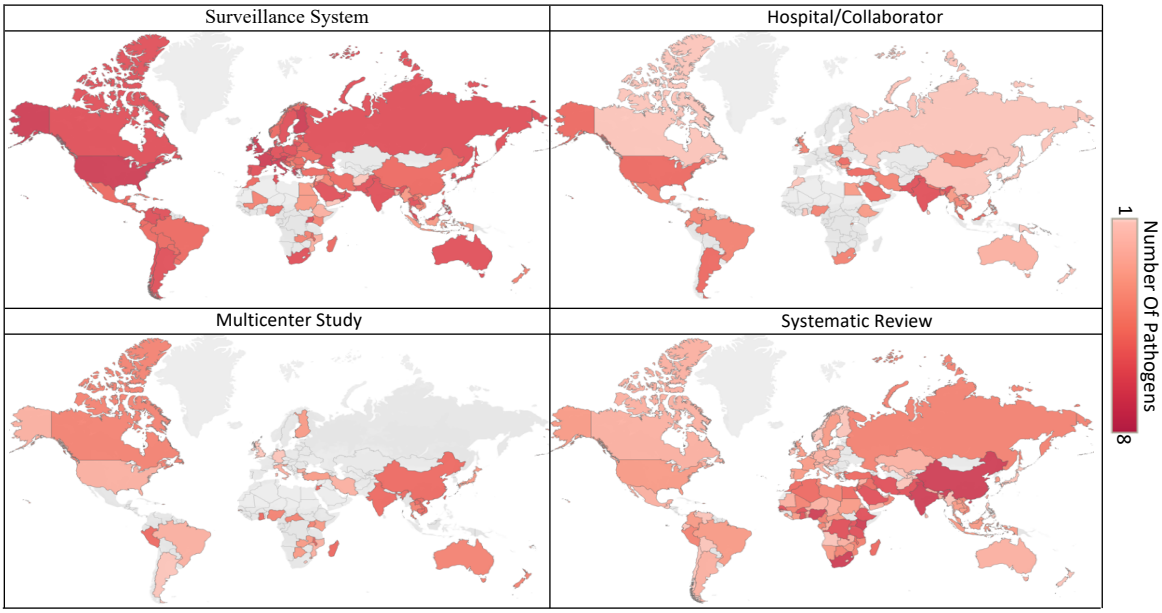

Figure 6.1: Availability of AMR prevalence data by country and data type for critical pathogens. Each map shows the countries where the GRAM project has collated that type of data, with the color indicating the number of pathogens for which data were acquired.

A pathogen is cultured in a laboratory in order to classify it after being isolated from a patient sample. Once the pathogen has been identified, an antimicrobial sensitivity test can be carried out utilizing a variety of testing techniques, including the minimum inhibitory concentration method and disk-diffusion method. [144] A high quality microbiological lab, qualified employees to conduct the tests, pricey laboratory equipment, and assays are all necessary for these testing. Without this equipment, the amount of samples that may be used for AST techniques is significantly constrained, making it difficult to identify infections. HICs have a large number of reputable laboratories that adhere to ISO accreditation, have qualified personnel, and have the necessary testing tools. Despite the fact that mortality and burden are higher in LMICs, it is difficult to meet this requirement. This limitation can be seen in the lack of data from many LMICs during data collection. My most significant data gap in the *Shigella* systematic review was in Africa, and these limitations may be the cause for

heterogeneous data in these countries.[145,146] Accurate microbiological diagnosis and AST from culture require professional knowledge and applying multiple techniques for different bacteria. There is no mechanism to train microbiologists quickly, and there is a lack of standardized training programs in LMICs.

EQA tools are crucial because they maintain a uniform standard among participating facilities, resulting in comparable data. 81 laboratories from 42 African nations were included in a study that examined the dependability of EQA instruments from 2011 to 2016. According to the survey, 42% of laboratories were rated as having "acceptable" AST performance, while 76% of laboratories had "acceptable" accuracy in detecting specific bacteria. [147] The accuracy of the data being gathered and whether these estimates are accurate at capturing the true prevalence of AMR are both seriously questioned by these findings. If the AST results are unreliable, reporting estimations that are inaccurate can result in a wrong diagnosis, an incorrect identification of the bacterium, or an improper course of treatment. The lack of resources to get control strains for the testing procedure is another issue that contributes to inaccurate laboratory results. It's common to hear that the effectiveness of AST is constrained by a lack of access to control strains.[144,148] It is crucial to set up a fully functional microbiology lab in LMICs in order to generate better-quality data and enable more focused and efficient interventions to address AMR.

6.3 BIASES IN AMR DATA

6.3.1 OVERVIEW

Surveillance of AMR is generally conducted in the form of passive surveillance for healthcare-associated infections (HCAI) and community-acquired infections (CAI).

The first stage of AMR surveillance is identifying persons with infections. Those with CAI must attend a formal healthcare setting with access to an established microbiology laboratory. At the same time, persons with HCAI need to be identified within such a facility or referred to one. Identification of infection is a subjective practice by a clinician and there is no gold standard test for this process.

Identification of an infection varies by nation, the attending clinician, and the hospital the patient presents at due to the subjective nature and variable factors including cost, healthcare insurance, and resource availability. The detection of infections in HCAI is subject to the clinician's observation. Before prescribing antibiotics in HICs, a practitioner will frequently take a diagnostic sample for testing because it will be inexpensive for the patient. The identification of the infection, however, frequently depends on how well an empirical antibiotic treatment works in LMICs. In most circumstances, this is because empirical treatments are less expensive than microbiology tests, and they can also be administered right away while microbiology tests require time for findings to be received.[55] Based on the expense and the severity of the patient's infection, the doctor will decide what to do next if empirical treatment is unsuccessful. The microbiology facility that is available after a practitioner takes a diagnostic sample from the patient for testing might not be of a high level. [56] Low accuracy of test results and antimicrobial sensitivity tests might be caused by inadequate microbiological facility infrastructure. [53] Lack of medical personnel with knowledge of infection control and microbiology is another issue in LMICs. This can ultimately lead to an overestimation of AMR.

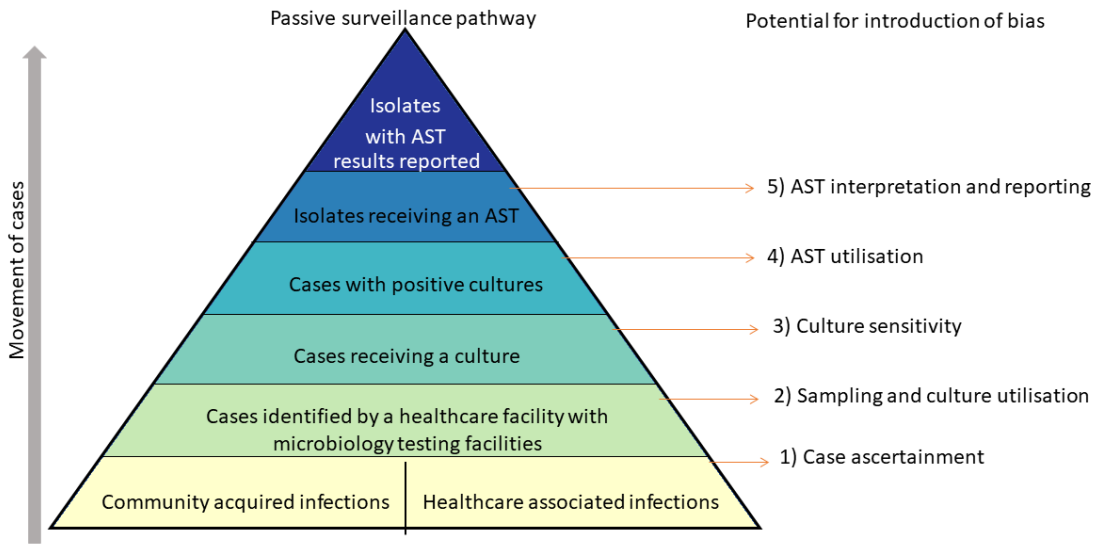

Figure 6.2: Biases in passive surveillance of AMR. The left side of the diagram describes the patient pathway from acquiring a pathogen, to the AST results being reported by the hospital. The right side of the diagram identifies the stages where the sample could be biased to the over- or under-identification of resistant strains.[149]

6.3.2 CASE ASCERTAINMENT

Attending a formal healthcare facility is the initial step in discovering cases of CAIs. Due to established healthcare systems in HICs that are frequently free at the point of entry, the proportion of cases seeking official healthcare is typically high. In LMICs, access to healthcare facilities is restricted, which adds to the difficulty of having insufficient resources and healthcare infrastructure. How expensive or difficult it is to obtain transportation can serve as motivation to seek therapy despite its difficulties.[150–153] how severe the condition is, whether there is access to self-care or local healing, whether the therapy was successful or not, and whether outside assistance is given financially or physically.[151,153,154] Before visiting a hospital, people frequently try to treat themselves at home with leftover medication, go to a local pharmacy, or consult a healer.[150–152,154] AMR cases are seen and reported less frequently due to the decreased attendance at healthcare facilities, which could introduce bias into the data. Even while there may be fewer cases of AMR presented at a healthcare facility, the patients who

do will have more severe illness cases and proportionally more cases of AMR than in the surrounding community.

E. coli data collected from the systematic review supports this hypothesis, with a statistically significant higher prevalence of resistance in *E. coli* isolates from hospital-based studies compared to community-based and referral laboratory studies in sub-Saharan Africa (Table 6.1).

Pathogen-antibiotic	Prevalence of resistance % (Number of studies)		
	Hospital-based study	Community-based study	Referral Laboratory study
E. coli - Fluoroquinolones	34% (278)	20% (13)	27% (57)*
E. coli - 3GC	42% (254)	22% (11)*	24% (36)*
E. coli - Aminoglycosides	35% (254)	18% (21)*	22% (52)*

*Table 6.1: Comparison of the prevalence of AMR in hospital-based, community-based and referral laboratory-based studies for **E. coli in sub-Saharan Africa**. Data supplied by the GRAM project systematic review of antimicrobial resistance in E. coli worldwide. T-test implemented to calculate the significance of the difference in the prevalence of resistance. *indicates statistical significance at a 5% level ($p \leq 0.05$). 3GC = third-generation cephalosporins.*

HCAI infections have been identified to have higher rates of AMR than CAI, with studies in Spain and China showing this for multiple pathogen-antibiotic combinations.[155,156] Many multi-drug resistant (MDR) organisms are found in HCAIs compared to CAIs.[157–160] In 2013, 25% of global HCAIs were reported as MDR.[161] AMR is commonly seen in patients with HCAIs as these patients have an increased number of invasive procedures and therapies, and are often older patients or those with compromised immune systems.[162] These infections often result in more extended hospital stays, increased costs, and potentially decreased quality of life. Rates of HCAI are higher in LMICs due to overstretched healthcare professionals working in

overcrowded healthcare facilities, with poor or no infection control and limited resources,[161] increasing the concern for poor health outcomes.

A national HCAI surveillance system is vital to estimate and spread awareness of the burden of these infections. There is evidence that a national surveillance system decreases the number of HCAIs.[163] Several studies contributed to this evidence, including one from Germany in which 580 ICUs and surgical departments participated in a surveillance system study.[164] Three major HAIs were followed, data on the incidence of infection was reported and fed back to each department twice a year to encourage infection control and after three years, the incidence of infection dropped around 10%. In addition, a study in the United States looked at 338 hospitals over five years and implemented an HAI surveillance system along with a trained infection control physician and nurse per 250 beds in each hospital.[165] Results showed a 32% decrease in the incidence of HAIs with these strategies implemented. However, these surveillance systems are demanding and challenging to implement, especially in countries with limited resources.

Using data from Becton Dickinson on AMR from multiple sites in the USA, a small but statistically significant higher prevalence of AMR is demonstrated in HCAI compared to CAI for key pathogens (Table 6.2). When reporting the prevalence of AMR it is essential to distinguish between HCAI and CAI to understand the prevalence of resistance and reduce sampling bias fully.

Pathogen-antibiotic	Prevalence of resistance (%)		Difference in resistance (%)	P-value
	CAI	HCAI		
E. coli - 3GC	13%	17%	4%	<0.005
K. pneumoniae - 3GC	13%	21%	8%	<0.005
S. aureus - Methicillin	54%	60%	6%	<0.005

Table 6.2: Comparison of the prevalence of AMR in HCAI and CAI for key pathogens. Data supplied by Becton Dickinson for multiple locations in the USA for the 3GC E. coli and K. pneumoniae, and MRSA. T-test was implemented to calculate the significance of the difference in the prevalence of resistance. 3GC = third-generation cephalosporins.

The type of institution and hospital ward can have a big impact on how much resistance is present. Tertiary hospitals make up the majority of the establishments conducting AMR surveillance. [166] Tertiary hospitals will include the more seriously ill patients with protracted disease and may exaggerate the prevalence of resistance because they have big laboratories and care for patients referred from smaller hospitals for further testing and management. Location affects how much of the AMR surveillance data comes from tertiary institutions. As well-established sampling and testing processes and networks assure uniform patient diagnosis and treatment, surveillance in HICs frequently collects data from all levels of healthcare. These networks are frequently nonexistent in LMICs, and a far higher percentage of surveillance data comes from tertiary facilities, hence the degree of bias will differ. [4] Intensive care units (ICU) have more resistance than other ward types, due to a higher use of antibiotics in patients (Table 6.3). Similar results from other studies indicate that AMR is rising in ICUs all across the world. [167–170] This difference in resistance between the ICU and other wards is likewise more pronounced in LMICs than HICs. [171]

Pathogen-antibiotic	Prevalence of resistance % (studies)		
	ICU Ward	Surgical Ward	Outpatient
E. coli - Fluoroquinolones	63% (20)	41% (24)*	35% (40)*
E. coli - 3GC	70% (25)	53% (30)*	21% (33)*

*Table 6.3:Comparison of the prevalence of AMR in an ICU ward compared to other hospital wards for E. coli. Data supplied by the GRAM project systematic review of antimicrobial resistance in E. coli worldwide. T-test was implemented to calculate the significance of the difference in the prevalence of resistance. 3GC = third-generation cephalosporins. *indicates statistical significance at a 5% level (p≤0.05).*

6.3.3 SAMPLING AND CULTURE UTILIZATION

When a patient receives official medical attention, a doctor can diagnose an infectious bacteria by taking a sample and testing it in a lab. A variety of sample types can be collected for culture and determining AMR profiles, depending on the presenting condition. Because blood cultures are the gold standard in AMR surveillance, bloodstream infections (BSI) represent the most clinically relevant presentation of AMR pathogens. Blood cultures and lab tests can be expensive, time-consuming, expensive, require a sterile setting, and educated personnel. [172,173] Due to this, only the sickest patients or those who are not responding to therapy receive blood cultures, which causes the reported prevalence of AMR to be overstated. [124,155,174]

As diagnostic microbiology testing is underused, AMR surveillance based on microbiology data alone will not accurately represent the community of interest. A case-based approach, such as ACORN,[138] where paring clinical data with diagnostic sample types, will provide a more robust estimate. However, caution should still be exercised when microbiology testing is underutilized.

Diagnostic sample type may also affect the prevalence of resistance reported. The sample type collected will differ respective of the syndrome, suspected pathogen and country. A study by Vihta et al[156] compared the proportion of resistance in *E. coli* isolates from blood and urine worldwide. They found that the proportion of resistance in the different sample types was within 10%, with resistance slightly higher in blood samples. We compared the prevalence of resistance in blood and urine isolates of *K. pneumoniae* and *E. coli* to third-generation cephalosporins, carbapenems and fluoroquinolones using data from The National Surveillance of Antimicrobial Resistance (NSAR) in Malaysia,[175] and in *K. pneumoniae* and *E. coli* to third-generation cephalosporins from Becton Dickinson (BD) data (personal communication). For all comparisons, we saw a less than 5% difference in the prevalence of resistance in blood and urine isolates. For the NSAR there was a slightly lower prevalence of resistance in blood compared to urine for all *E. coli* combinations, but this was only significant for fluoroquinolones. For the BD data, there was a slightly higher prevalence of resistance in blood compared to urine for all combinations studied.

The evidence suggests a minimal difference in resistance between sterile and non-sterile sites, indicating that the proportion of resistance in non-sterile sites can be used as a proxy or indicator for sterile sites. However, knowing which sample types being tested for AMR is still important to inform treatment options.

Pathogen-antibiotic	Prevalence of resistance (%)		Difference in resistance (%)	P-value
	Blood	Urine		
Becton Dickinson, USA				
E. coli - 3GC	14%	13%	-1%	0.637
K. pneumoniae - 3GC	16%	14%	-2%	0.057
NSAR, Malaysia				
E. coli - fluoroquinolones	24%	26%	2%	0.0002
E. coli - 3GC	20%	19%	-1%	0.28
K. pneumoniae - 3GC	32%	33%	1%	0.23
E. coli - carbapenems	51%	55%	4%	0.34
K. pneumoniae - carbapenems	3%	3%	0%	0.34

Table 6.4: Comparison of the prevalence of AMR in blood and urine samples for key pathogens. Data supplied by Becton Dickinson for multiple locations in the USA and National Surveillance of Antimicrobial Resistance, Malaysia 2008-2013. T-test was implemented to calculate the significance of the difference in the prevalence of resistance. 3GC = third-generation cephalosporins.

6.3.4 CULTURE SENSITIVITY

The pathogen and the type of sample have an impact on the sensitivity of culture. Blood cultures, for instance, only detect S. Typhi with a sensitivity of about 50%. [176] The quantity of positive blood cultures reported is impacted by the lack of infrastructure and resources required to perform blood cultures. [177] Additionally, studies have shown that pre-healthcare antibiotic use affects how sensitive blood cultures are. [155,178,179] The collection of the sample without contamination has the biggest impact on the specificity of urine culture. The collection into a sterile container and a midstream sample are both necessary. [180] Because of the higher potential of contamination, cultures from non-sterile settings can be difficult to interpret. Results of a non-sterile culture must be matched with patient history and physical examination when concluding a diagnosis.[180]

The capacity to conduct AMR surveillance is significantly impacted in groups with substantial pre-admission antibiotic consumption or when cultures are taken after the start of antibiotic therapy, as these situations make it difficult to detect bacteria and

increase the risk of bias. If a person has taken antibiotics before samples are taken, drug-susceptible bacteria are less likely to grow in cultures. In contrast, drug-resistant germs could continue to proliferate and cause an overestimation of AMR.

6.3.5 ANTIMICROBIAL SUSCEPTIBILITY TESTING UTILIZATION

Accurately classifying resistance and susceptibility to antimicrobials presents difficulties in addition to the difficulties associated with reliable culture results. Control strains are a crucial but difficult to reach tool that can help boost accuracy. The inability to do AST precisely is frequently hampered by this lack of access and the absence of the proper antibiotic disks. [144,148] The disk-diffusion approach has other drawbacks; it is regarded as rather a rudimentary mode of AMR detection because it cannot be used to monitor temporal trends in MIC values (and thus monitor diminishing susceptibility, offering an early warning for developing resistance), and it has limited relevance for finding resistance in specific pathogen-antimicrobial combinations. [181] AMR is overestimated as a result of the paucity of supplies that cause biases similar to those with blood cultures and reserve any available supplies for people with acute sickness.

6.3.6 ANTIMICROBIAL SUSCEPTIBILITY TESTING INTERPRETATION AND REPORTING

Guidelines for antimicrobial susceptibility testing have been a crucial standardization for combining AMR data from numerous sources. As susceptibility shifts over time, these recommendations frequently change.[182] When integrating different datasets, setting breakpoints presents certain difficulties. The most popular AST guidelines are those from the Clinical Laboratory Standards Institute (CLSI) and the European

Committee on Antimicrobial Susceptibility Testing, which both have distinct breakpoints (EUCAST). [183] The AST standards were either not indicated or the year used was not provided in the majority of the systematic report data and datasets received during data collection. The MIC values were only present in a small number of the datasets, and the AST criteria were absent from many of them as well. It is impossible to change the breakpoints to be consistent across the data if MIC values are not supplied along with the SIR results. When considering the change in resistance over time, this poses a problem.

During the systematic reviews, many different variables were collected to determine antibiotic resistance and help adjust for bias in the data. These variables included the MIC values, the SIR values, AST methods used, syndromes, HAI or CAI, guidelines followed (including year), and diagnostic samples. Unfortunately, a majority of this information was not recorded in the publications. Recording this information in the papers gives a full picture of the study and how it was conducted, allowing researchers to assess the quality of the study and results. This is especially important as AMR study results are scarce and usually only a few are done in particular countries and time points. When collecting data from surveillance systems, reports or datasets sent directly from the researcher, some of these variables were more available, however, overall it was rarely reported. The lack of MIC values reported created a significant limitation for this study as it was not possible to harmonize the resistance rates over time. From all the data collected, a handful of different guidelines were followed to determine the SIR value. CLSI/NCCLS was the most common guideline, and EUCAST/BSAC was used in a few publications. These parameters differ between guidelines and change over time. If the MIC values were reported, it would have been possible to adjust the SIR

values to reflect today's current guidelines. This results in an underestimation of AMR in the pathogen and antimicrobial combination in which the guidelines changed significantly over time. [183] To help alleviate this, antimicrobials were focused on which the breakpoints changed the least over time within an antimicrobial class. For example, one of the antimicrobials of interest is fluoroquinolones. One of the main fluoroquinolones tested is ciprofloxacin, however, for Enterobacteriaceae, the guidelines changed significantly in 2019, resulting in an underestimation of AMR. The breakpoints for nalidixic acid, ofloxacin, ofloxacin and gatifloxacin have stayed constant over time, so combining these antibiotics results in a more accurate picture of antimicrobial resistance in fluoroquinolones.

The CLSI breakpoints for ciprofloxacin resistance for typhoidal Salmonella were decreased in 2012, for other Enterobacteriaceae in 2019, and for third generation cephalosporin resistance in 2010. Breakpoints for Pseudomonas aeruginosa resistance to fluoroquinolones, piperacillin, and ticarcillin were dropped in 2012, while those for Acinetobacter spp. resistance to carbapenems were lowered in 2014. [184] The percentage of isolates classified as non-susceptible could significantly rise as a result of these adjustments. On the other hand, the breakpoints for S. pneumoniae and penicillin resistance for illnesses other than meningitis were raised in 2008, dramatically lowering the number of isolates categorized as non-susceptible (Figure 6.3).

Using a dataset from JMI (Jones Microbiology Institute) SENTRY Antimicrobial Surveillance Program containing AMR data for numerous countries (personal communication), the prevalence of resistance is interpreted in certain pathogen-antimicrobial combinations using different versions of the breakpoints to assess the

impact of breakpoint changes on the prevalence of resistance reported. The minimum inhibitory concentrations (MICs) provided in the dataset was used to classify isolates as sensitive, intermediate or resistant based on the CLSI 2005 and CLSI 2020 breakpoints (pre and post the previously mentioned changes). The proportion of intermediate or full resistance isolates for third-generation cephalosporins, carbapenems, and fluoroquinolones in *Escherichia coli* and third-generation cephalosporins and carbapenems in *K. pneumoniae* and penicillin in *S. pneumoniae* were then calculated. A paired t-test was used to assess the statistical significance of the prevalence of resistance interpreted by the two sets of breakpoints. Secondly, data on the MIC values of *S.* Typhi isolates was extracted from Capoor et al. [71] and calculated the prevalence of fluoroquinolone resistance based on the CLSI 2005 and CLSI 2012 breakpoints.

In *K. pneumoniae*, *E. coli* and *S. pneumoniae* there was a statistically significant increase in the prevalence of resistance when interpreting based on the CLSI 2020 breakpoints compared to CLSI 2005 (p-values of <0·001). This difference was most notable for 3rd generation cephalosporins in *K. pneumoniae* and *Escherichia coli,* carbapenems in *K. pneumoniae,* and aminopenicillins in *S. pneumoniae* (Figure 6.3). For *S.* Typhi, the prevalence of resistance was significant, with just 2% of isolates classified as intermediate or resistant based on the CLSI 2005 breakpoints, compared to 51% intermediate or resistant using the CLSI 2012 breakpoints. Limited data availability precluded this analysis's extension, but this highlights the importance of knowing the breakpoints used to determine resistance and the impact that this may have on the prevalence of resistance reported for various pathogen-antimicrobial combinations.

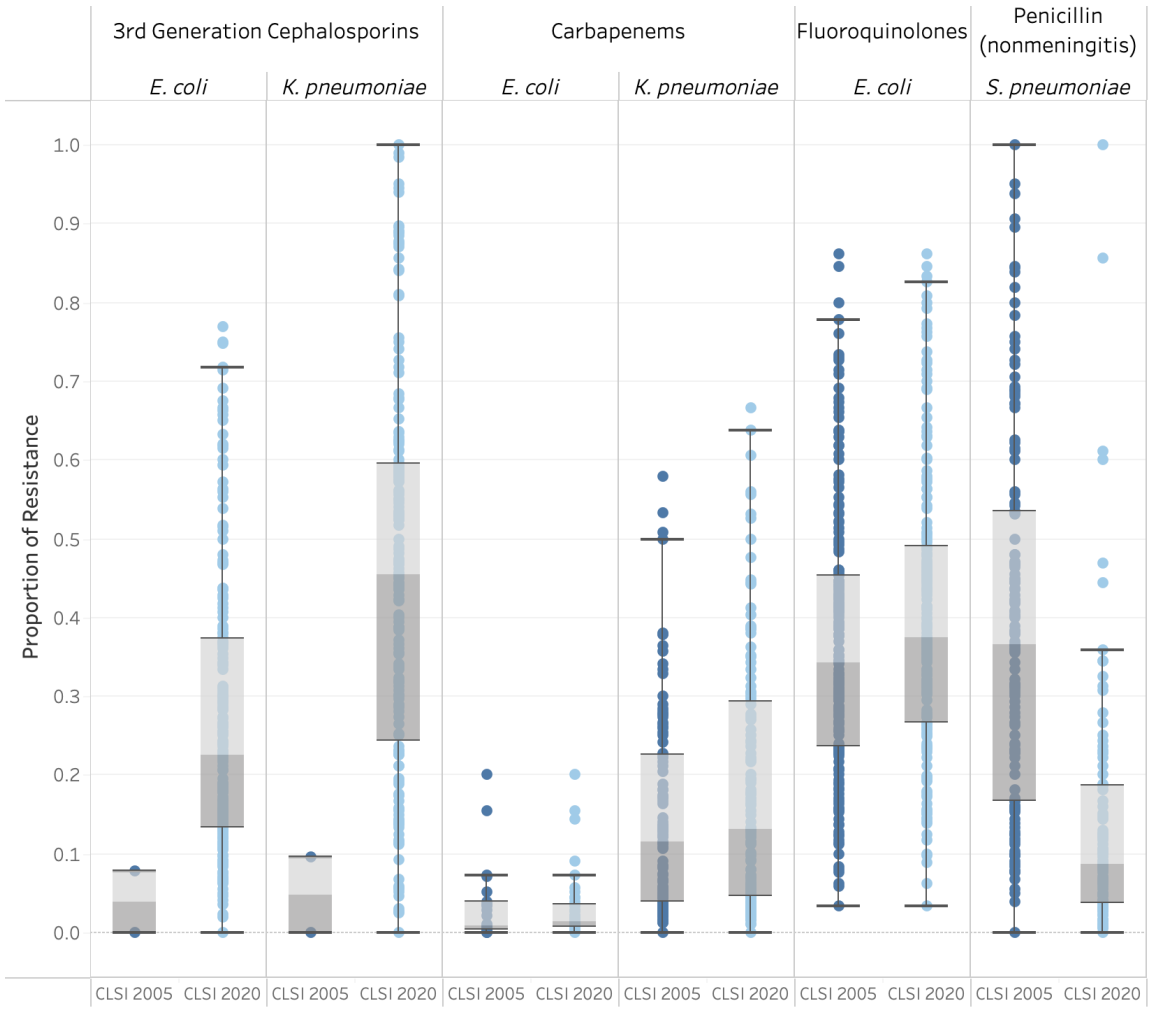

Figure 6.3: Comparison of the prevalence of AMR using different versions of CLSI guidelines. X-axis indicates breakpoint guideline version used. Data supplied by JMI SENTRY of AMR in Europe, South and Southeast Asia, Latin America, and the United States 2013-2018. CLSI 2005: 3rd generation cephalosporins = Ceftriaxone= S≤8 I=36 R≥64 µg/ml, Ceftazidime = S≤8 I=20 R≥32 µg/ml, Cefoperazone = S≤16 I=40 R≥64 µg/ml; Carbapenems = Doripenem/Imipenem/Meropenem = S≤4 I=10 R≥ 16 µg/ml, Ertapenem = S≤ 2 I=4 R≥ 8 µg/ml; Fluoroquinolones = Ciprofloxacin = S≤ 1 I=2 R≥ 4 µg/ml, Levofloxacin = S≤2 I=4 R≤8 µg/ml. CLSI 2020: 3rd generation cephalosporins = Ceftriaxone =S≤ 1 I= 2 R≥4 µg/ml, Ceftazidime = S≤ 4 I=8 R≥16 µg/ml, Cefoperazone = S≤ 16 I=32 R≥ 64 µg/ml; Carbapenems = Doripenem/Imipenem/Meropenem = S≤ 1 I= 2 R≥ 4 µg/ml, Ertapenem = S≤ 0.5 I=1 R≥ 2 µg/ml; Fluoroquinolones = Ciprofloxacin = S≤0.25 I=0.5 R≥ 1 µg/ml, Levofloxacin = S≤ 0.5 I=1 R≥ 2 µg/ml.

A surveillance or reporting system is needed in order to include the pathogen's AMR profile after it has been identified. For gathering, processing, and sharing AMR data, electronic reporting systems are very helpful. [185] These can not only make data entry easier but also enable data standardization and validation, fast assessment of temporal trends in resistance, and detection of regional or global outbreaks. Few LMICs have implemented electronic reporting systems due to infrastructure and staff limitations,

such as a lack of a qualified IT workforce. There isn't much proof that biases are introduced when AMR profiles are reported. There may be negative connotations to a hospital reporting high AMR rates, such as decreased reputation and loss of funding sources. There is no clear evidence that this leads to inaccurate reporting of AMR.[186]

6.3.6 DUPLICATED DATA

Antimicrobial susceptibility testing is frequently performed, typically on different sample types, on each patient during a hospital stay, which results in several AST findings for the same episode of infection. The infecting bacterium is cultured as a result. Deduplication techniques used by various organizations and researchers undertaking AMR surveillance can produce varying levels of resistance for the same data set.[187,188] The following are some crucial deduplication techniques: (1) including all isolates regardless of specimen type, the number of samples per episode, or the patient; (2) taking the first isolate of a particular bacterial species per patient per analysis period; (3) taking the first isolate of a particular sample type per patient per analysis period; and (4) taking isolates from different infection episodes for the same patient within the analysis period, such as only removing duplicates that occurred; (5) including every isolate with a deviating antimicrobial susceptibility profile; (6) incorporating every isolate with a diverging antimicrobial susceptibility profile; (7) combining any of the aforementioned approaches.[189] Only the initial isolate of a given bacterial species is used in the CLSI technique for each patient throughout each analysis period. The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network, WHO GLASS, and the European Antimicrobial Resistance Surveillance Network (EARS-Net) follow this method. [187] When combining AMR data from many sources to take into consideration the various deduplication

techniques, consistency is crucial (or lack thereof). However, in practice, this can be very challenging because AMR data are frequently provided in the form of microbiology data unrelated to patient information and without any mention of any deduplication methods that have been used. This substantially restricts the alternatives for precise data deduplication, which should be taken into account when estimating the burden of AMR.

6.3.7 METHODS ACCOUNTING FOR BIAS IN PASSIVE SURVEILLANCE DATA

The observed biases must be taken into account when predicting the prevalence of AMR from passive surveillance data to prevent overestimation. Examples include techniques for adjusting for biases related to case identification, sampling, and culture use, as well as culture sensitivity and AST use. The breakpoints used to interpret the AMR data are also significant, but this is not further explored here because it may be taken into account by only including data that specifies interpretation based on current breakpoints.

As far as I am aware, no studies have yet adequately accounted for the biases seen in AMR data. Kalanxhi et al. [190] show the significance of taking into account the clustered structure of the data when processing AMR surveillance data from several facilities. This is similar to processing survey data. These techniques increase the 95% confidence intervals and take into account different sampling and testing techniques, but they have no effect on the precision or take into account a potential overestimation of the point estimations of AMR prevalence.

Assigning a quality score to the data source may help assess the studies' validity and account for some of the identified biases. Once a score is given to the study dataset, it can be used as a weighting factor when building models of AMR prevalence. This approach is subjective as there is no gold standard criteria list for determining a quality score and the method differs between researchers. Quality scores are difficult to measure and require enough information variables to assess the data's quality. The necessary information to assign a quality score is often not reported, weakening the validity of the score or rendering the approach difficult to implement.[146]

Direct adjustment of passive surveillance data would be considered the most straightforward method to account for the identified biases. Matching the studies on AMR prevalence from active and passive surveillance would be required, and a conversion between the two methods of estimation calculated to account for the specified biases. Sugianli *et al.* demonstrated this by comparing the prevalence of resistance in *E. coli* and *K. pneumoniae* urine samples from a retrospective laboratory-based study and a population-based study in Indonesia.[191] They found a considerably higher prevalence of resistance in the laboratory-based study compared to the population-based study, supporting the hypothesis of an overestimation of resistance in passive surveillance. However, these results are not generalizable to all locations as the magnitude of the biases likely differs between locations. Many matched studies would be required to adjust the passive surveillance data, suitably dispersed in time and space. Such studies are infrequently undertaken due to the high costs and the low incidence of many diseases being studied.

Modeling the extent of each bias and making adjustments within the data would be the third method for correcting for the discovered biases. In their most recent estimates of the burden of AMR, the GBD incorporates modifications for data from tertiary hospitals. They assigned tertiary, non-tertiary, mixed, or other facilities to all prevalence of AMR data points and fitted linear models to assess the variation in resistance. [4] Due to the large number of data points that were integrated with the non-tertiary data and were given the mixed/other classification, the magnitude of this modification was, however, very small. For a complete understanding of this prejudice, additional information and analysis are needed. The STRATAA study used a modeling framework to quantify and correct for biases in passive surveillance data when estimating location-specific incidence of typhoid fever, despite the fact that no studies implementing adjustments for multiple biases in AMR data were found. [192] For treatment-seeking behavior, blood culture rate, and blood culture sensitivity, they made changes. With this method, data must be supplied for each bias across the datasets used for the analysis. Studies on the prevalence of AMR frequently fail to report this information, which makes it difficult to correct for these biases. [146] Comparisons are challenging since different datasets use different criteria, and there are little data from LMICs and a general lack of epidemiological data connected to clinical information. The STRATAA study, on the other hand, demonstrates unequivocally the possibility of modeling bias adjustment factors and suggests a promising direction for future research assessing the prevalence and burden of AMR.

6.4 DISCUSSION

When determining the prevalence of AMR in significant pathogen-antimicrobial combinations, this chapter looks at the constraints and biases in the data. The quality of

data in LMICs has been reviewed and large data gaps have been investigated. The prevalence of resistance was statistically significantly overestimated in hospital-based studies as compared to community-based studies, according to data gathered for the purpose of this thesis (as an indicator of passive versus active surveillance). Low rates of treatment seeking, culture use, culture sensitivity (or high contamination), and AST use were shown to be crucial causes of potential bias after a review of the literature was conducted. The necessity of taking this into account is emphasized in data collection and analysis by revealing a statistically significant difference in the prevalence of resistance reported in HCAI and CAI, as well as in ICUs compared to outpatients and surgical wards. Breakpoint adjustments must also be taken into account when conducting a case-by-case study because they have a minor but statistically significant impact on the prevalence of resistance reported in *E. coli* and *K. pneumoniae* and a considerable impact on *S.* Typhi fluoroquinolone resistance. We were surprised to discover that there was no difference in resistance between isolates from blood and urine, proving that this is not always a source of bias or heterogeneity in AMR data. To more effectively diagnose patients and examine their AMR profiles, laboratories must improve their standards and capabilities. Securing resource access, automating culturing, and increasing microbiological knowledge for healthcare professionals are all ways to advance. This must be put into practice in conjunction with training healthcare professionals to enhance cultivation techniques and offer no-cost or low-cost services to encourage use.

This chapter emphasizes the significance of disclosing quality control indicators in publications since a lack of standards when disseminating microbiology data makes it difficult to evaluate the caliber of the methodology employed and rank the overall

caliber of investigations. Breakpoint recommendations were not followed, a controlled strain was not utilized, a diagnostic sample was not taken, antibiotic sensitivity tests were not employed, and external quality evaluation guidelines were not followed in many studies. It was difficult to determine which study was more reliable or the apparent causes of the reported discrepancy in resistance when contradicting data was found from the same country and time period. Adherence to reporting rules, Microbiology Investigation Criteria for Reporting Objectively (MICRO) guidelines[93], can standardize this procedure and produce more comparable data as well as more accurate estimates of AMR. These informational elements are extremely crucial.

6.5 CONCLUSIONS

There are numerous constraints and biases while working with AMR, which differ in scope for HICs and LMICs. Many of these biases result from the lack of guidelines and defined reporting process for AMR data. The number of cases of AMR reported in communities may be skewed by behavioral choices towards seeking treatment or attitudes toward antibiotics. These biases and constraints lead to an overestimation of AMR, making it challenging to interpret the real trends in AMR around the world.

To account for data bias, a wide variety of data variables were gathered during the systematic reviews of *Shigella* and *E. coli*. Many of these informational characteristics were absent from the published studies. To fully explore and quantify these biases and to make it possible to adjust passive surveillance AMR data to accurately reflect the community, more research must be done. In the meantime, particularly in settings with limited resources, this must be taken into account as a constraint when estimating the prevalence of AMR using passive surveillance data. However, if carefully analyzed,

passive surveillance data can still be useful in determining the extent and patterns of resistance prevalence.

CHAPTER 7

Conclusions and Future Work

AMR is a multifactorial issue, with different drivers of resistance and a multitude of intervention approaches. It is a multifaceted significant public health threat that affects many modern-day medical treatments and increases mortality rates in LMICs and HICs. AMR directly affects progress in healthcare, food production, and human life expectancy. The WHOs priority pathogen list featured the pathogen-antimicrobial combinations *Shigella* and fluoroquinolones, *E. coli* and carbapenems. Across all combinations, India and China have consistently shown very high rates of resistance for a long time. The output from this study is important and vital to making informed decisions regarding appropriate treatment on a national level. Additionally, this study identifies where AMR surveillance and interventions need to be implemented.

Although many people are aware of AMR, knowledge of AMR needs improvement. Many people believe if they do not overuse antimicrobials, they are not at risk of developing a resistant infection. This is not a problem isolated to LMICs and improvement is also needed in HICs to stop the increase in AMR infections. Actions needed to help alleviate AMR in the world are: policy change to antimicrobial availability, antimicrobial prescribing habits, improvement in public education, more resources provided to LMICs, and enforcement of laws and regulations pertaining to antimicrobial prescribing, use and availability. Additionally, infection control in

communities and inside healthcare facilities such as regular handwashing, improved water quality and sanitation, and no cross contamination between patients. More research towards creating new antimicrobials is needed take the pressure off of existing antimicrobials. A decrease in selective pressures, such as reduced antimicrobial use in agriculture, less antimicrobial misuse and overprescribing, more policy and regulation of antimicrobials and more public education about best practices. Finally, more infrastructure is needed to set up national and international surveillance systems of AMR. The results from this thesis will hopefully prompt an update in treatment recommendations and shift towards more local recommendations instead of general international recommendations. I hope the publication of this work and other work in the GRAM project will bring more awareness on this topic, providing an opportunity for action to follow.

7.1 OVERVIEW

To date, there has not been a systematic review published looking at the prevalence of resistance in *Shigella* and *E. coli* worldwide. In **Chapters 2 and 4** the systematic reviews conducted for this thesis were discussed. Both systematic reviews were unique in covering 28 years, spanning every country worldwide and with no language restrictions on publications. This ensured a comprehensive search for relevant publications and a comprehensive collection of available *Shigella* and *E. coli* AMR data. The results of these systematic reviews revealed widespread *Shigella* and *E. coli* resistance to antimicrobials and identified many data gaps that exist in published literature. These gaps were ultimately filled to the best of my ability by also collecting surveillance system data, data from GRAM collaborators and other sources. This portion of my thesis exceeded my expectations of how time-consuming this process

was. Collecting data through a systematic review at a gold standard requires going over each publication multiple times and double-checking each extraction of the data. When exporting the extracted systematic review data from DistillerSR, a lot of data cleaning was required, such as categorizing any qualitative data collected and transforming the data format into something more readable by R statistical software. Extracting data from other data sources required changing the format to match the format of my systematic review data.

As I discussed in **Chapter 6**, once I analyzed all the data collected, I found that many variables of information were missing. For a complete list of the extracted variables from all datasets/publications see figure A.3 in the appendix. My methodology plans then needed shifting as many planned adjustments to the data and analyses were impossible without further information. A quality score of datasets and publications was not possible to assess with many methodology variables missing, such as; testing methodology, sampling strategy, hospital/lab information, and whether the lab had any EQA. Additional geospatial maps I had hoped to produce with separate prevalence of resistance in hospital-acquired *E. coli* and community-acquired *E. coli* maps, *E. coli* resistance in neonates, differences in the prevalence of resistance in age brackets, differences in the prevalence of resistance in sterile vs. non-sterile culture sites, and the prevalence of resistance in MDR *Shigella*, were not possible with the missing data.

In the outliering process of the data, multiple methods were trialed until I settled on the MAD method, as described in Chapter 3, which was effective at outliering following the trend of the data in each country. The geospatial modeling process described in **Chapters 3 and 5** was a very iterative process, with many adjustments of model

parameters, various combinations of covariates, multiple combinations of child models, and checking the trends in the final output matches AMR as stated in the current literature. As new data was collected, I extracted the data into the format needed and updated my datasets. I then reran the outliering and geospatial modeling processes to update and improve my estimates with additional data. The results revealed the prevalence of resistance in *Shigella* and fluoroquinolones and *E. coli* and fluoroquinolones, 3rd generation cephalosporins and carbapenems. We can see which countries are most heavily burdened with high resistance in particular antimicrobials and where intervention and policy change and other public health efforts should be targeted.

Mapping the prevalence of resistance worldwide helps to highlight and identify trends in resistance, further informing the understanding of how quick the emergence of resistance can be and how it spreads across the globe. Seeing how resistance increases and decreases over time alongside the change in treatment recommendations can provide vital information for the future and help predict how quickly resistance may decrease when treatment is changed. Maps can also identify hotspots of resistance, highlighting where further research and where interventions are most needed. Understanding which countries suffer from the highest rates of resistance can help in identifying risk factors as to why they are suffering the most and indicate what may be causing the higher rates of resistance. Countries with a high prevalence of resistance would be able to look at countries in the same region with a lower prevalence of resistance or in countries facing similar resistance challenges and seek to exchange best practices for managing and controlling resistance. These maps can help guide treatment decisions, as resistance differs by country, treatment decisions need to be based on the

country or region's current prevalence of resistance. Additionally, the knowledge of the state of resistance in different countries can encourage behavior change to prevent infection when living or visiting those areas.

The most concerning result from this thesis is the alarming high resistance in *E.coli* to several first and second-line antimicrobials. India, Cambodia, Pakistan, Iraq, Egypt, Myanmar, Afghanistan, Bangladesh, Sudan, Bhutan, Iran, Guatemala, Macedonia, Syria, Cameroon, Indonesia, Ethiopia, Mexico, Honduras, Nigeria, Laos, Sri Lanka, Haiti, and China are all estimated to have had over 50% resistance to fluoroquinolones, carbapenems, and 3rd generation cephalosporins in 2020. India is estimated to have had over 80% resistance to all three antimicrobials. Additionally, it is estimated over 90% fluoroquinolone resistance in *Shigella* in China and India, which is also a first-line treatment. As discussed in Chapter.3, some antimicrobials have a resistance threshold set for when an antimicrobial should no longer be used and first-line treatment needs to change in order to stop exacerbating resistance. This threshold is typically set between 10%-20% reported resistance. There is no official threshold set for FQR in *E.coli* or *Shigella,* or for 3rd generation cephalosporin and carbapenems resistance in *E.coli*. As the majority of deaths from AMR are in children under five living in LMICs and resistance is so high in these LMICs mentioned above, action needs to be taken to help generate better-quality data and enable more focused and efficient interventions to address AMR.

In addition to achieving the aim of this thesis, estimating the prevalence of disease over time in every country in the world, in selected pathogen-antimicrobial combinations, many other insights into AMR were uncovered. The significant data gaps in AMR make

conducting studies like this challenging and also limit the understanding of the impact of AMR in the world. Significant data gaps also indicate a lack of infrastructure in countries, restricting the ability to culture samples, run AST, and have a national surveillance system. The lack of reporting essential details, such as those in the MICRO checklist, linked to AMR data severely restricts how the data can be used. By being aware of the many challenges and limitations of AMR data, we can better report results and adjust for bias producing more accurate and representative rates of resistance.

7.2 FUTURE WORK

This thesis was only the beginning of this work, by laying the foundation to investigate the state of AMR worldwide and understand the burden of AMR. The next step from where I left off would be to model the estimates of the prevalence of *Shigella* and *E. coli* at a finer spatial resolution. Each data point would need to be linked by coordinates to the city or hospital where the infection was acquired. Modeling the data collected at a finer resolution will provide additional information on where interventions should be targeted inside a country. The significant disparities in the prevalence of resistance between some cities within the same country will be captured in these estimates. Estimates of the prevalence of resistance at the city level can also reveal drivers of AMR within the country.

Another analysis I would perform next would be to look at the difference in the prevalence of resistance pre and post COVID-19. As discussed in Chapter 2, it has been reported that COVID-19 has only exacerbated the AMR crisis and in many countries, resistance will worsen from the misuse of antimicrobials since the COVID-19 pandemic. I revealed the unnecessary antimicrobial prescriptions and over-the-counter

use of antimicrobials used to treat COVID-19 in many countries worldwide. It would be essential to understand the pandemic's impact on AMR and potentially what impact another pandemic or worldwide illness could cause.

Finally, predictions of the estimates of resistance were produced in this thesis, however, no inference of the drivers of AMR was possible. Many covariates were used in the geospatial models to capture socio-economic status, health system access, food consumption, climate, and demographic data. These covariates were used to aid in the prediction of the prevalence of AMR and did not provide insight into the causes of AMR. Determining the relationship between AMR and these covariates could also be helpful in future modeling efforts. Exploring factors that influence an increase in resistance is especially important for intervention efforts. In addition, looking at the impacts of AMR on the environment and agriculture. The AMR crisis will continue to exasperate without addressing the impact and negative consequences of extensive antimicrobial use in agriculture.

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189 Rebekka K, G. G Sören. Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data – The Influence of Different Parameters in a Routine Clinical Microbiology Laboratory. ; 11: e0147965.

190 Erta K, Gilbert O, Geetanjali K, Eili K. Confidence interval methods for antimicrobial resistance surveillance data. 2021; 10: 91.

191 Kristianto S Adhi, Franciscus G, Lia K R, Ida P, D. de J Menno, Frank van L *et al.* Laboratory-based versus population-based surveillance of antimicrobial resistance to inform empirical treatment for suspected urinary tract infection in Indonesia. ; 15: e0230489.

192 T. P Maile, E. M James, Merryn V, L. W Joshua, Stephen B, Buddha B *et al.* A Bayesian approach for estimating typhoid fever incidence from large-scale facility-based passive surveillance data. ; : 2020.10.05.20206938.

A

Appendix to Chapter. 2

The appendix to Chapter 2 contains additional tables and figures. Chapter 2: Antimicrobial Drug Resistance in Shigella Isolates Worldwide, from 1990 to 2018: A Systematic Review of the Literature. This section includes the search strategy for the systematic review, the PRISMA checklist, pooled prevalence forest plots for each study extracted, and the variables extracted from each study.

Search Number	Search Term
1	*Shigella/
2	shigellosis
3	shigella
4	1 or 2 or 3
5	exp *Drug Resistance, Bacterial/
6	exp Microbial Sensitivity Tests/
7	"antibacterial resistan*"
8	"antibacterial drug resistan*"
9	"bacterial drug resistan*"
10	"antimicrobial resistan*"
11	"antibiotic drug resistan*"
12	"bacterial resistan*"
13	"antibiotic resistan*"
14	"bacterial surveillan*"
15	"antibiotic surveillan*"
16	"antibacterial surveillan*"
17	"antimicrobial surveillan*"
18	"antimicrobial susceptib*"
19	"antibiotic susceptib*"
20	"antibacterial susceptib*"
21	"antibiotic resistan*"
22	"antibiotic sensitiv*"
23	"antimicrobial sensitiv*"
24	"antibacterial sensitiv*"
25	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	4 and 25
27	limit 26 to yr="1990 -Current"

Table A.1: Search strategy developed in MedLine, Embase and Global Health

Section/topic	#	Checklist item	Reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	☒
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	☒
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	☒
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	☒
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be, and, if available, provide registration information including registration number.	☒
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	☒
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	☒
Search	8	Present full electronic search strategy for at least one database, including limits used.	☒
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	☒
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	☒
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	☒
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies and how this information is to be used in any data synthesis.	☒
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	☒
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	☒
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	☒
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	☒
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	☒
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	☒
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment	☒
Results of individual studies	20	All outcomes considered), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	☒
Synthesis of results	21	Present results of each meta-analysis done, confidence intervals and measures of consistency.	☒
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	☒
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression)	☒
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	☒
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	☒
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	☒
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	☒

Table A.2 PRISMA checklist of items to include when reporting a systematic review or meta-analysis

	Variable Name	Description
1	Start Date	The date in which the study was initiated (dd-mm-yyyy) If month or day is not available, input 00 (ex. 00-00-2018)
2	End Date	The date in which the study was completed (dd-mm-yyyy) If month or day is not available, input 00 (ex. 00-00-2018)
3	Setting	The setting in which the study was performed.
4	Suspected cases	The number of people who were screened for the presence of Shigella (S. dysenteriae, S. flexneri, S. boydii, S. sonnei)
5	Lower age	Enter the lower age limit of the individuals included in the study.
6	Upper age	Enter the upper age limit of the individuals included in the study.
7	Mean age	Mean age of persons sampled.
8	SD age	Standard deviation of the age of persons sampled.
9	Median age	Mean age of persons sampled.
10	Percent male	Of the samples tested the percentage that were from males.
11	Study population notes	Any additional information to describe the study population (ex. children with malaria)
12	Diagnostic Sample	The type of sample cultured. Select all that apply.
13	Diagnostic method	The type of sample cultured for presence of Shigella (S. dysenteriae, S. flexneri, S. boydii, S. sonnei). Select all that apply.
14	Presence of drug resistance	Field indicates the detection of drug resistance within the isolate; choose either “yes“ (resistance/intermediate resistance/decreased susceptibility) or “no“ (no resistance) from the dropdown list
15	Guidelines used	Enter the guidelines used to determine the resistance profile. Choose guideline from the dropdown list, or select “Not specified”. If breakpoints but no guidelines are defined then enter them in the following format: S≤XX; I = YY-ZZ; R≥VV ug/ml with SIR referring to susceptible, intermediate and resistant, and the XX/YY/ZZ/VV the breakpoints
16	Guidelines/breakpoints notes	If you entered guidelines above but the study also mentions specific breakpoints used, please enter them here (ex.S≤XX; I = YY-ZZ; R≥VV)
17	Lab quality control	What measures of quality control are mentioned in the study. Select all that were mentioned.
18	Control strain	Field indicates the strain used as a control during AMR testing. If the study gives the name of the strain used as a control, select the name of the strain from the list, otherwise select ‘Not stated’
19	Surveillance networks	Is the data collected used in this reference part of one of the following global surveillance studies
20	Suspected cases	The number of people who were screened for the presence of E. coli
21	Escherichia coli positive	The number of people who tested positive for E. coli
22	Infection rate	If stated, what was the number of infection per 1000 patient days
23	Suspected cases	The number of people who were screened for the presence of Staph aureus
24	Staphylococcus aureus positive	The number of people who tested positive for Staph aureus
25	Infection rate	If stated, what was the number of infection per 1000 patient days
26	Suspected cases	The number of people who were screened for the presence of K.pneumoniae
27	Klebsiella pneumoniae positive	The number of people who tested positive for K.pneumoniae
28	Infection rate	If stated, what was the number of infection per 1000 patient days
29	Suspected cases	The number of people who were screened for the presence of S.pneumoniae
30	Streptococcus pneumoniae positive	The number of people who tested positive for S.pneumoniae
31	Infection rate	If stated, what was the number of infection per 1000 patient days
32	Suspected cases	The number of people who were screened for the presence of Streptococcus pneumoniae

33	Comorbidities	Does this study include patients with the following comorbidities? A comorbidity is an underlying disease not directly related to the current infection.
34	If stated, what is the prevalence of cancer patients in the study?	
35	If stated, what is the prevalence of cystic fibrosis patients in the study?	
36	If stated, what is the prevalence of diabetes patients in the study?	
37	If stated, what is the prevalence of HIV patients in the study?	
38	If stated, what is the prevalence of tuberculosis patients in the study?	
39	If stated, what is the prevalence of COPD patients in the study?	
40	If stated, what is the prevalence of cirrhosis patients in the study?	
41	Please Specify	
42	If stated, what is the prevalence of the comorbidity in the study?	
43	Study population notes	Any additional information to describe the study population (ex. children with malaria)
44	Guidelines used	Enter the guidelines used to determine the resistance profile. Choose guideline from the dropdown list, or select ,Not specified
45	Clinical outcome available?	if whether information on the clinical outcome of the cases are available. This includes deaths, mortality rate or other outcomes
46	Pre admission antibiotics?	Did the patients receive antibiotics prior to cultures being taken?
47	Pre admission antibiotics %	The percentage of cases who received antibiotics prior to cultures being taken.
48	Which antibiotics?	
49	Pre admission antibiotics is generally reported as within the past 48 hours, 7 or 14 days. Please add any of this information here.	
50	Inpatient/outpatient	Were the patients in the study inpatient or outpatient or both?
51	Study notes	Any discrepancies in the study (ex. different number of patients written in abstract vs. the full text) Please write this here.
52	Comorbidities	Some studies will split the data by comorbidities.
53	Please specify which comorbidity	
54	Country	Chose the country in which the infection was acquired from
55	City name	Enter the name of the study site/location from which the infection was acquired. If this is a community study this is the location where the study participants were from, if this is a hospital or laboratory study enter the city of the hospital/laboratory
56	Site name notes	Please enter any notes or information on district/province/region where the site/s are located
57	Source of infection If stated, was the infection	

	community or hospital acquired?	
58	Definition of hospital acquired infections Was hospital acquired defined as an infection that started more that 2 days (48h) after admition?	
59	Syndrome	Select the pathogen associated syndrome
60	Setting	The setting in which the study was performed. Select all that apply.
61	Hospital Size	If mentioned, please note the number of beds in the hospital. If more that one hospital is mentioned and the data is not split by hospital please enter the data using the following format: hospital A (bed number); hospital B (bed number)
62	Ward type	If mentioned, please state which ward type the patients were recruited from.
63	Source of infection	If stated, was the infection community or hospital acquired?
64	Definition of hospital acquired infections	Was hospital acquired defined as an infection that started more that 2 days (48h) after admition?
65	Syndrome	Pathogen associated syndrome
66	Please Specify	
67	Diagnostic Sample	The type of sample cultured
68	Sensitivity test	The testing method used to detect antimicrobial resistance within the isolated strain. Select all that apply
69	Notes	Any notes on isolates tested.
70	Number examined	Enter the number of isolates used for antimicrobial testing.
71	Antimicrobials	Antimicrobials tested in the study
72	Number of isolates tested	
73	Number resistant	Enter the number of tested isolates that showed resistance to the antimicrobial used (if stated in the text).
74	Percent resistant	Enter the stated percentage of tested isolates that showed resistance to the specified antimicrobial.
75	Number intermediate	Enter the number of tested isolates that showed intermediate resistance to the antimicrobial used (if stated in the text).
76	Percent intermediate	Enter the stated percentage of tested isolates that showed intermediate resistance to the specified.
77	Number decreased susceptibility	Enter the number of tested isolates that showed decreased susceptibility to the antimicrobial used (if stated in the text). This can also be referred to as reduced sensitivity
78	Percent decreased susceptibility	Enter the number of tested isolates that showed decreased susceptibility to the antimicrobial used (if stated in the text). This can also be referred to as reduced sensitivity
79	Number susceptible	Enter the number of tested isolates that showed sensitivity to the antimicrobial used (if stated in the text).
80	Percent susceptible	Enter the percentage of tested isolates that showed sensitivity to the antimicrobial used.
81	MIC 50	If this information is provided, please record the MIC 50# here
82	MIC 90	If this information is provided, please record the MIC 90# here
83	Breakpoints	If this information is provided, please record the breakpoint# here

Table A.3 Variables of information extracted from each publication, if available.

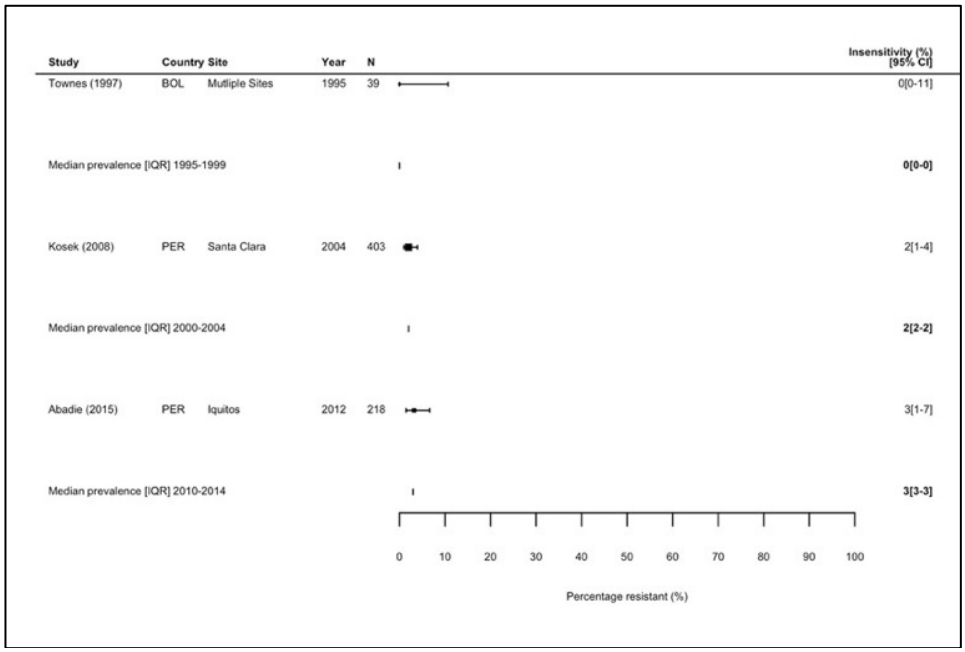


Figure A.1 Forest plot of nalidixic acid resistance in Shigella in Andean Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

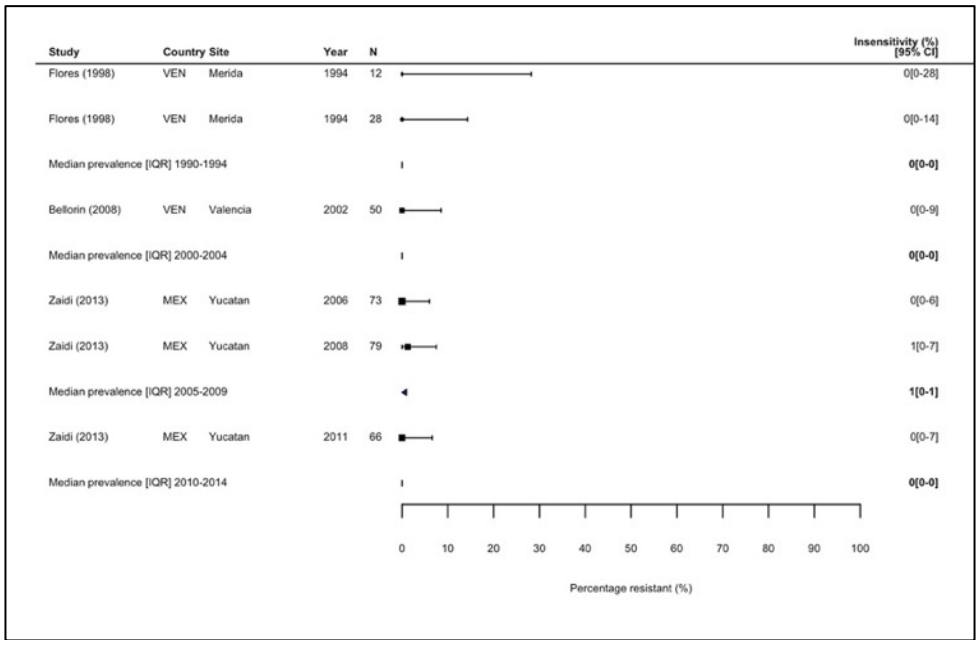


Figure A.2 Forest plot of nalidixic acid resistance in Shigella in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

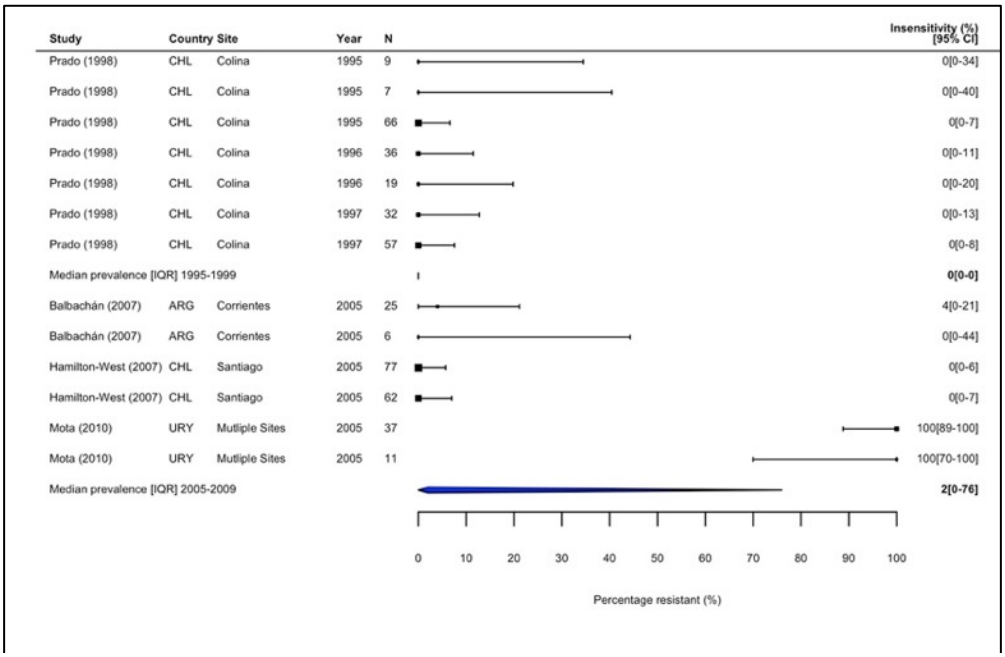


Figure A.3 Forest plot of nalidixic acid resistance in Shigella in Southern Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

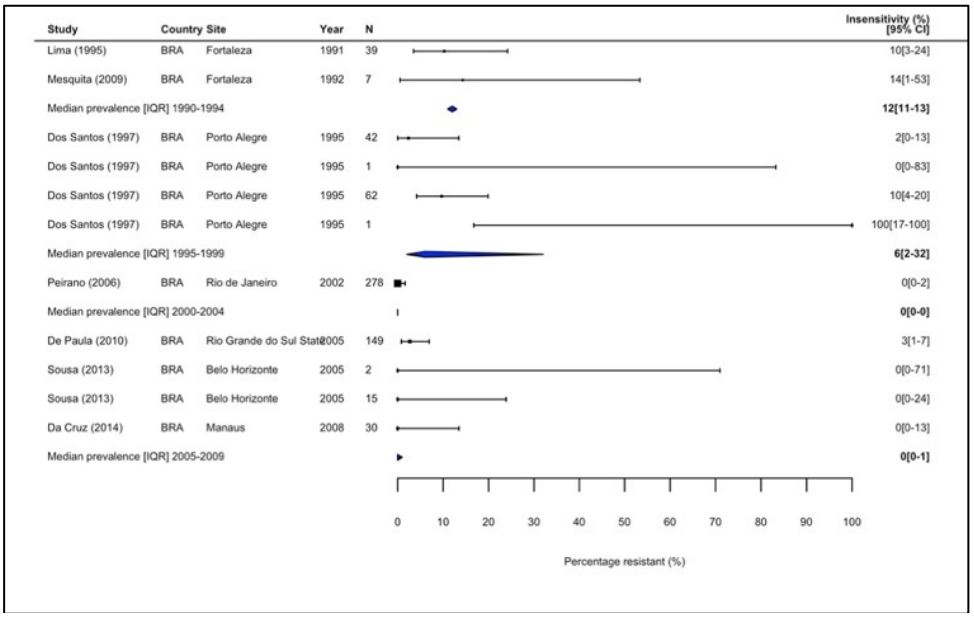


Figure A.4 Forest plot of nalidixic acid resistance in Shigella in Tropical Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

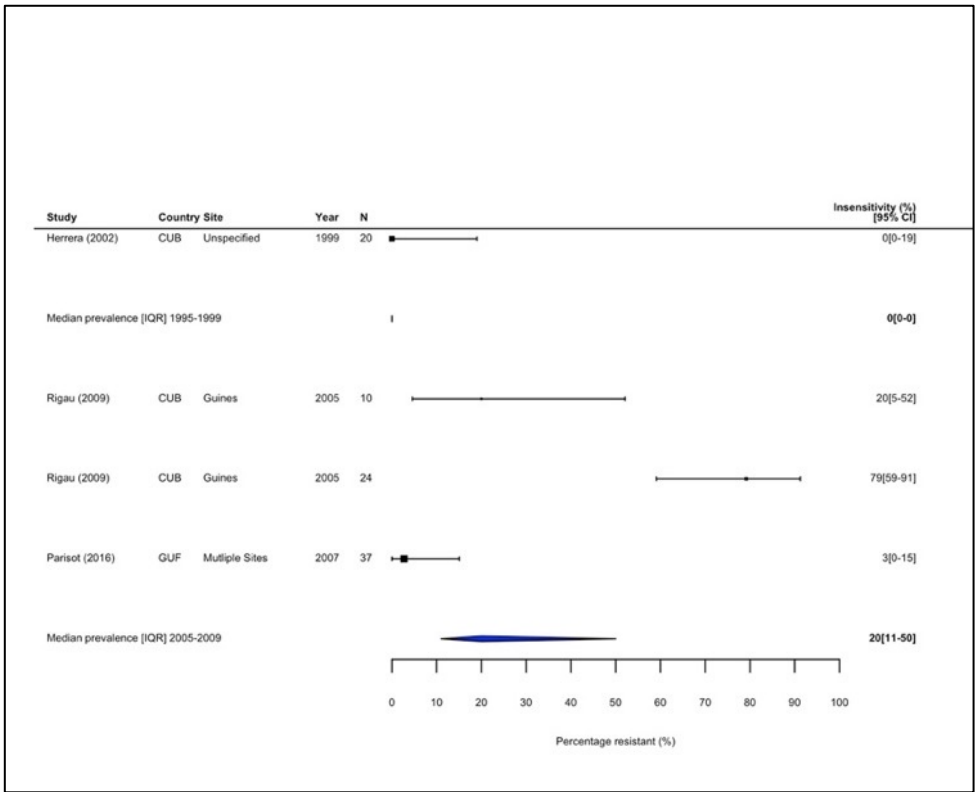


Figure A.5 Forest plot of nalidixic acid resistance in the Caribbean. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

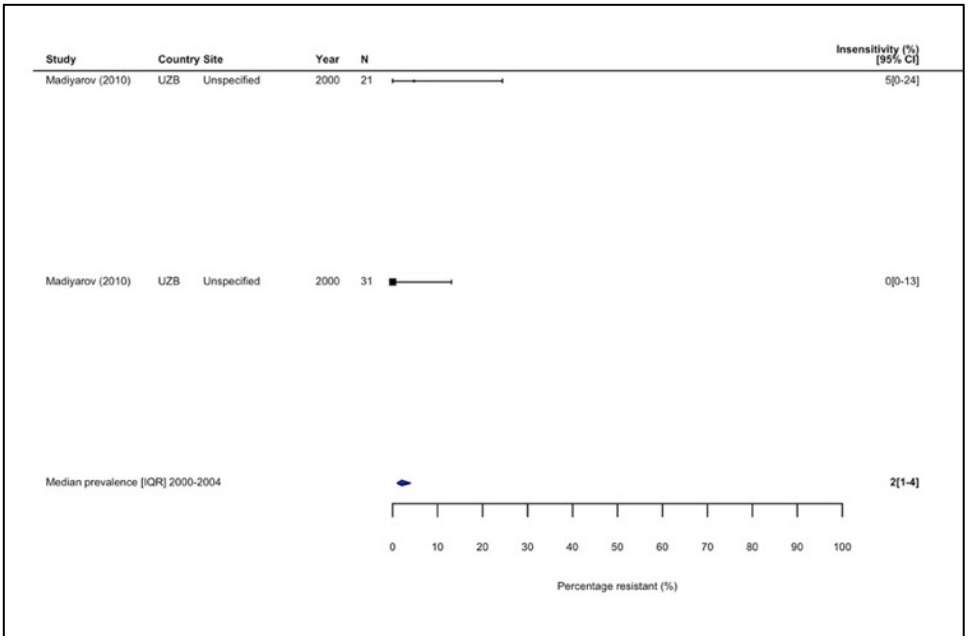
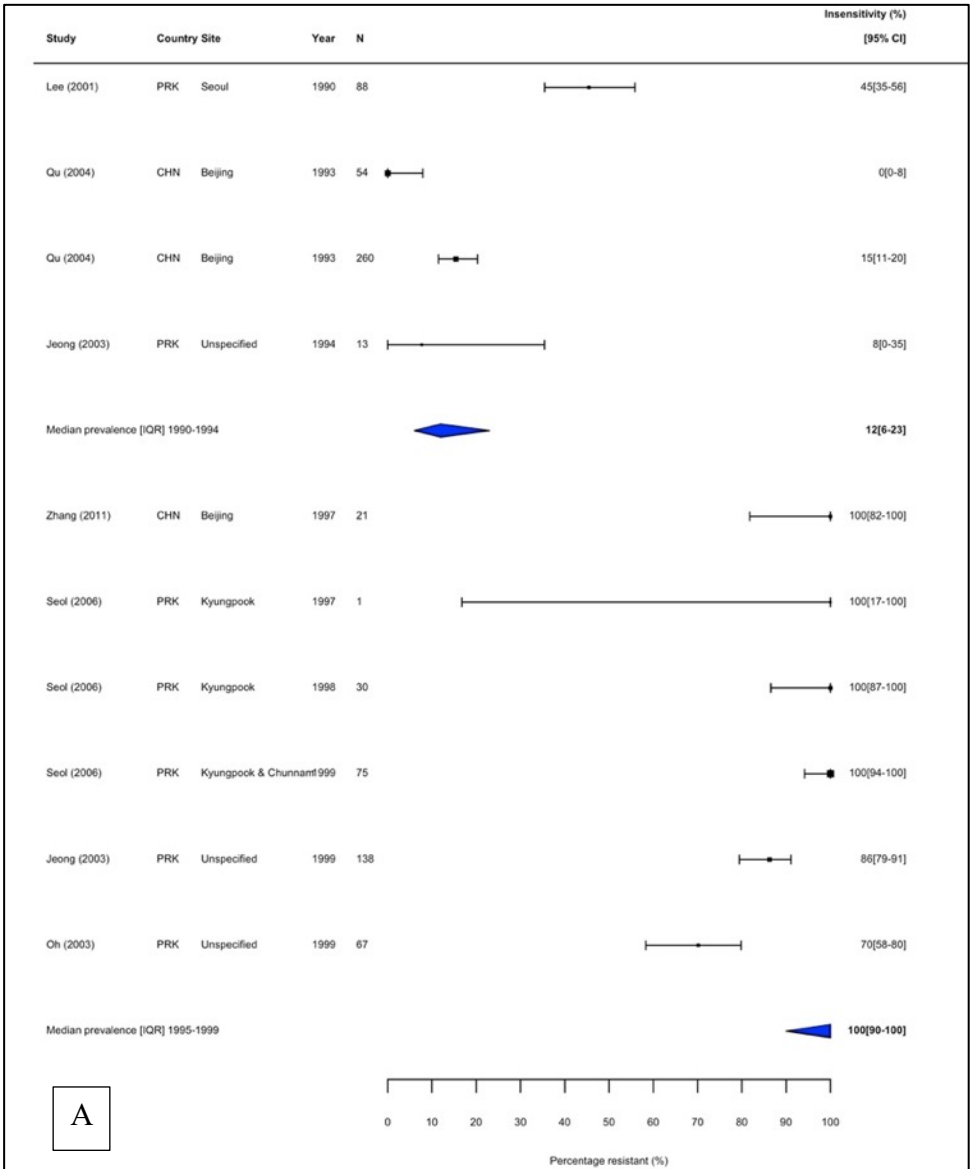
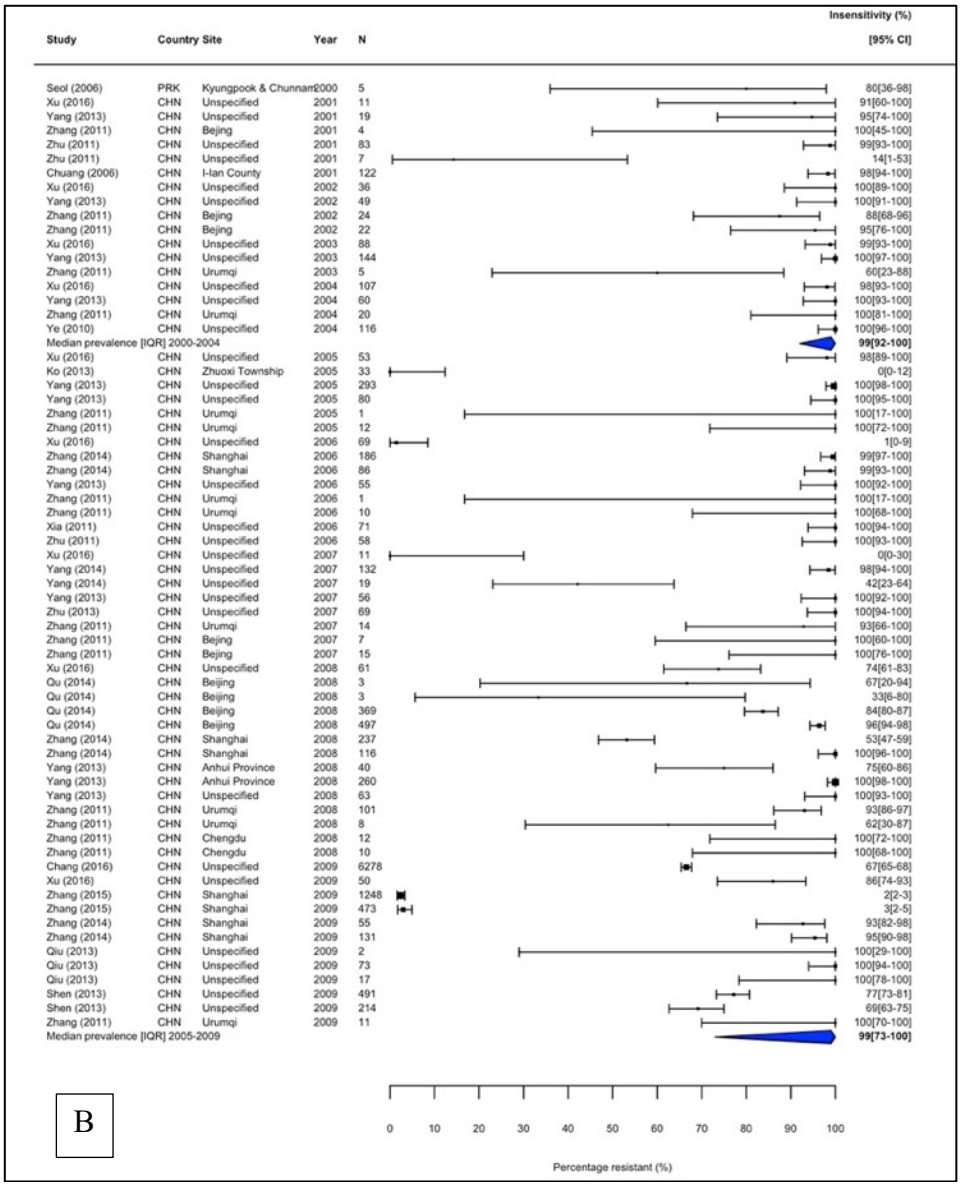


Figure A.6 Forest plot of nalidixic acid resistance in Shigella in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Insensitivity (%) [95% CI]
Lee (2001) PRK Seoul 1990 88 45[35-56]
Qu (2004) CHN Beijing 1993 54 0[0-8]
Qu (2004) CHN Beijing 1993 260 15[11-20]
Jeong (2003) PRK Unspecified 1994 13 8[0-35]
Median prevalence [IQR] 1990-1994 12[6-23]
Zhang (2011) CHN Beijing 1997 21 100[82-100]
Seol (2006) PRK Kyungpock 1997 1 100[17-100]
Seol (2006) PRK Kyungpock 1998 30 100[87-100]
Seol (2006) PRK Kyungpock & Chunnam 1999 75 100[94-100]
Jeong (2003) PRK Unspecified 1999 138 86[79-91]
Oh (2003) PRK Unspecified 1999 67 70[58-80]
Median prevalence [IQR] 1995-1999 100[90-100]
A
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)


Insensitivity (%)
Study
Country
Site
Year
N
[95% CI]
Seol (2006) PRK Kyungpook & Chunnam 2000 5 80[36-98]
Xu (2016) CHN Unspecified 2001 11 91[60-100]
Yang (2013) CHN Unspecified 2001 19 95[74-100]
Zhang (2011) CHN Bejing 2001 4 100[45-100]
Zhu (2011) CHN Unspecified 2001 83 99[93-100]
Zhu (2011) CHN Unspecified 2001 7 14[1-53]
Chuang (2006) CHN I-lan County 2001 122 98[94-100]
Xu (2016) CHN Unspecified 2002 36 100[89-100]
Yang (2013) CHN Unspecified 2002 49 100[91-100]
Zhang (2011) CHN Bejing 2002 24 88[68-96]
Zhang (2011) CHN Bejing 2002 22 95[76-100]
Xu (2016) CHN Unspecified 2003 88 99[93-100]
Yang (2013) CHN Unspecified 2003 144 100[97-100]
Zhang (2011) CHN Urumqi 2003 5 60[23-88]
Xu (2016) CHN Unspecified 2004 107 98[93-100]
Yang (2013) CHN Unspecified 2004 60 100[93-100]
Zhang (2011) CHN Urumqi 2004 20 100[81-100]
Ye (2010) CHN Unspecified 2004 116 100[96-100]
Median prevalence [IQR] 2000-2004 99[92-100]
Xu (2016) CHN Unspecified 2005 53 98[89-100]
Ko (2013) CHN Zhuoxi Township 2005 33 0[0-12]
Yang (2013) CHN Unspecified 2005 293 100[98-100]
Yang (2013) CHN Unspecified 2005 80 100[95-100]
Zhang (2011) CHN Urumqi 2005 1 100[17-100]
Zhang (2011) CHN Urumqi 2005 12 100[72-100]
Xu (2016) CHN Unspecified 2006 69 1[0-9]
Zhang (2014) CHN Shanghai 2006 186 99[97-100]
Zhang (2014) CHN Shanghai 2006 86 99[93-100]
Yang (2013) CHN Unspecified 2006 55 100[92-100]
Zhang (2011) CHN Urumqi 2006 1 100[17-100]
Zhang (2011) CHN Urumqi 2006 10 100[68-100]
Xia (2011) CHN Unspecified 2006 71 100[94-100]
Zhu (2011) CHN Unspecified 2006 58 100[93-100]
Xu (2016) CHN Unspecified 2007 11 0[0-30]
Yang (2014) CHN Unspecified 2007 132 98[94-100]
Yang (2014) CHN Unspecified 2007 19 42[23-64]
Yang (2013) CHN Unspecified 2007 56 100[92-100]
Zhu (2013) CHN Unspecified 2007 69 100[94-100]
Zhang (2011) CHN Urumqi 2007 14 93[66-100]
Zhang (2011) CHN Bejing 2007 7 100[60-100]
Zhang (2011) CHN Bejing 2007 15 100[76-100]
Xu (2016) CHN Unspecified 2008 61 74[61-83]
Qu (2014) CHN Beijing 2008 3 67[20-94]
Qu (2014) CHN Beijing 2008 3 33[6-80]
Qu (2014) CHN Beijing 2008 369 84[80-87]
Qu (2014) CHN Beijing 2008 497 96[94-98]
Zhang (2014) CHN Shanghai 2008 237 53[47-59]
Zhang (2014) CHN Shanghai 2008 116 100[96-100]
Yang (2013) CHN Anhui Province 2008 40 75[60-86]
Yang (2013) CHN Anhui Province 2008 260 100[98-100]
Yang (2013) CHN Unspecified 2008 63 100[93-100]
Zhang (2011) CHN Urumqi 2008 101 93[86-97]
Zhang (2011) CHN Urumqi 2008 8 62[30-87]
Zhang (2011) CHN Chengdu 2008 12 100[72-100]
Zhang (2011) CHN Chengdu 2008 10 100[68-100]
Chang (2016) CHN Unspecified 2009 6278 67[65-68]
Xu (2016) CHN Unspecified 2009 50 86[74-93]
Zhang (2015) CHN Shanghai 2009 1248 2[2-3]
Zhang (2015) CHN Shanghai 2009 473 3[2-5]
Zhang (2014) CHN Shanghai 2009 55 93[82-98]
Zhang (2014) CHN Shanghai 2009 131 95[90-98]
Qiu (2013) CHN Unspecified 2009 2 100[29-100]
Qiu (2013) CHN Unspecified 2009 73 100[94-100]
Qiu (2013) CHN Unspecified 2009 17 100[78-100]
Shen (2013) CHN Unspecified 2009 491 77[73-81]
Shen (2013) CHN Unspecified 2009 214 69[63-75]
Zhang (2011) CHN Urumqi 2009 11 100[70-100]
Median prevalence [IQR] 2005-2009 99[73-100]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B

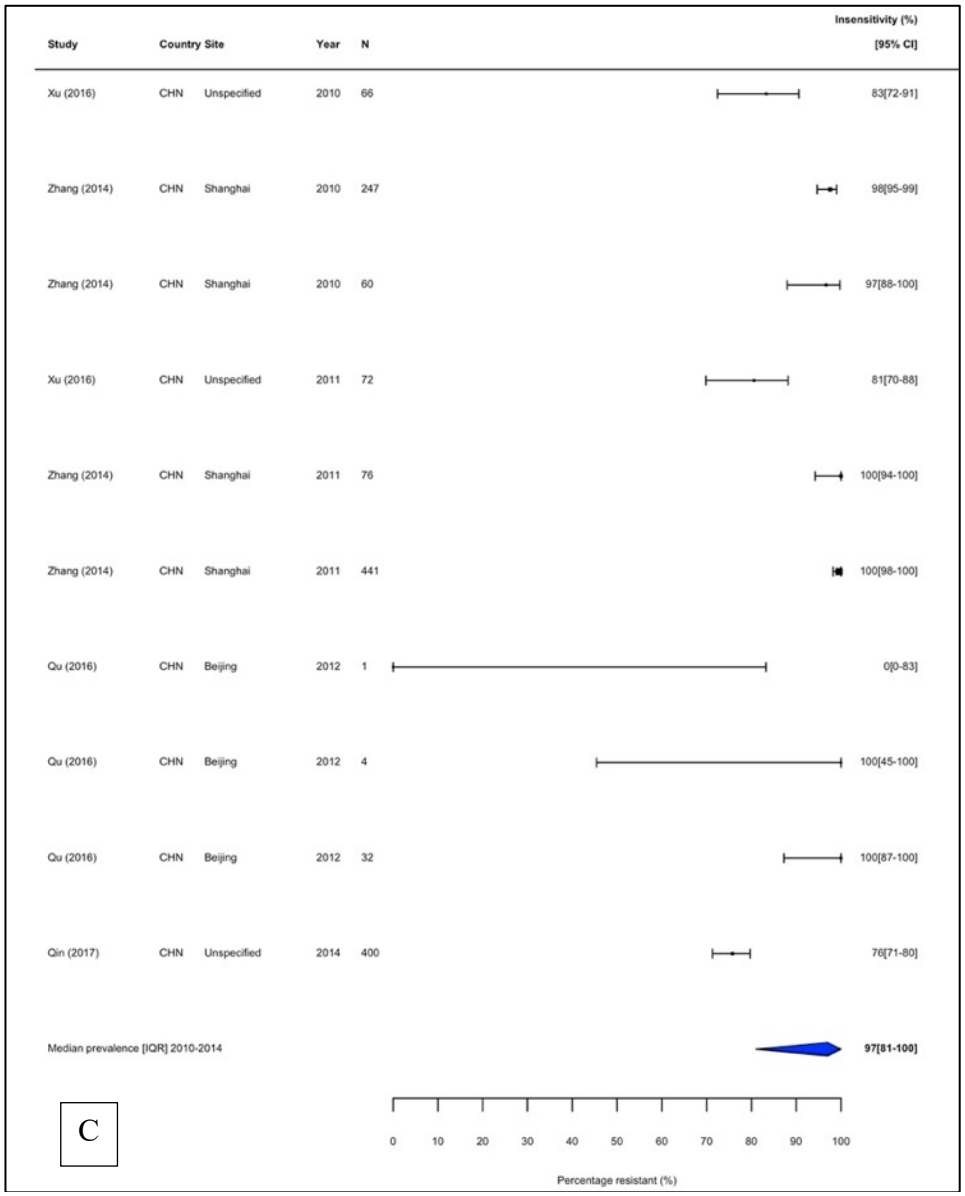


Figure A.7 Forest plot of nalidixic acid resistance in Shigella in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.

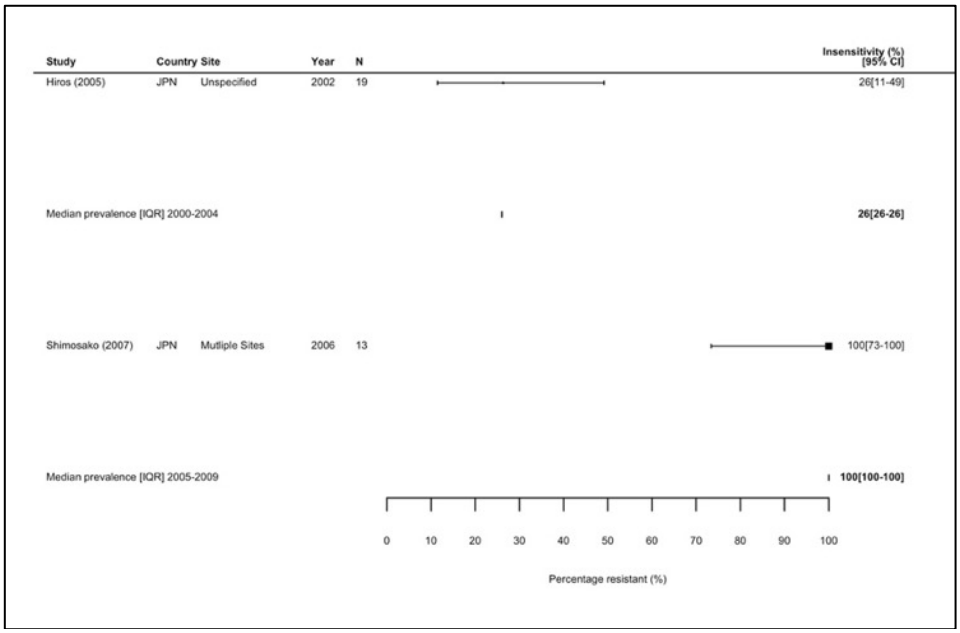
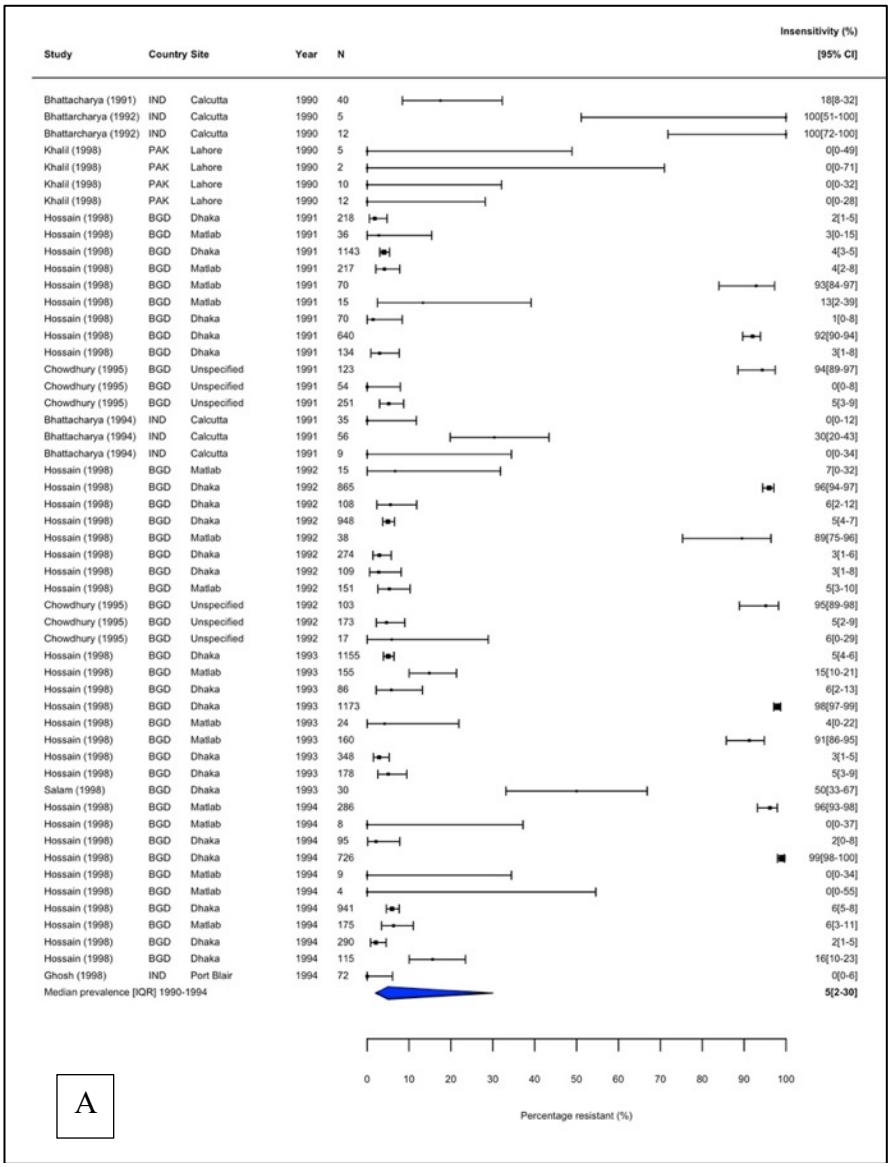


Figure A.8 Forest plot of nalidixic acid resistance in Shigella in High-income Asia Pacific. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Insensitivity (%) [95% CI]
Bhattacharya (1991) IND Calcutta 1990 40 18[8-32]
Bhattarcharya (1992) IND Calcutta 1990 5 100[51-100]
Bhattarcharya (1992) IND Calcutta 1990 12 100[72-100]
Khalil (1998) PAK Lahore 1990 5 0[0-49]
Khalil (1998) PAK Lahore 1990 2 0[0-71]
Khalil (1998) PAK Lahore 1990 10 0[0-32]
Khalil (1998) PAK Lahore 1990 12 0[0-28]
Hossain (1998) BGD Dhaka 1991 218 2[1-5]
Hossain (1998) BGD Matlab 1991 36 3[0-15]
Hossain (1998) BGD Dhaka 1991 1143 4[3-5]
Hossain (1998) BGD Matlab 1991 217 4[2-8]
Hossain (1998) BGD Matlab 1991 70 93[84-97]
Hossain (1998) BGD Matlab 1991 15 13[2-39]
Hossain (1998) BGD Dhaka 1991 70 1[0-8]
Hossain (1998) BGD Dhaka 1991 640 92[90-94]
Hossain (1998) BGD Dhaka 1991 134 3[1-8]
Chowdhury (1995) BGD Unspecified 1991 123 94[89-97]
Chowdhury (1995) BGD Unspecified 1991 54 0[0-8]
Chowdhury (1995) BGD Unspecified 1991 251 5[3-9]
Bhattacharya (1994) IND Calcutta 1991 35 0[0-12]
Bhattacharya (1994) IND Calcutta 1991 56 30[20-43]
Bhattacharya (1994) IND Calcutta 1991 9 0[0-34]
Hossain (1998) BGD Matlab 1992 15 7[0-32]
Hossain (1998) BGD Dhaka 1992 865 96[94-97]
Hossain (1998) BGD Dhaka 1992 108 6[2-12]
Hossain (1998) BGD Dhaka 1992 948 5[4-7]
Hossain (1998) BGD Matlab 1992 38 89[75-96]
Hossain (1998) BGD Dhaka 1992 274 3[1-6]
Hossain (1998) BGD Dhaka 1992 109 3[1-8]
Hossain (1998) BGD Matlab 1992 151 5[3-10]
Chowdhury (1995) BGD Unspecified 1992 103 95[89-98]
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Chowdhury (1995) BGD Unspecified 1992 17 6[0-29]
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Hossain (1998) BGD Matlab 1993 24 4[0-22]
Hossain (1998) BGD Matlab 1993 160 91[86-95]
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Hossain (1998) BGD Matlab 1994 8 0[0-37]
Hossain (1998) BGD Dhaka 1994 95 2[0-8]
Hossain (1998) BGD Dhaka 1994 726 99[98-100]
Hossain (1998) BGD Matlab 1994 9 0[0-34]
Hossain (1998) BGD Matlab 1994 4 0[0-55]
Hossain (1998) BGD Dhaka 1994 941 6[5-8]
Hossain (1998) BGD Matlab 1994 175 6[3-11]
Hossain (1998) BGD Dhaka 1994 290 2[1-5]
Hossain (1998) BGD Dhaka 1994 115 16[10-23]
Ghosh (1998) IND Port Blair 1994 72 0[0-6]
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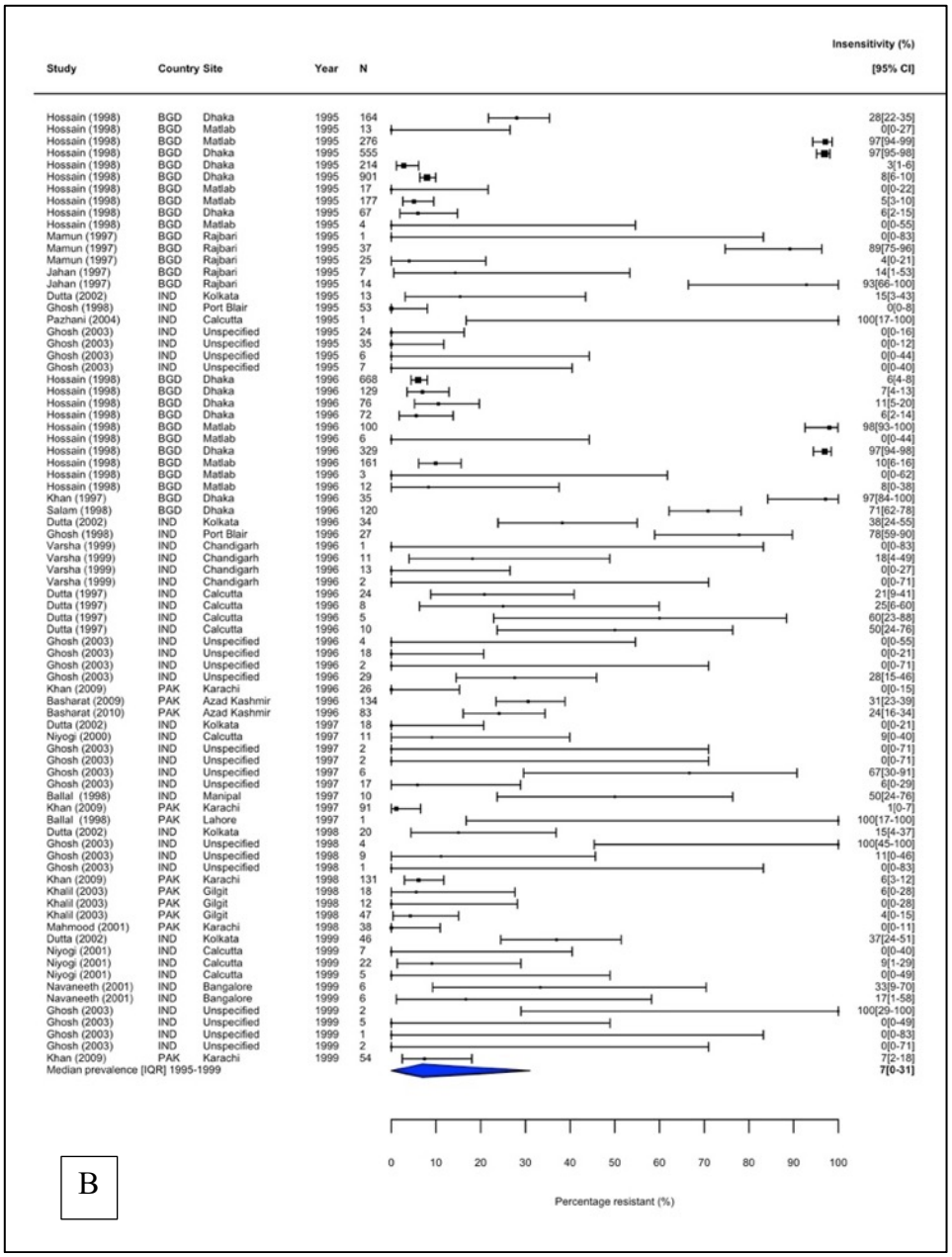
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Insensitivity (%)
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Hossain (1998) BGD Matlab 1995 177 5[3-10]
Hossain (1998) BGD Dhaka 1995 67 6[2-15]
Hossain (1998) BGD Matlab 1995 4 0[0-55]
Mamun (1997) BGD Rajbari 1995 1 0[0-83]
Mamun (1997) BGD Rajbari 1995 37 89[75-96]
Mamun (1997) BGD Rajbari 1995 25 4[0-21]
Jahan (1997) BGD Rajbari 1995 7 14[1-53]
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Dutta (2002) IND Kolkata 1995 13 15[3-43]
Ghosh (1998) IND Port Blair 1995 53 0[0-8]
Pazhani (2004) IND Calcutta 1995 1 100[17-100]
Ghosh (2003) IND Unspecified 1995 24 0[0-16]
Ghosh (2003) IND Unspecified 1995 35 0[0-12]
Ghosh (2003) IND Unspecified 1995 6 0[0-44]
Ghosh (2003) IND Unspecified 1995 7 0[0-40]
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Hossain (1998) BGD Dhaka 1996 129 7[4-13]
Hossain (1998) BGD Dhaka 1996 76 11[5-20]
Hossain (1998) BGD Dhaka 1996 72 6[2-14]
Hossain (1998) BGD Matlab 1996 100 98[93-100]
Hossain (1998) BGD Matlab 1996 6 0[0-44]
Hossain (1998) BGD Dhaka 1996 329 97[94-98]
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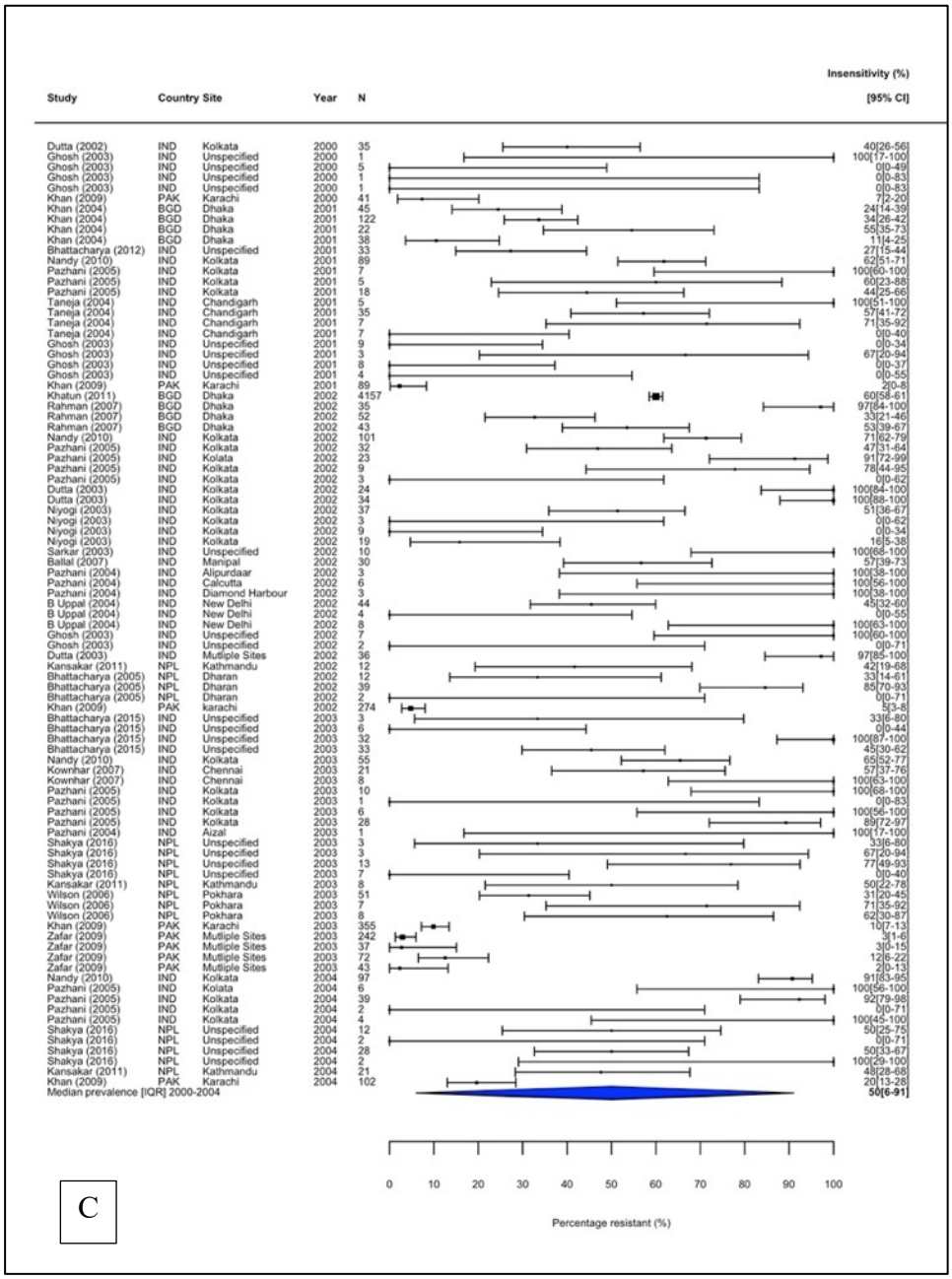
Hossain (1998) BGD Matlab 1996 3 0[0-62]
Hossain (1998) BGD Matlab 1996 12 8[0-38]
Khan (1997) BGD Dhaka 1996 35 97[84-100]
Salam (1998) BGD Dhaka 1996 120 71[62-78]
Dutta (2002) IND Kolkata 1996 34 38[24-55]
Ghosh (1998) IND Port Blair 1996 27 78[59-90]
Varsha (1999) IND Chandigarh 1996 1 0[0-83]
Varsha (1999) IND Chandigarh 1996 11 18[4-49]
Varsha (1999) IND Chandigarh 1996 13 0[0-27]
Varsha (1999) IND Chandigarh 1996 2 0[0-71]
Dutta (1997) IND Calcutta 1996 24 21[9-41]
Dutta (1997) IND Calcutta 1996 8 25[6-60]
Dutta (1997) IND Calcutta 1996 5 60[23-88]
Dutta (1997) IND Calcutta 1996 10 50[24-76]
Ghosh (2003) IND Unspecified 1996 4 0[0-55]
Ghosh (2003) IND Unspecified 1996 18 0[0-21]
Ghosh (2003) IND Unspecified 1996 2 0[0-71]
Ghosh (2003) IND Unspecified 1996 29 28[15-46]
Khan (2009) PAK Karachi 1996 26 0[0-15]
Basharat (2009) PAK Azad Kashmir 1996 134 31[23-39]
Basharat (2010) PAK Azad Kashmir 1996 83 24[16-34]
Dutta (2002) IND Kolkata 1997 18 0[0-21]
Niyogi (2000) IND Calcutta 1997 11 9[0-40]
Ghosh (2003) IND Unspecified 1997 2 0[0-71]
Ghosh (2003) IND Unspecified 1997 2 0[0-71]
Ghosh (2003) IND Unspecified 1997 6 67[30-91]
Ghosh (2003) IND Unspecified 1997 17 6[0-29]
Ballal (1998) IND Manipal 1997 10 50[24-76]
Khan (2009) PAK Karachi 1997 91 1[0-7]
Ballal (1998) PAK Lahore 1997 1 100[17-100]
Dutta (2002) IND Kolkata 1998 20 15[4-37]
Ghosh (2003) IND Unspecified 1998 4 100[45-100]
Ghosh (2003) IND Unspecified 1998 9 11[0-46]
Ghosh (2003) IND Unspecified 1998 1 0[0-83]
Khan (2009) PAK Karachi 1998 131 6[3-12]
Khalil (2003) PAK Gilgit 1998 18 6[0-28]
Khalil (2003) PAK Gilgit 1998 12 0[0-28]
Khalil (2003) PAK Gilgit 1998 47 4[0-15]
Mahmood (2001) PAK Karachi 1998 38 0[0-11]
Dutta (2002) IND Kolkata 1999 46 37[24-51]
Niyogi (2001) IND Calcutta 1999 7 0[0-40]
Niyogi (2001) IND Calcutta 1999 22 9[1-29]
Niyogi (2001) IND Calcutta 1999 5 0[0-49]
Navaneeth (2001) IND Bangalore 1999 6 33[9-70]
Navaneeth (2001) IND Bangalore 1999 6 17[1-58]
Ghosh (2003) IND Unspecified 1999 2 100[29-100]
Ghosh (2003) IND Unspecified 1999 5 0[0-49]
Ghosh (2003) IND Unspecified 1999 1 0[0-83]
Ghosh (2003) IND Unspecified 1999 2 0[0-71]
Khan (2009) PAK Karachi 1999 54 7[2-18]
Median prevalence [IQR] 1995-1999 7[0-31]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
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Ghosh (2003) IND Unspecified 2000 1 100[17-100]
Ghosh (2003) IND Unspecified 2000 5 0[0-49]
Ghosh (2003) IND Unspecified 2000 1 0[0-83]
Ghosh (2003) IND Unspecified 2000 1 0[0-83]
Khan (2009) PAK Karachi 2000 41 7[2-20]
Khan (2004) BGD Dhaka 2001 45 24[14-39]
Khan (2004) BGD Dhaka 2001 122 34[26-42]
Khan (2004) BGD Dhaka 2001 22 55[35-73]
Khan (2004) BGD Dhaka 2001 38 11[4-25]
Bhattacharya (2012) IND Unspecified 2001 33 27[15-44]
Nandy (2010) IND Kolkata 2001 89 62[51-71]
Pazhani (2005) IND Kolkata 2001 7 100[60-100]
Pazhani (2005) IND Kolkata 2001 5 60[23-88]
Pazhani (2005) IND Kolkata 2001 18 44[25-66]
Taneja (2004) IND Chandigarh 2001 5 100[51-100]
Taneja (2004) IND Chandigarh 2001 35 57[41-72]
Taneja (2004) IND Chandigarh 2001 7 71[35-92]
Taneja (2004) IND Chandigarh 2001 7 0[0-40]
Ghosh (2003) IND Unspecified 2001 9 0[0-34]
Ghosh (2003) IND Unspecified 2001 3 67[20-94]
Ghosh (2003) IND Unspecified 2001 8 0[0-37]
Ghosh (2003) IND Unspecified 2001 4 0[0-55]
Khan (2009) PAK Karachi 2001 89 2[0-8]
Khatun (2011) BGD Dhaka 2002 4157 60[58-61]
Rahman (2007) BGD Dhaka 2002 35 97[84-100]
Rahman (2007) BGD Dhaka 2002 52 33[21-46]
Rahman (2007) BGD Dhaka 2002 43 53[39-67]
Nandy (2010) IND Kolkata 2002 101 71[62-79]
Pazhani (2005) IND Kolkata 2002 32 47[31-64]
Pazhani (2005) IND Kolata 2002 23 91[72-99]
Pazhani (2005) IND Kolkata 2002 9 78[44-95]
Pazhani (2005) IND Kolkata 2002 3 0[0-62]
Dutta (2003) IND Kolkata 2002 24 100[84-100]
Dutta (2003) IND Kolkata 2002 34 100[88-100]
Niyogi (2003) IND Kolkata 2002 37 51[36-67]
Niyogi (2003) IND Kolkata 2002 3 0[0-62]
Niyogi (2003) IND Kolkata 2002 9 0[0-34]
Niyogi (2003) IND Kolkata 2002 19 16[5-38]
Sarkar (2003) IND Unspecified 2002 10 100[68-100]
Ballal (2007) IND Manipal 2002 30 57[39-73]
Pazhani (2004) IND Alipurdaar 2002 3 100[38-100]
Pazhani (2004) IND Calcutta 2002 6 100[56-100]
Pazhani (2004) IND Diamond Harbour 2002 3 100[38-100]
B Uppal (2004) IND New Delhi 2002 44 45[32-60]
B Uppal (2004) IND New Delhi 2002 4 0[0-55]
B Uppal (2004) IND New Delhi 2002 8 100[63-100]
Ghosh (2003) IND Unspecified 2002 7 100[60-100]
Ghosh (2003) IND Unspecified 2002 2 0[0-71]
Dutta (2003) IND Mutliple Sites 2002 36 97[85-100]
Kansakar (2011) NPL Kathmandu 2002 12 42[19-68]
Bhattacharya (2005) NPL Dharan 2002 12 33[14-61]
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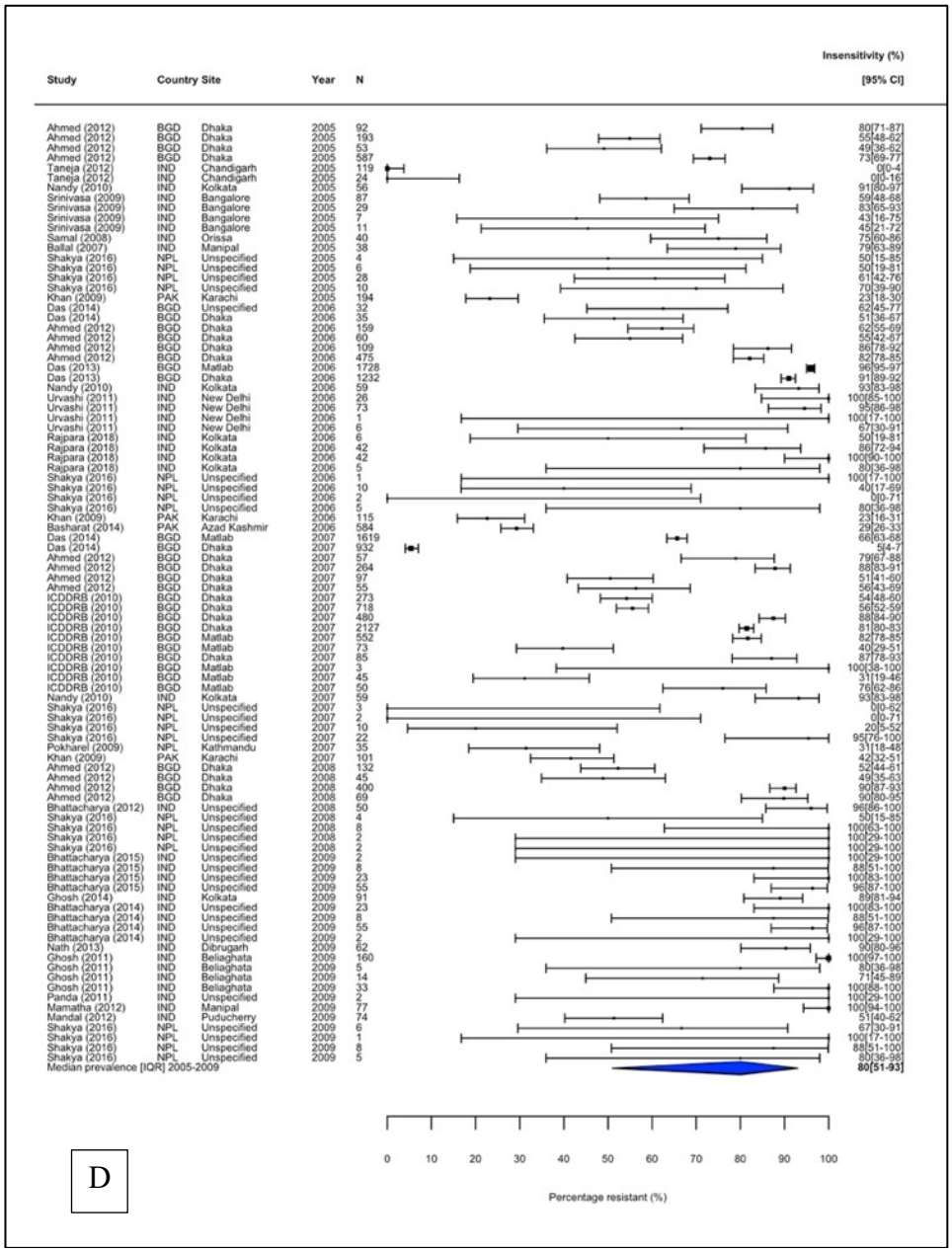
Bhattacharya (2005) NPL Dharan 2002 2 0[0-71]
Khan (2009) PAK karachi 2002 274 5[3-8]
Bhattacharya (2015) IND Unspecified 2003 3 33[6-80]
Bhattacharya (2015) IND Unspecified 2003 6 0[0-44]
Bhattacharya (2015) IND Unspecified 2003 32 100[87-100]
Bhattacharya (2015) IND Unspecified 2003 33 45[30-62]
Nandy (2010) IND Kolkata 2003 55 65[52-77]
Kownhar (2007) IND Chennai 2003 21 57[37-76]
Kownhar (2007) IND Chennai 2003 8 100[63-100]
Pazhani (2005) IND Kolkata 2003 10 100[68-100]
Pazhani (2005) IND Kolkata 2003 1 0[0-83]
Pazhani (2005) IND Kolkata 2003 6 100[56-100]
Pazhani (2005) IND Kolkata 2003 28 89[72-97]
Pazhani (2004) IND Aizal 2003 1 100[17-100]
Shakya (2016) NPL Unspecified 2003 3 33[6-80]
Shakya (2016) NPL Unspecified 2003 3 67[20-94]
Shakya (2016) NPL Unspecified 2003 13 77[49-93]
Shakya (2016) NPL Unspecified 2003 7 0[0-40]
Kansakar (2011) NPL Kathmandu 2003 8 50[22-78]
Wilson (2006) NPL Pokhara 2003 51 31[20-45]
Wilson (2006) NPL Pokhara 2003 7 71[35-92]
Wilson (2006) NPL Pokhara 2003 8 62[30-87]
Khan (2009) PAK Karachi 2003 355 10[7-13]
Zafar (2009) PAK Mutliple Sites 2003 242 3[1-6]
Zafar (2009) PAK Mutliple Sites 2003 37 3[0-15]
Zafar (2009) PAK Mutliple Sites 2003 72 12[6-22]
Zafar (2009) PAK Mutliple Sites 2003 43 2[0-13]
Nandy (2010) IND Kolkata 2004 97 91[83-95]
Pazhani (2005) IND Kolata 2004 6 100[56-100]
Pazhani (2005) IND Kolkata 2004 39 92[79-98]
Pazhani (2005) IND Kolkata 2004 2 0[0-71]
Pazhani (2005) IND Kolkata 2004 4 100[45-100]
Shakya (2016) NPL Unspecified 2004 12 50[25-75]
Shakya (2016) NPL Unspecified 2004 2 0[0-71]
Shakya (2016) NPL Unspecified 2004 28 50[33-67]
Shakya (2016) NPL Unspecified 2004 2 100[29-100]
Kansakar (2011) NPL Kathmandu 2004 21 48[28-68]
Khan (2009) PAK Karachi 2004 102 20[13-28]
Median prevalence [IQR] 2000-2004 50[6-91]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
C


Study
Country Site
Year
N
Insensitivity (%)
[95% CI]
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Ahmed (2012) BGD Dhaka 2005 53 49[36-62]
Ahmed (2012) BGD Dhaka 2005 587 73[69-77]
Taneja (2012) IND Chandigarh 2005 119 0[0-4]
Taneja (2012) IND Chandigarh 2005 24 0[0-16]
Nandy (2010) IND Kolkata 2005 56 91[80-97]
Srinivasa (2009) IND Bangalore 2005 87 59[48-68]
Srinivasa (2009) IND Bangalore 2005 29 83[65-93]
Srinivasa (2009) IND Bangalore 2005 7 43[16-75]
Srinivasa (2009) IND Bangalore 2005 11 45[21-72]
Samal (2008) IND Orissa 2005 40 75[60-86]
Ballal (2007) IND Manipal 2005 38 79[63-89]
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Ahmed (2012) BGD Dhaka 2006 60 55[42-67]
Ahmed (2012) BGD Dhaka 2006 109 86[78-92]
Ahmed (2012) BGD Dhaka 2006 475 82[78-85]
Das (2013) BGD Matlab 2006 1728 96[95-97]
Das (2013) BGD Dhaka 2006 1232 91[89-92]
Nandy (2010) IND Kolkata 2006 59 93[83-98]
Urvashi (2011) IND New Delhi 2006 26 100[85-100]
Urvashi (2011) IND New Delhi 2006 73 95[86-98]
Urvashi (2011) IND New Delhi 2006 1 100[17-100]
Urvashi (2011) IND New Delhi 2006 6 67[30-91]
Rajpara (2018) IND Kolkata 2006 6 50[19-81]
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Rajpara (2018) IND Kolkata 2006 42 100[90-100]
Rajpara (2018) IND Kolkata 2006 5 80[36-98]
Shakya (2016) NPL Unspecified 2006 1 100[17-100]
Shakya (2016) NPL Unspecified 2006 10 40[17-69]
Shakya (2016) NPL Unspecified 2006 2 0[0-71]
Shakya (2016) NPL Unspecified 2006 5 80[36-98]
Khan (2009) PAK Karachi 2006 115 23[16-31]
Basharat (2014) PAK Azad Kashmir 2006 584 29[26-33]
Das (2014) BGD Matlab 2007 1619 66[63-68]
Das (2014) BGD Dhaka 2007 932 5[4-7]
Ahmed (2012) BGD Dhaka 2007 57 79[67-88]
Ahmed (2012) BGD Dhaka 2007 264 88[83-91]
Ahmed (2012) BGD Dhaka 2007 97 51[41-60]
Ahmed (2012) BGD Dhaka 2007 55 56[43-69]
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ICDDRB (2010) BGD Dhaka 2007 718 56[52-59]
ICDDRB (2010) BGD Dhaka 2007 480 88[84-90]
ICDDRB (2010) BGD Dhaka 2007 2127 81[80-83]
ICDDRB (2010) BGD Matlab 2007 552 82[78-85]
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ICDDRB (2010) BGD Dhaka 2007 85 87[78-93]
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Nandy (2010) IND Kolkata 2007 59 93[83-98]
Shakya (2016) NPL Unspecified 2007 3 0[0-62]
Shakya (2016) NPL Unspecified 2007 2 0[0-71]
Shakya (2016) NPL Unspecified 2007 10 20[5-52]
Shakya (2016) NPL Unspecified 2007 22 95[76-100]
Pokharel (2009) NPL Kathmandu 2007 35 31[18-48]
Khan (2009) PAK Karachi 2007 101 42[32-51]
Ahmed (2012) BGD Dhaka 2008 132 52[44-61]
Ahmed (2012) BGD Dhaka 2008 45 49[35-63]
Ahmed (2012) BGD Dhaka 2008 400 90[87-93]
Ahmed (2012) BGD Dhaka 2008 69 90[80-95]
Bhattacharya (2012) IND Unspecified 2008 50 96[86-100]
Shakya (2016) NPL Unspecified 2008 4 50[15-85]
Shakya (2016) NPL Unspecified 2008 8 100[63-100]
Shakya (2016) NPL Unspecified 2008 2 100[29-100]
Shakya (2016) NPL Unspecified 2008 2 100[29-100]
Bhattacharya (2015) IND Unspecified 2009 2 100[29-100]
Bhattacharya (2015) IND Unspecified 2009 8 88[51-100]
Bhattacharya (2015) IND Unspecified 2009 23 100[83-100]
Bhattacharya (2015) IND Unspecified 2009 55 96[87-100]
Ghosh (2014) IND Kolkata 2009 91 89[81-94]
Bhattacharya (2014) IND Unspecified 2009 23 100[83-100]
Bhattacharya (2014) IND Unspecified 2009 8 88[51-100]
Bhattacharya (2014) IND Unspecified 2009 55 96[87-100]
Bhattacharya (2014) IND Unspecified 2009 2 100[29-100]
Nath (2013) IND Dibrugarh 2009 62 90[80-96]
Ghosh (2011) IND Beliaghata 2009 160 100[97-100]
Ghosh (2011) IND Beliaghata 2009 5 80[36-98]
Ghosh (2011) IND Beliaghata 2009 14 71[45-89]
Ghosh (2011) IND Beliaghata 2009 33 100[88-100]
Panda (2011) IND Unspecified 2009 2 100[29-100]
Mamatha (2012) IND Manipal 2009 77 100[94-100]
Mandal (2012) IND Puducherry 2009 74 51[40-62]
Shakya (2016) NPL Unspecified 2009 6 67[30-91]
Shakya (2016) NPL Unspecified 2009 1 100[17-100]
Shakya (2016) NPL Unspecified 2009 8 88[51-100]
Shakya (2016) NPL Unspecified 2009 5 80[36-98]
Median prevalence [IQR] 2005-2009 80[51-93]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
D

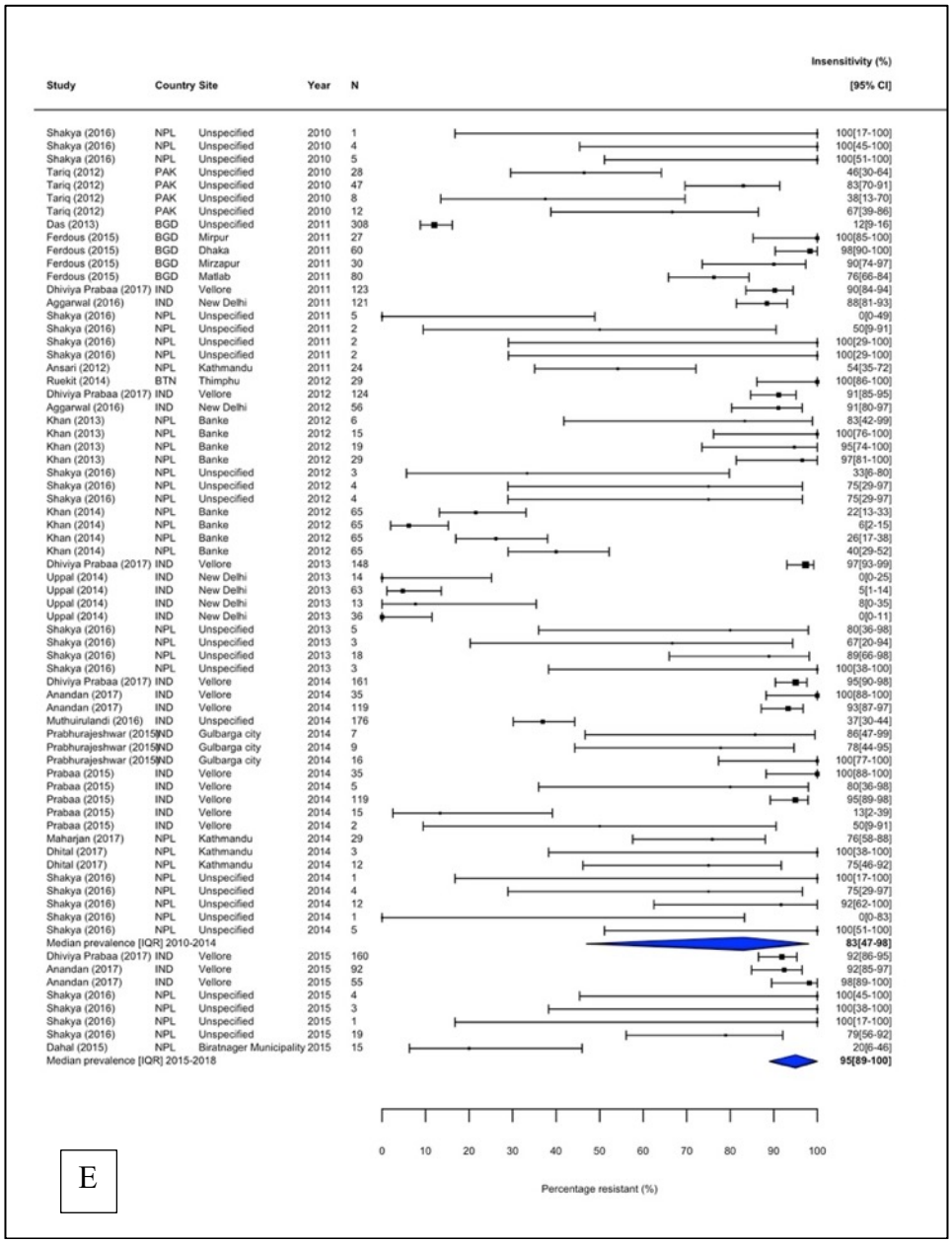


Figure A.9 Forest plot of nalidixic acid resistance in Shigella in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1994, B: 1995-1999, C: 2000-2004, D: 2005-2009, E: 2010-2018

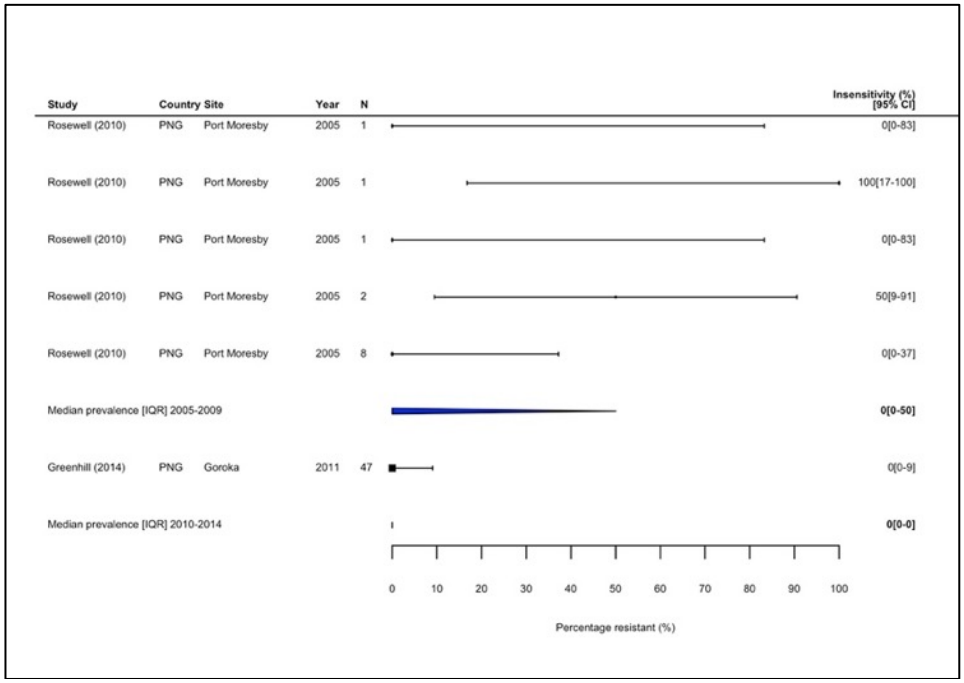


Figure A.10 Forest plot of nalidixic acid resistance in Shigella in Oceania. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

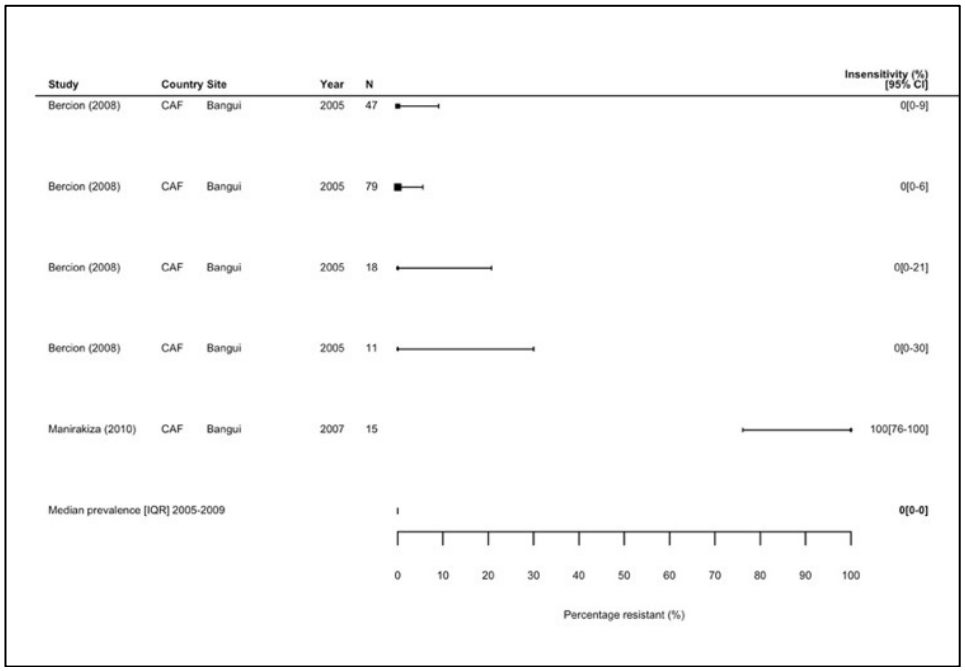
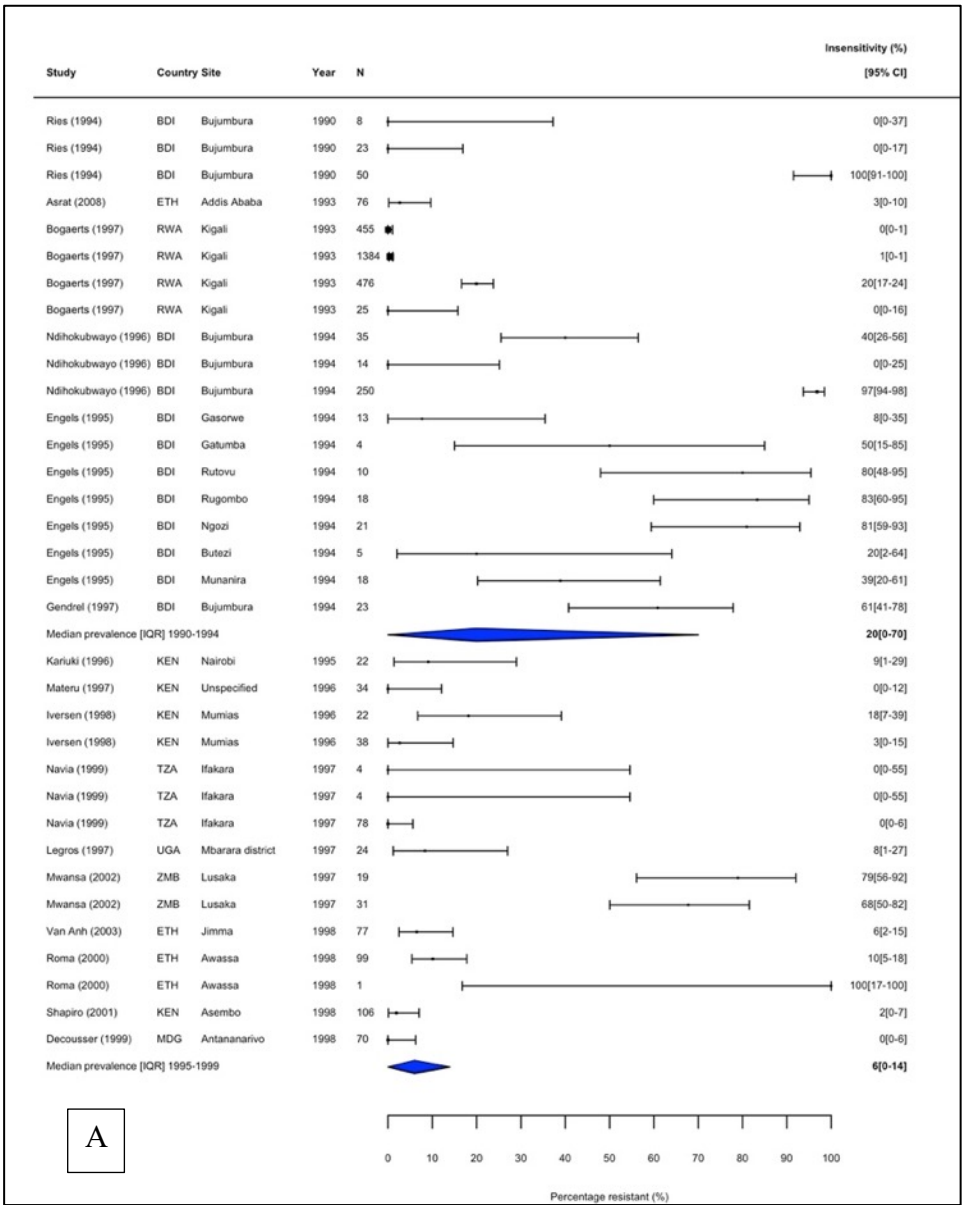


Figure A.11 Forest plot of nalidixic acid resistance in Shigella in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
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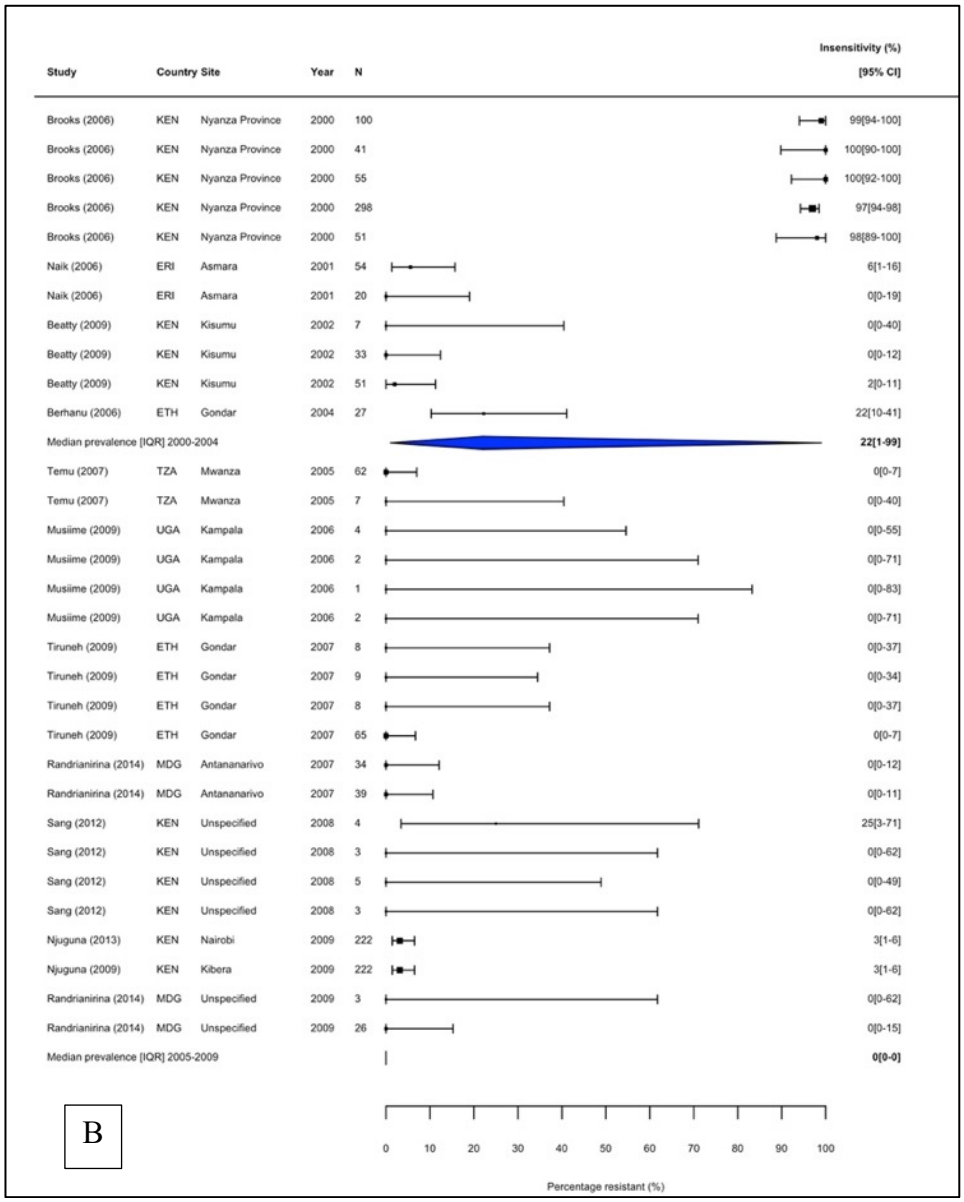
Ries (1994) BDI Bujumbura 1990 23 0[0-17]
Ries (1994) BDI Bujumbura 1990 50 100[91-100]
Asrat (2008) ETH Addis Ababa 1993 76 3[0-10]
Bogaerts (1997) RWA Kigali 1993 455 0[0-1]
Bogaerts (1997) RWA Kigali 1993 1384 1[0-1]
Bogaerts (1997) RWA Kigali 1993 476 20[17-24]
Bogaerts (1997) RWA Kigali 1993 25 0[0-16]
Ndihokubwayo (1996) BDI Bujumbura 1994 35 40[26-56]
Ndihokubwayo (1996) BDI Bujumbura 1994 14 0[0-25]
Ndihokubwayo (1996) BDI Bujumbura 1994 250 97[94-98]
Engels (1995) BDI Gasorwe 1994 13 8[0-35]
Engels (1995) BDI Gatumba 1994 4 50[15-85]
Engels (1995) BDI Rutovu 1994 10 80[48-95]
Engels (1995) BDI Rugombo 1994 18 83[60-95]
Engels (1995) BDI Ngozi 1994 21 81[59-93]
Engels (1995) BDI Butezi 1994 5 20[2-64]
Engels (1995) BDI Munanira 1994 18 39[20-61]
Gendrel (1997) BDI Bujumbura 1994 23 61[41-78]
Median prevalence [IQR] 1990-1994 20[0-70]
Kariuki (1996) KEN Nairobi 1995 22 9[1-29]
Materu (1997) KEN Unspecified 1996 34 0[0-12]
Iversen (1998) KEN Mumias 1996 22 18[7-39]
Iversen (1998) KEN Mumias 1996 38 3[0-15]
Navia (1999) TZA Ifakara 1997 4 0[0-55]
Navia (1999) TZA Ifakara 1997 4 0[0-55]
Navia (1999) TZA Ifakara 1997 78 0[0-6]
Legros (1997) UGA Mbarara district 1997 24 8[1-27]
Mwansa (2002) ZMB Lusaka 1997 19 79[56-92]
Mwansa (2002) ZMB Lusaka 1997 31 68[50-82]
Van Anh (2003) ETH Jimma 1998 77 6[2-15]
Roma (2000) ETH Awassa 1998 99 10[5-18]
Roma (2000) ETH Awassa 1998 1 100[17-100]
Shapiro (2001) KEN Asembo 1998 106 2[0-7]
Decousser (1999) MDG Antananarivo 1998 70 0[0-6]
Median prevalence [IQR] 1995-1999 6[0-14]
A
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
Brooks (2006) KEN Nyanza Province 2000 100 99[94-100]
Brooks (2006) KEN Nyanza Province 2000 41 100[90-100]
Brooks (2006) KEN Nyanza Province 2000 55 100[92-100]
Brooks (2006) KEN Nyanza Province 2000 298 97[94-98]
Brooks (2006) KEN Nyanza Province 2000 51 98[89-100]
Naik (2006) ERI Asmara 2001 54 6[1-16]
Naik (2006) ERI Asmara 2001 20 0[0-19]
Beatty (2009) KEN Kisumu 2002 7 0[0-40]
Beatty (2009) KEN Kisumu 2002 33 0[0-12]
Beatty (2009) KEN Kisumu 2002 51 2[0-11]
Berhanu (2006) ETH Gondar 2004 27 22[10-41]
Median prevalence [IQR] 2000-2004 22[1-99]
Temu (2007) TZA Mwanza 2005 62 0[0-7]
Temu (2007) TZA Mwanza 2005 7 0[0-40]
Musiime (2009) UGA Kampala 2006 4 0[0-55]
Musiime (2009) UGA Kampala 2006 2 0[0-71]
Musiime (2009) UGA Kampala 2006 1 0[0-83]
Musiime (2009) UGA Kampala 2006 2 0[0-71]
Tiruneh (2009) ETH Gondar 2007 8 0[0-37]
Tiruneh (2009) ETH Gondar 2007 9 0[0-34]
Tiruneh (2009) ETH Gondar 2007 8 0[0-37]
Tiruneh (2009) ETH Gondar 2007 65 0[0-7]
Randrianirina (2014) MDG Antananarivo 2007 34 0[0-12]
Randrianirina (2014) MDG Antananarivo 2007 39 0[0-11]
Sang (2012) KEN Unspecified 2008 4 25[3-71]
Sang (2012) KEN Unspecified 2008 3 0[0-62]
Sang (2012) KEN Unspecified 2008 5 0[0-49]
Sang (2012) KEN Unspecified 2008 3 0[0-62]
Njuguna (2013) KEN Nairobi 2009 222 3[1-6]
Njuguna (2009) KEN Kibera 2009 222 3[1-6]
Randrianirina (2014) MDG Unspecified 2009 3 0[0-62]
Randrianirina (2014) MDG Unspecified 2009 26 0[0-15]
Median prevalence [IQR] 2005-2009 0[0-0]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B

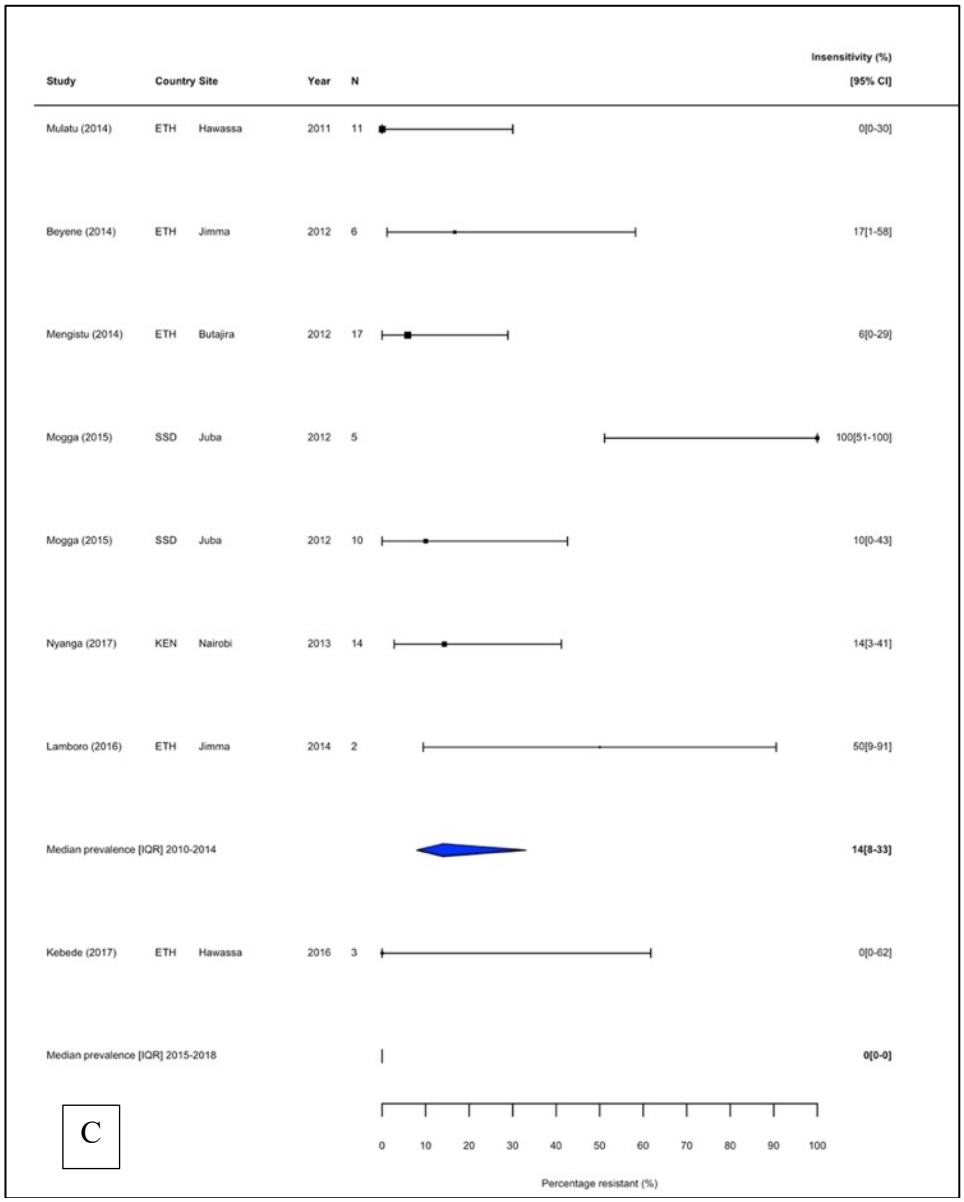
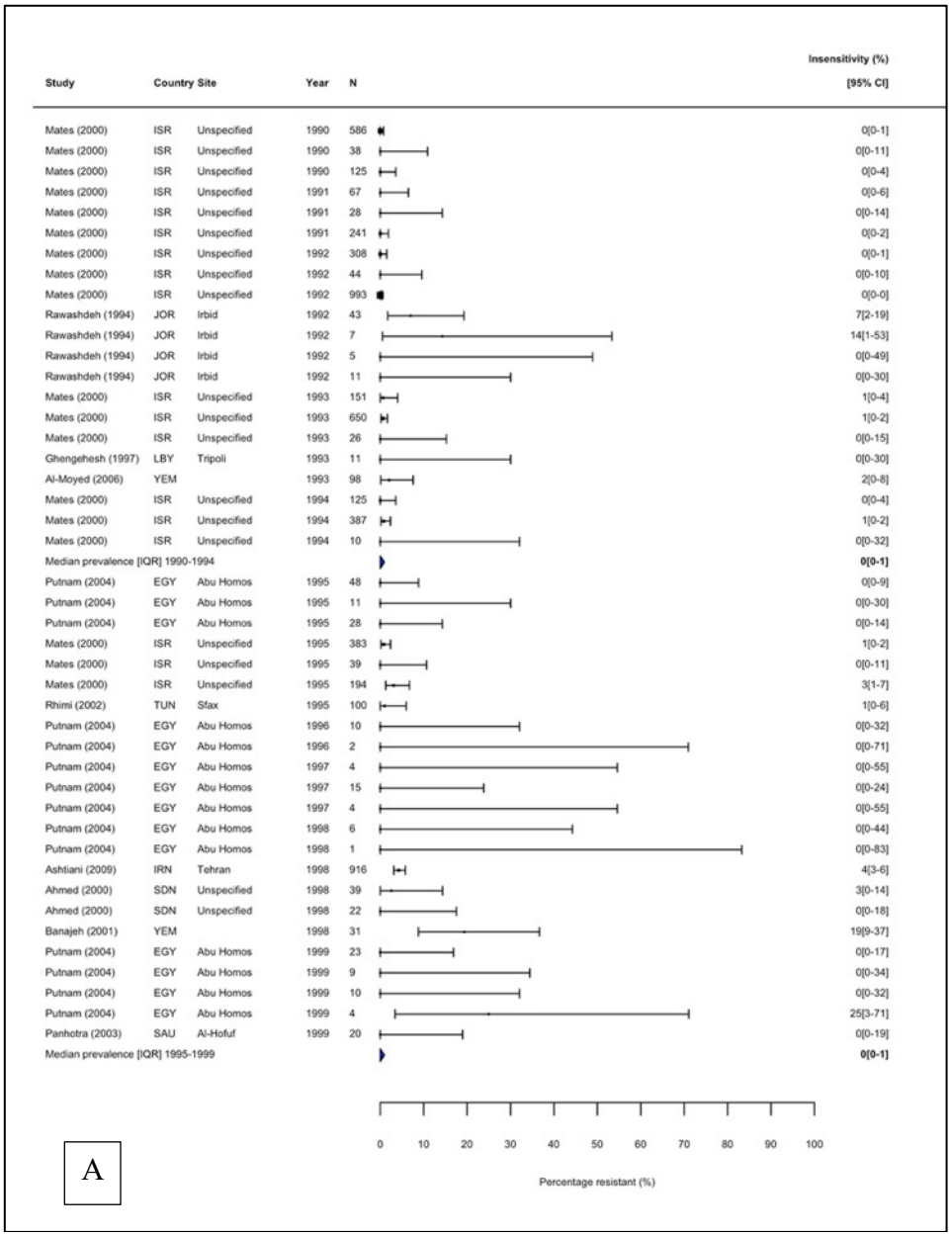
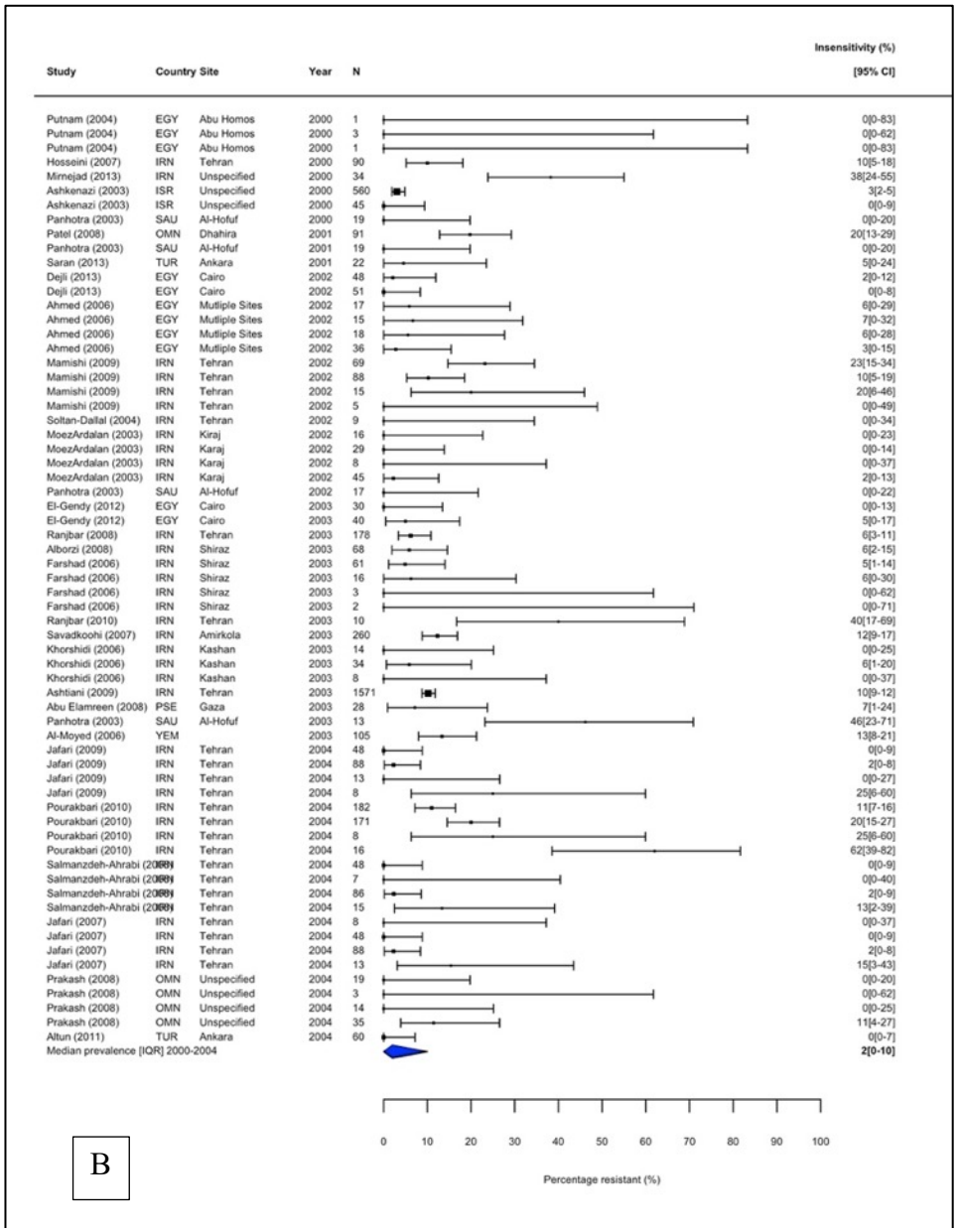
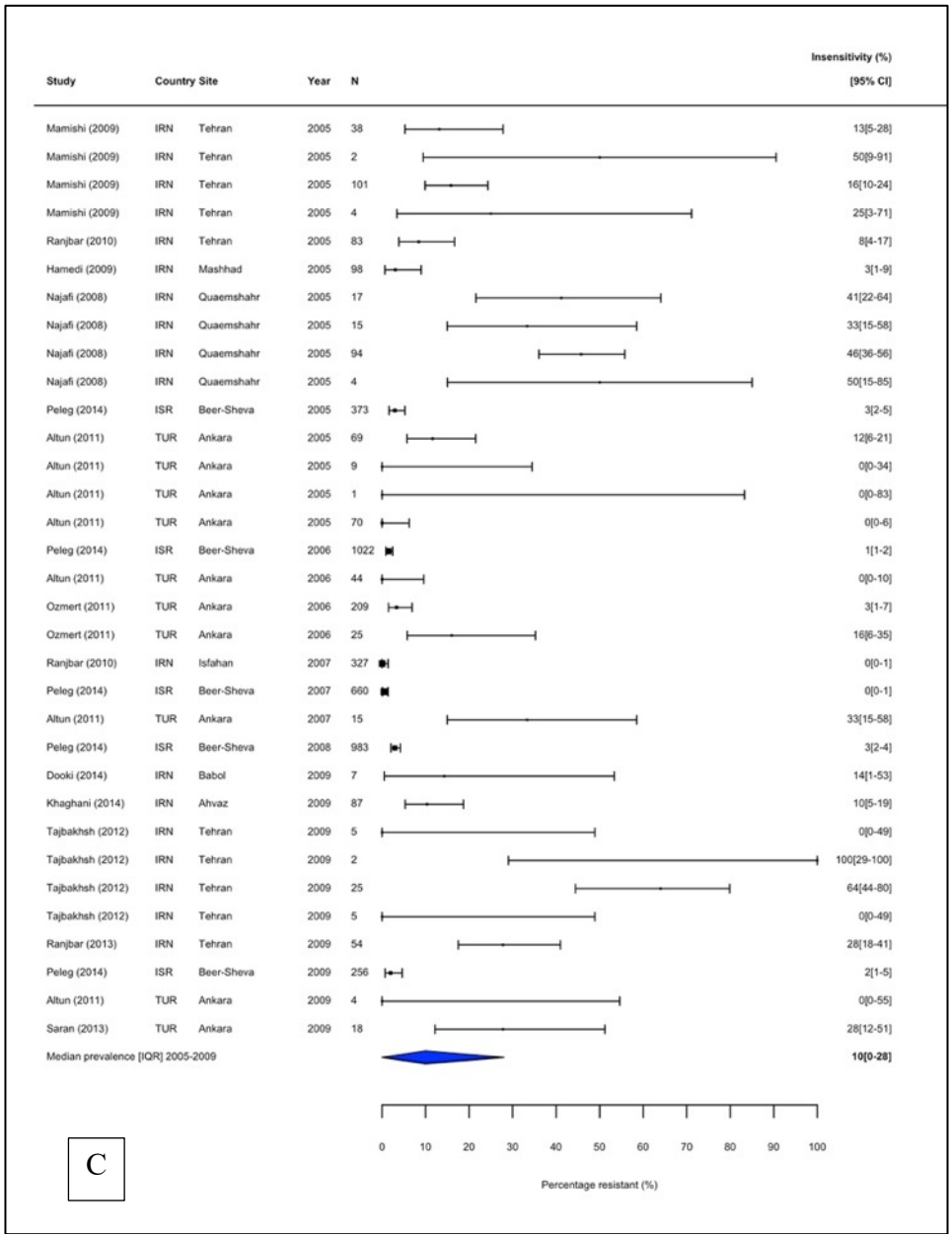


Figure A.12 Forest plot of nalidixic acid resistance in Shigella in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
Mates (2000) ISR Unspecified 1990 586 0[0-1]
Mates (2000) ISR Unspecified 1990 38 0[0-11]
Mates (2000) ISR Unspecified 1990 125 0[0-4]
Mates (2000) ISR Unspecified 1991 67 0[0-6]
Mates (2000) ISR Unspecified 1991 28 0[0-14]
Mates (2000) ISR Unspecified 1991 241 0[0-2]
Mates (2000) ISR Unspecified 1992 308 0[0-1]
Mates (2000) ISR Unspecified 1992 44 0[0-10]
Mates (2000) ISR Unspecified 1992 993 0[0-0]
Rawashdeh (1994) JOR Irbid 1992 43 7[2-19]
Rawashdeh (1994) JOR Irbid 1992 7 14[1-53]
Rawashdeh (1994) JOR Irbid 1992 5 0[0-49]
Rawashdeh (1994) JOR Irbid 1992 11 0[0-30]
Mates (2000) ISR Unspecified 1993 151 1[0-4]
Mates (2000) ISR Unspecified 1993 650 1[0-2]
Mates (2000) ISR Unspecified 1993 26 0[0-15]
Ghengehesh (1997) LBY Tripoli 1993 11 0[0-30]
Al-Moyed (2006) YEM 1993 98 2[0-8]
Mates (2000) ISR Unspecified 1994 125 0[0-4]
Mates (2000) ISR Unspecified 1994 387 1[0-2]
Mates (2000) ISR Unspecified 1994 10 0[0-32]
Median prevalence [IQR] 1990-1994 0[0-1]
Putnam (2004) EGY Abu Homos 1995 48 0[0-9]
Putnam (2004) EGY Abu Homos 1995 11 0[0-30]
Putnam (2004) EGY Abu Homos 1995 28 0[0-14]
Mates (2000) ISR Unspecified 1995 383 1[0-2]
Mates (2000) ISR Unspecified 1995 39 0[0-11]
Mates (2000) ISR Unspecified 1995 194 3[1-7]
Rhimi (2002) TUN Sfax 1995 100 1[0-6]
Putnam (2004) EGY Abu Homos 1996 10 0[0-32]
Putnam (2004) EGY Abu Homos 1996 2 0[0-71]
Putnam (2004) EGY Abu Homos 1997 4 0[0-55]
Putnam (2004) EGY Abu Homos 1997 15 0[0-24]
Putnam (2004) EGY Abu Homos 1997 4 0[0-55]
Putnam (2004) EGY Abu Homos 1998 6 0[0-44]
Putnam (2004) EGY Abu Homos 1998 1 0[0-83]
Ashtiani (2009) IRN Tehran 1998 916 4[3-6]
Ahmed (2000) SDN Unspecified 1998 39 3[0-14]
Ahmed (2000) SDN Unspecified 1998 22 0[0-18]
Banajeh (2001) YEM 1998 31 19[9-37]
Putnam (2004) EGY Abu Homos 1999 23 0[0-17]
Putnam (2004) EGY Abu Homos 1999 9 0[0-34]
Putnam (2004) EGY Abu Homos 1999 10 0[0-32]
Putnam (2004) EGY Abu Homos 1999 4 25[3-71]
Panhotra (2003) SAU Al-Hofuf 1999 20 0[0-19]
Median prevalence [IQR] 1995-1999 0[0-1]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
Putnam (2004) EGY Abu Homos 2000 1 0[0-83]
Putnam (2004) EGY Abu Homos 2000 3 0[0-62]
Putnam (2004) EGY Abu Homos 2000 1 0[0-83]
Hosseini (2007) IRN Tehran 2000 90 10[5-18]
Mirnejad (2013) IRN Unspecified 2000 34 38[24-55]
Ashkenazi (2003) ISR Unspecified 2000 560 3[2-5]
Ashkenazi (2003) ISR Unspecified 2000 45 0[0-9]
Panhotra (2003) SAU Al-Hofuf 2000 19 0[0-20]
Patel (2008) OMN Dhahira 2001 91 20[13-29]
Panhotra (2003) SAU Al-Hofuf 2001 19 0[0-20]
Saran (2013) TUR Ankara 2001 22 5[0-24]
Dejli (2013) EGY Cairo 2002 48 2[0-12]
Dejli (2013) EGY Cairo 2002 51 0[0-8]
Ahmed (2006) EGY Mutiple Sites 2002 17 6[0-29]
Ahmed (2006) EGY Mutiple Sites 2002 15 7[0-32]
Ahmed (2006) EGY Mutiple Sites 2002 18 6[0-28]
Ahmed (2006) EGY Mutiple Sites 2002 36 3[0-15]
Mamishi (2009) IRN Tehran 2002 69 23[15-34]
Mamishi (2009) IRN Tehran 2002 88 10[5-19]
Mamishi (2009) IRN Tehran 2002 15 20[6-46]
Mamishi (2009) IRN Tehran 2002 5 0[0-49]
Soltan-Dallal (2004) IRN Tehran 2002 9 0[0-34]
MoezArdalan (2003) IRN Kiraj 2002 16 0[0-23]
MoezArdalan (2003) IRN Karaj 2002 29 0[0-14]
MoezArdalan (2003) IRN Karaj 2002 8 0[0-37]
MoezArdalan (2003) IRN Karaj 2002 45 2[0-13]
Panhotra (2003) SAU Al-Hofuf 2002 17 0[0-22]
El-Gendy (2012) EGY Cairo 2003 30 0[0-13]
El-Gendy (2012) EGY Cairo 2003 40 5[0-17]
Ranjbar (2008) IRN Tehran 2003 178 6[3-11]
Alborzi (2008) IRN Shiraz 2003 68 6[2-15]
Farshad (2006) IRN Shiraz 2003 61 5[1-14]
Farshad (2006) IRN Shiraz 2003 16 6[0-30]
Farshad (2006) IRN Shiraz 2003 3 0[0-62]
Farshad (2006) IRN Shiraz 2003 2 0[0-71]
Ranjbar (2010) IRN Tehran 2003 10 40[17-69]
Savadkoohi (2007) IRN Amirkola 2003 260 12[9-17]
Khorshidi (2006) IRN Kashan 2003 14 0[0-25]
Khorshidi (2006) IRN Kashan 2003 34 6[1-20]
Khorshidi (2006) IRN Kashan 2003 8 0[0-37]
Ashtiani (2009) IRN Tehran 2003 1571 10[9-12]
Abu Elamreen (2008) PSE Gaza 2003 28 7[1-24]
Panhotra (2003) SAU Al-Hofuf 2003 13 46[23-71]
Al-Moyed (2006) YEM 2003 105 13[8-21]
Jafari (2009) IRN Tehran 2004 48 0[0-9]
Jafari (2009) IRN Tehran 2004 88 2[0-8]
Jafari (2009) IRN Tehran 2004 13 0[0-27]
Jafari (2009) IRN Tehran 2004 8 25[6-60]
Pourakbari (2010) IRN Tehran 2004 182 11[7-16]
Pourakbari (2010) IRN Tehran 2004 171 20[15-27]
Pourakbari (2010) IRN Tehran 2004 8 25[6-60]
Pourakbari (2010) IRN Tehran 2004 16 62[39-82]
Salmanzdeh-Ahrabi (2008) IRN Tehran 2004 48 0[0-9]
Salmanzdeh-Ahrabi (2008) IRN Tehran 2004 7 0[0-40]
Salmanzdeh-Ahrabi (2008) IRN Tehran 2004 86 2[0-9]
Salmanzdeh-Ahrabi (2008) IRN Tehran 2004 15 13[2-39]
Jafari (2007) IRN Tehran 2004 8 0[0-37]
Jafari (2007) IRN Tehran 2004 48 0[0-9]
Jafari (2007) IRN Tehran 2004 88 2[0-8]
Jafari (2007) IRN Tehran 2004 13 15[3-43]
Prakash (2008) OMN Unspecified 2004 19 0[0-20]
Prakash (2008) OMN Unspecified 2004 3 0[0-62]
Prakash (2008) OMN Unspecified 2004 14 0[0-25]
Prakash (2008) OMN Unspecified 2004 35 11[4-27]
Altun (2011) TUR Ankara 2004 60 0[0-7]
Median prevalence [IQR] 2000-2004 2[0-10]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Insensitivity (%)
[95% CI]
Mamishi (2009) IRN Tehran 2005 38 13[5-28]
Mamishi (2009) IRN Tehran 2005 2 50[9-91]
Mamishi (2009) IRN Tehran 2005 101 16[10-24]
Mamishi (2009) IRN Tehran 2005 4 25[3-71]
Ranjbar (2010) IRN Tehran 2005 83 8[4-17]
Hamedi (2009) IRN Mashhad 2005 98 3[1-9]
Najafi (2008) IRN Quaemshahr 2005 17 41[22-64]
Najafi (2008) IRN Quaemshahr 2005 15 33[15-58]
Najafi (2008) IRN Quaemshahr 2005 94 46[36-56]
Najafi (2008) IRN Quaemshahr 2005 4 50[15-85]
Peleg (2014) ISR Beer-Sheva 2005 373 3[2-5]
Altun (2011) TUR Ankara 2005 69 12[6-21]
Altun (2011) TUR Ankara 2005 9 0[0-34]
Altun (2011) TUR Ankara 2005 1 0[0-83]
Altun (2011) TUR Ankara 2005 70 0[0-6]
Peleg (2014) ISR Beer-Sheva 2006 1022 1[1-2]
Altun (2011) TUR Ankara 2006 44 0[0-10]
Ozmert (2011) TUR Ankara 2006 209 3[1-7]
Ozmert (2011) TUR Ankara 2006 25 16[6-35]
Ranjbar (2010) IRN Isfahan 2007 327 0[0-1]
Peleg (2014) ISR Beer-Sheva 2007 660 0[0-1]
Altun (2011) TUR Ankara 2007 15 33[15-58]
Peleg (2014) ISR Beer-Sheva 2008 983 3[2-4]
Dooki (2014) IRN Babol 2009 7 14[1-53]
Khaghani (2014) IRN Ahvaz 2009 87 10[5-19]
Tajbakhsh (2012) IRN Tehran 2009 5 0[0-49]
Tajbakhsh (2012) IRN Tehran 2009 2 100[29-100]
Tajbakhsh (2012) IRN Tehran 2009 25 64[44-80]
Tajbakhsh (2012) IRN Tehran 2009 5 0[0-49]
Ranjbar (2013) IRN Tehran 2009 54 28[18-41]
Peleg (2014) ISR Beer-Sheva 2009 256 2[1-5]
Altun (2011) TUR Ankara 2009 4 0[0-55]
Saran (2013) TUR Ankara 2009 18 28[12-51]
Median prevalence [IQR] 2005-2009 10[0-28]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

C

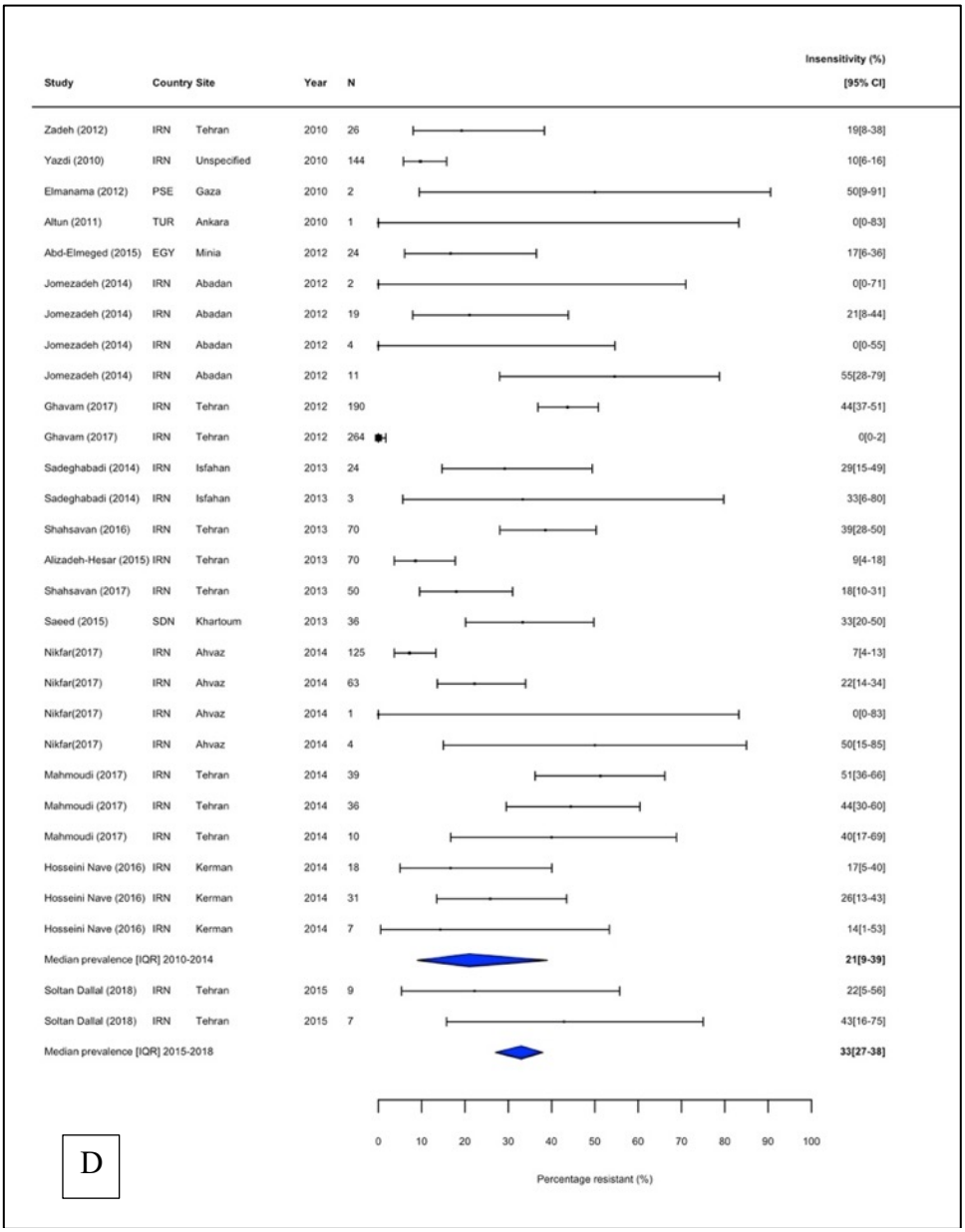


Figure A.13 Forest plot of nalidixic acid resistance in Shigella in North Africa and the Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2004, C:2005-2009, D: 2010-2018.

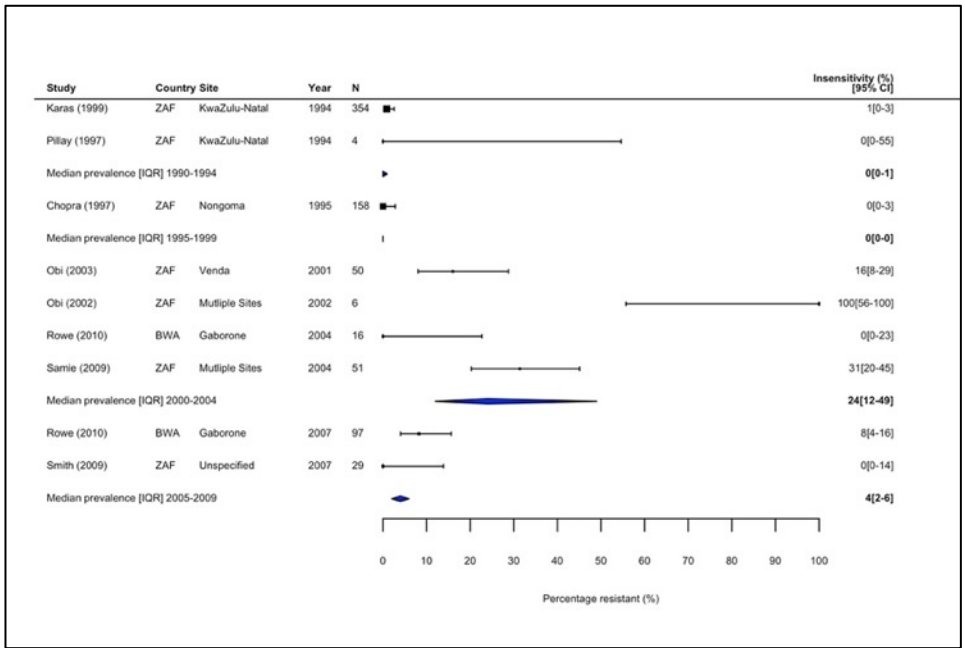


Figure A.14 Forest plot of nalidixic acid resistance in Shigella in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

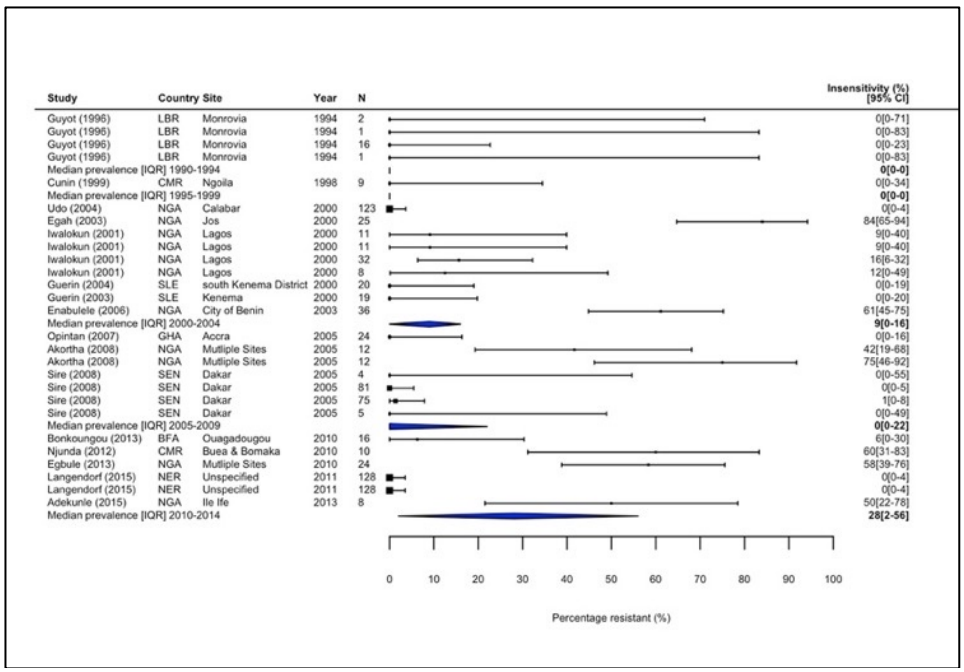


Figure A.15 Forest plot of nalidixic acid resistance in Shigella in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

B

Appendix to Chapter. 3

The appendix to Chapter 3 contains additional tables and figures. Chapter 3: Global geospatial modelling of antimicrobial drug resistance in *Shigella*. This section includes the outliering output details, *Shigella* model uncertainty, table describing the data sources types and finally the modeling validation statistics.

Country	Antimicrobial	Pathogen	Data Source	Data Points	Isolates
Argentina	fluoroquinolones	Shigella	Dataset	1	2,810
Argentina	fluoroquinolones	Shigella	Surveillance Report	10	19,197
Argentina	fluoroquinolones	Shigella	Systematic Review	1	70
Australia	fluoroquinolones	Shigella	Surveillance Report	4	538
Austria	fluoroquinolones	Shigella	Dataset	1	42
Bahrain	fluoroquinolones	Shigella	Dataset	1	25
Bangladesh	fluoroquinolones	Shigella	Systematic Review	32	29,368
Belgium	fluoroquinolones	Shigella	Dataset	2	689
Bhutan	fluoroquinolones	Shigella	Systematic Review	1	29
Bolivia	fluoroquinolones	Shigella	Surveillance Report	14	4,868
Bolivia	fluoroquinolones	Shigella	Systematic Review	1	39
Botswana	fluoroquinolones	Shigella	Systematic Review	2	113
Brazil	fluoroquinolones	Shigella	Surveillance Report	10	1,004
Brazil	fluoroquinolones	Shigella	Systematic Review	7	626
Bulgaria	fluoroquinolones	Shigella	Systematic Review	1	93
Burkina Faso	fluoroquinolones	Shigella	Systematic Review	2	26
Burundi	fluoroquinolones	Shigella	Systematic Review	7	456
Cambodia	fluoroquinolones	Shigella	Systematic Review	2	52
Cameroon	fluoroquinolones	Shigella	Systematic Review	2	19
Central African Republic	fluoroquinolones	Shigella	Dataset	1	5
Central African Republic	fluoroquinolones	Shigella	Systematic Review	2	170
Chile	fluoroquinolones	Shigella	Surveillance Report	12	3,864

Chile	fluoroquinolones	Shigella	Systematic Review	4	365
China	fluoroquinolones	Shigella	Systematic Review	43	5,133
Colombia	fluoroquinolones	Shigella	Surveillance Report	13	4,328
Costa Rica	fluoroquinolones	Shigella	Surveillance Report	11	4,405
Cuba	fluoroquinolones	Shigella	Surveillance Report	9	1,054
Dominican Republic	fluoroquinolones	Shigella	Surveillance Report	2	62
Ecuador	fluoroquinolones	Shigella	Surveillance Report	7	491
Egypt	fluoroquinolones	Shigella	Systematic Review	10	459
El Salvador	fluoroquinolones	Shigella	Surveillance Report	4	184
Eritrea	fluoroquinolones	Shigella	Systematic Review	1	74
Estonia	fluoroquinolones	Shigella	Dataset	1	4
Ethiopia	fluoroquinolones	Shigella	Systematic Review	14	488
France	fluoroquinolones	Shigella	Dataset	2	87
French Guiana	fluoroquinolones	Shigella	Systematic Review	1	37
Ghana	fluoroquinolones	Shigella	Dataset	1	6
Ghana	fluoroquinolones	Shigella	Systematic Review	1	24
Guatemala	fluoroquinolones	Shigella	Surveillance Report	8	721
Honduras	fluoroquinolones	Shigella	Surveillance Report	5	228
India	fluoroquinolones	Shigella	Systematic Review	72	4,365
Indonesia	fluoroquinolones	Shigella	Systematic Review	22	2,455
Iran	fluoroquinolones	Shigella	Systematic Review	33	5,682
Ireland	fluoroquinolones	Shigella	Dataset	2	50
Israel	fluoroquinolones	Shigella	Systematic Review	12	8,294
Japan	fluoroquinolones	Shigella	Dataset	1	156
Japan	fluoroquinolones	Shigella	Systematic Review	1	19
Jordan	fluoroquinolones	Shigella	Systematic Review	1	66
Kenya	fluoroquinolones	Shigella	Dataset	13	875
Kenya	fluoroquinolones	Shigella	Systematic Review	9	786
Korea	fluoroquinolones	Shigella	Systematic Review	7	404
Laos	fluoroquinolones	Shigella	Systematic Review	2	173
Lebanon	fluoroquinolones	Shigella	Dataset	1	18
Lebanon	fluoroquinolones	Shigella	Systematic Review	3	167
Liberia	fluoroquinolones	Shigella	Systematic Review	1	20
Libya	fluoroquinolones	Shigella	Systematic Review	1	11
Lithuania	fluoroquinolones	Shigella	Dataset	1	7
Lithuania	fluoroquinolones	Shigella	Systematic Review	1	98

Madagascar	fluoroquinolones	Shigella	Dataset	1	34
Madagascar	fluoroquinolones	Shigella	Systematic Review	3	172
Malawi	fluoroquinolones	Shigella	Dataset	1	7
Malaysia	fluoroquinolones	Shigella	Systematic Review	2	177
Mexico	fluoroquinolones	Shigella	Surveillance Report	5	692
Mexico	fluoroquinolones	Shigella	Systematic Review	3	218
Myanmar	fluoroquinolones	Shigella	Systematic Review	4	125
Nepal	fluoroquinolones	Shigella	Systematic Review	20	582
New Zealand	fluoroquinolones	Shigella	Surveillance Report	13	635
Nicaragua	fluoroquinolones	Shigella	Surveillance Report	13	432
Niger	fluoroquinolones	Shigella	Systematic Review	1	256
Nigeria	fluoroquinolones	Shigella	Systematic Review	8	239
Oman	fluoroquinolones	Shigella	Dataset	1	42
Oman	fluoroquinolones	Shigella	Systematic Review	2	162
Pakistan	fluoroquinolones	Shigella	Dataset	1	68
Pakistan	fluoroquinolones	Shigella	Surveillance Report	4	473
Pakistan	fluoroquinolones	Shigella	Systematic Review	21	3,008
Palestine	fluoroquinolones	Shigella	Systematic Review	1	28
Panama	fluoroquinolones	Shigella	Surveillance Report	9	823
Papua New Guinea	fluoroquinolones	Shigella	Systematic Review	2	60
Paraguay	fluoroquinolones	Shigella	Surveillance Report	12	3,497
Peru	fluoroquinolones	Shigella	Dataset	1	152
Peru	fluoroquinolones	Shigella	Surveillance Report	9	1,973
Peru	fluoroquinolones	Shigella	Systematic Review	2	621
Philippines	fluoroquinolones	Shigella	Dataset	1	20
Philippines	fluoroquinolones	Shigella	Surveillance Report	3	124
Romania	fluoroquinolones	Shigella	Dataset	1	8
Rwanda	fluoroquinolones	Shigella	Systematic Review	1	2,340
Saudi Arabia	fluoroquinolones	Shigella	Dataset	1	11
Saudi Arabia	fluoroquinolones	Shigella	Systematic Review	4	75
Senegal	fluoroquinolones	Shigella	Systematic Review	2	255
Sierra Leone	fluoroquinolones	Shigella	Systematic Review	2	39
South Africa	fluoroquinolones	Shigella	Dataset	1	759
South Africa	fluoroquinolones	Shigella	Systematic Review	6	646
South Sudan	fluoroquinolones	Shigella	Systematic Review	1	15
Sudan	fluoroquinolones	Shigella	Systematic Review	2	97

Switzerland	fluoroquinolones	Shigella	Dataset	1	144
Taiwan	fluoroquinolones	Shigella	Systematic Review	1	122
Tanzania	fluoroquinolones	Shigella	Systematic Review	2	155
Thailand	fluoroquinolones	Shigella	Dataset	1	17
Thailand	fluoroquinolones	Shigella	Systematic Review	7	416
Tunisia	fluoroquinolones	Shigella	Systematic Review	1	100
Turkey	fluoroquinolones	Shigella	Systematic Review	12	658
Uganda	fluoroquinolones	Shigella	Dataset	1	16
Uganda	fluoroquinolones	Shigella	Systematic Review	2	33
United Arab Emirates	fluoroquinolones	Shigella	Dataset	1	86
United Kingdom	fluoroquinolones	Shigella	Dataset	2	289
Uruguay	fluoroquinolones	Shigella	Surveillance Report	8	661
United States of America	fluoroquinolones	Shigella	Dataset	25	7,484
Uzbekistan	fluoroquinolones	Shigella	Systematic Review	1	52
Venezuela	fluoroquinolones	Shigella	Surveillance Report	9	3,260
Vietnam	fluoroquinolones	Shigella	Systematic Review	12	1,032
Yemen	fluoroquinolones	Shigella	Systematic Review	3	234
Zambia	fluoroquinolones	Shigella	Systematic Review	1	50

Table B.1 Data source type by country.

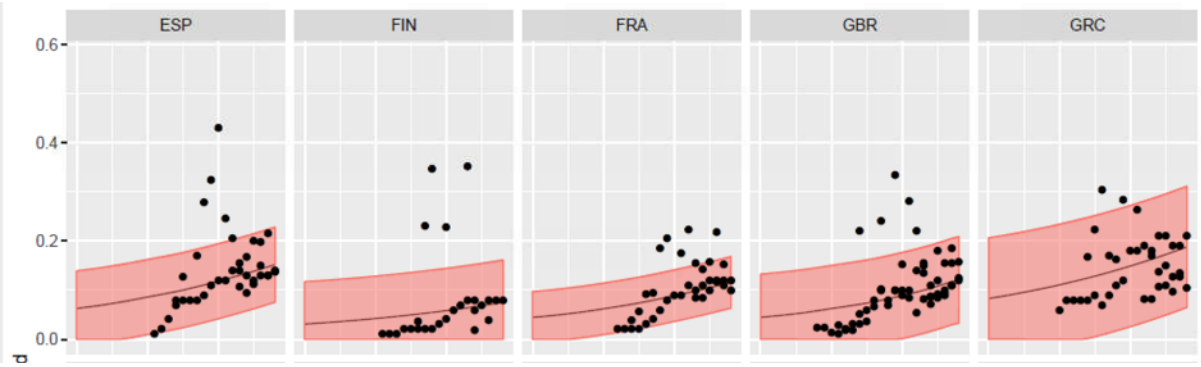


Figure B.1. Outliering output for FQR Shigella. Data points within the red band are included in the dataset and those outside the red band are therefore excluded from the dataset.

Stacked ensemble /ST-GPR	**Out of sample**		**In sample**	
Pathogen/ antimicrobial	**R2**	**RMSE**	**R2**	**RMSE**
Shigella fluoroquinolones	0.29	0.31	0.85	0.13

Table B.2. Shigella and fluoroquinolones model validation statistics. In- and out-of-sample validation metrics of RMSE and R^2.

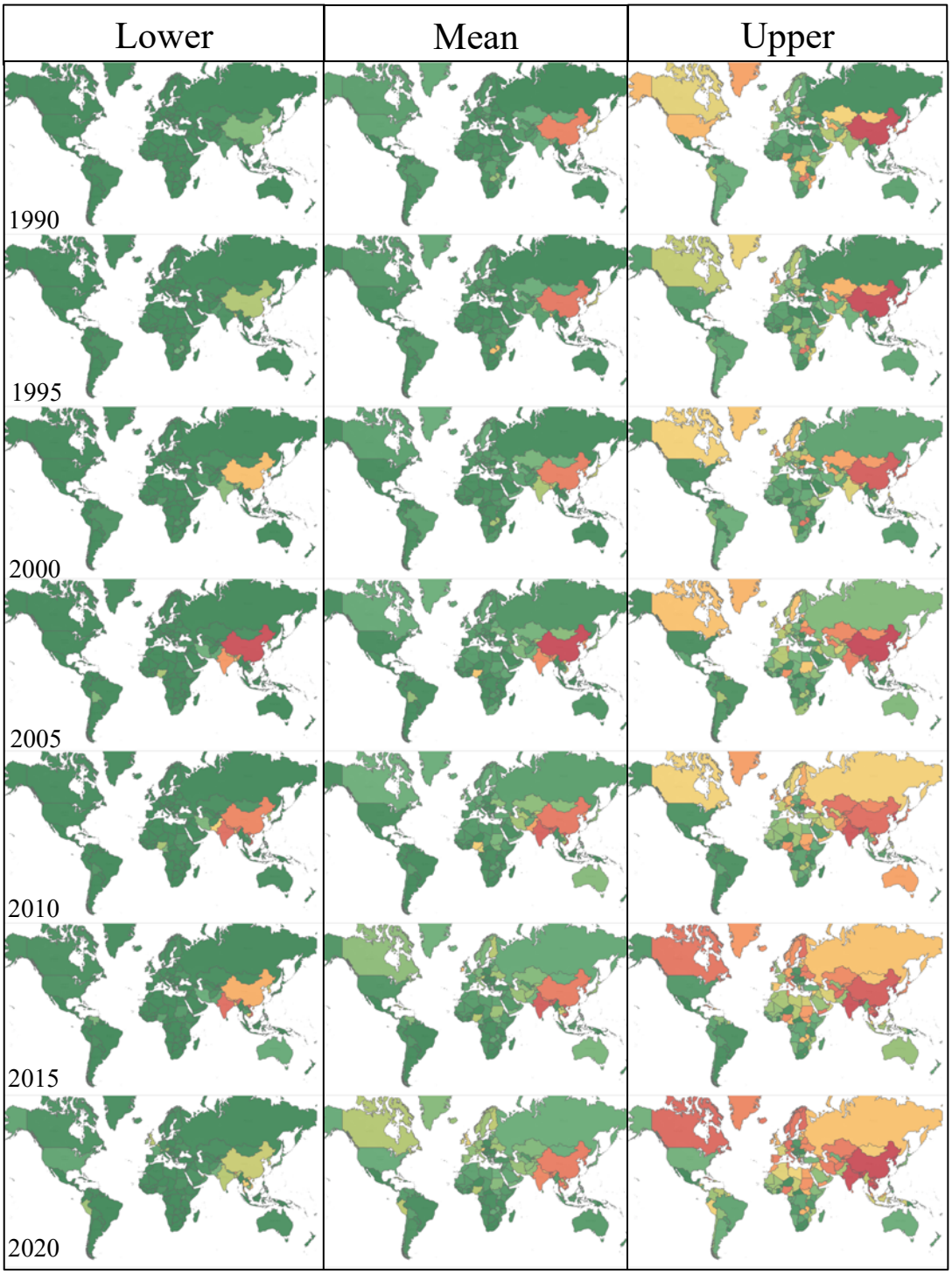


Figure B.2 Prevalence of FQR in Shigella in 2018, model uncertainty. The lower, median, and upper 95% uncertainty interval estimates for each country. Modeled estimates from the stacked ensemble and ST-GPR model.

C

Appendix to Chapter. 4

The appendix to Chapter 4 contains additional tables and figures. Chapter 4: Systematic review of antimicrobial drug resistance in *E. Coli* from 1990-2018. This section includes thee systematic review search strategy, a table of antibiotic class classifications, and the forest plots of meta-analysis for each GBD region available.

Search Number	Search Term
1	exp E. coli
2	"E. coli"
3	"e coli"
4	"e.coli"
5	Klebsiella pneumoniae
6	"klebsiella pneumoniae"
7	Streptococcus pneumoniae
8	pneumococcus
9	"streptococcus pneumoniae"
10	exp Staphylococcus aureus
11	"staphylococcus aureus"
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	exp Urinary Tract Infections
14	"urinary tract infection*"
15	(UTI or UTIs)
16	ventilator*
17	"central line*"
18	catheter*
19	(bacteremi* or bacteraemi*)
20	exp Sepsis
21	(sepsis or septicemi* or septicaemi*)
22	"blood stream infection*"
23	"blood poison*"
24	exp Bacteremia
25	exp PNEUMONIA
26	pneumoni*
27	((newborn* or "new born" or neonat*) adj5 (infect* or sepsis or septic*))
28	"intra-abdominal infection*"
29	"intrabdominal infection*"
30	("post surg*" adj3 infect*)
31	(postsurg* adj3 infect*)
32	(surg* adj3 infect*)
33	exp Otitis Media
34	"otitis media"

35	"middle ear inflammation*"
36	exp Meningitis
37	meningitis
38	exp Wound Infection
39	"wound infection*"
40	microbiology
41	bacteriology
42	exp Microbiology
43	(antimicrobial* adj3 resistan*)
44	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45	exp Drug Resistance, Bacterial
46	exp Microbial Sensitivity Tests
47	exp Bacteremia
48	(bacteremi* or bacteraemi*)
49	(antimicrobial* adj3 test*)
50	(antimicrobial* adj3 resistan*)
51	(antimicrobial* adj3 surveillan*)
52	(antimicrobial* adj3 susceptib*)
53	(antimicrobial* adj3 sensitiv*)
54	(anti-microbial* adj3 test*)
55	(anti-microbial* adj3 resistan*)
56	(anti-microbial* adj3 surveillan*)
57	(anti-microbial* adj3 susceptib*)
58	(anti-microbial* adj3 sensitiv*)
59	(antibiotic* adj3 test*)
60	(antibiotic* adj3 resistan*)
61	(antibiotic* adj3 surveillan*)
62	(bacterial* adj3 resistan*)
63	(bacterial* adj3 surveillan*)
64	(antibacterial* adj3 resistan*)
65	(antibacterial* adj3 surveillan*)
66	(antibacterial* adj3 susceptib*)
67	(antibacterial* adj3 sensitiv*)
68	(anti-bacterial* adj3 resistan*)
69	(anti-bacterial* adj3 surveillan*)
70	(anti-bacterial* adj3 susceptib*)
71	(anti-bacterial* adj3 sensitiv*)
72	AST
73	45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74	clinical.
75	44 or 74

76	12 and 73 and 75
77	76
78	limit 77 to yr="1990 -Current"

Table C.1. Search strategy developed in MEDLINE, Ovid Embase, Global Health, and Cochrane.

Antimicrobial Class	Antimicrobials
Fluoroquinolones	Ofloxacin, Ciprofloxacin, Levofloxacin, Moxifloxacin
Fourth-generation cephalosporins	Cefepime
Third-generation cephalosporins	Cefotaxime, Ceftriaxone, Ceftazidime
Carbapenems	Meropenem, Imipenem, Ertapenem
Aminoglycosides	Amikacin, Netilmicin sulphate, Tobramycin, Gentamicin
Aminopenicillin	Ampicillin, Amoxicillin-clavulanic acid, Amoxicillin

Table C.2. Antimicrobial class classifications.

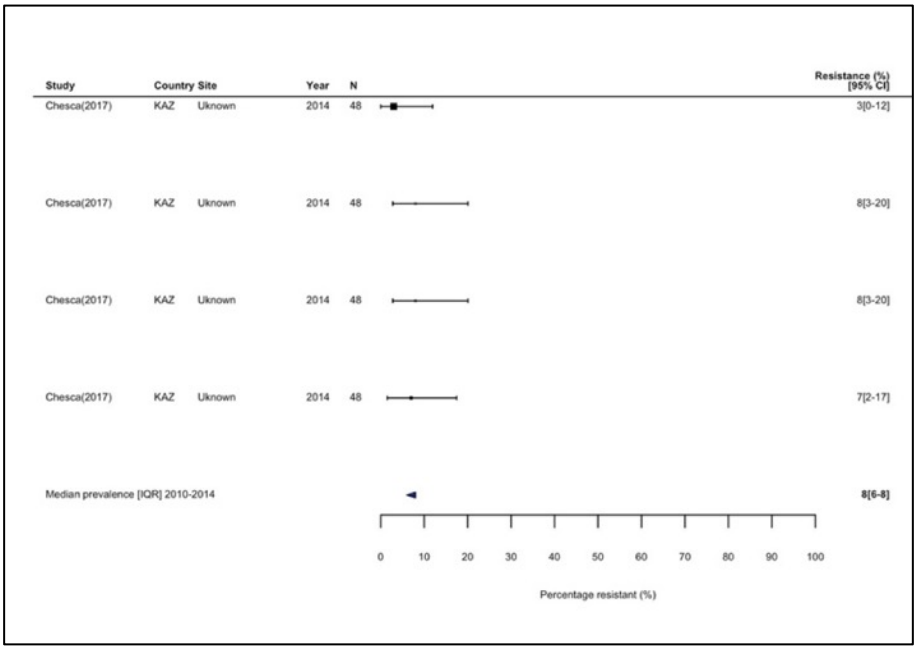
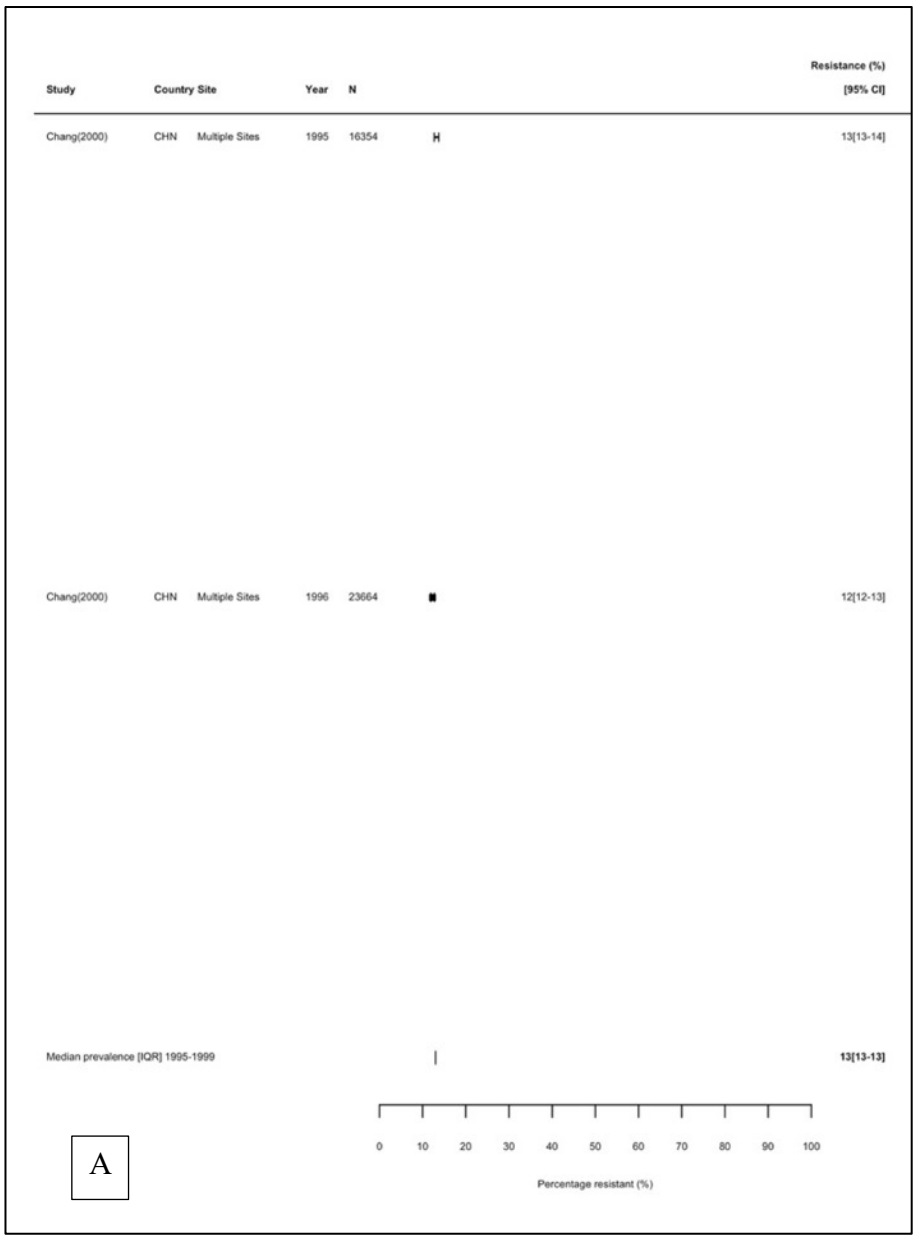
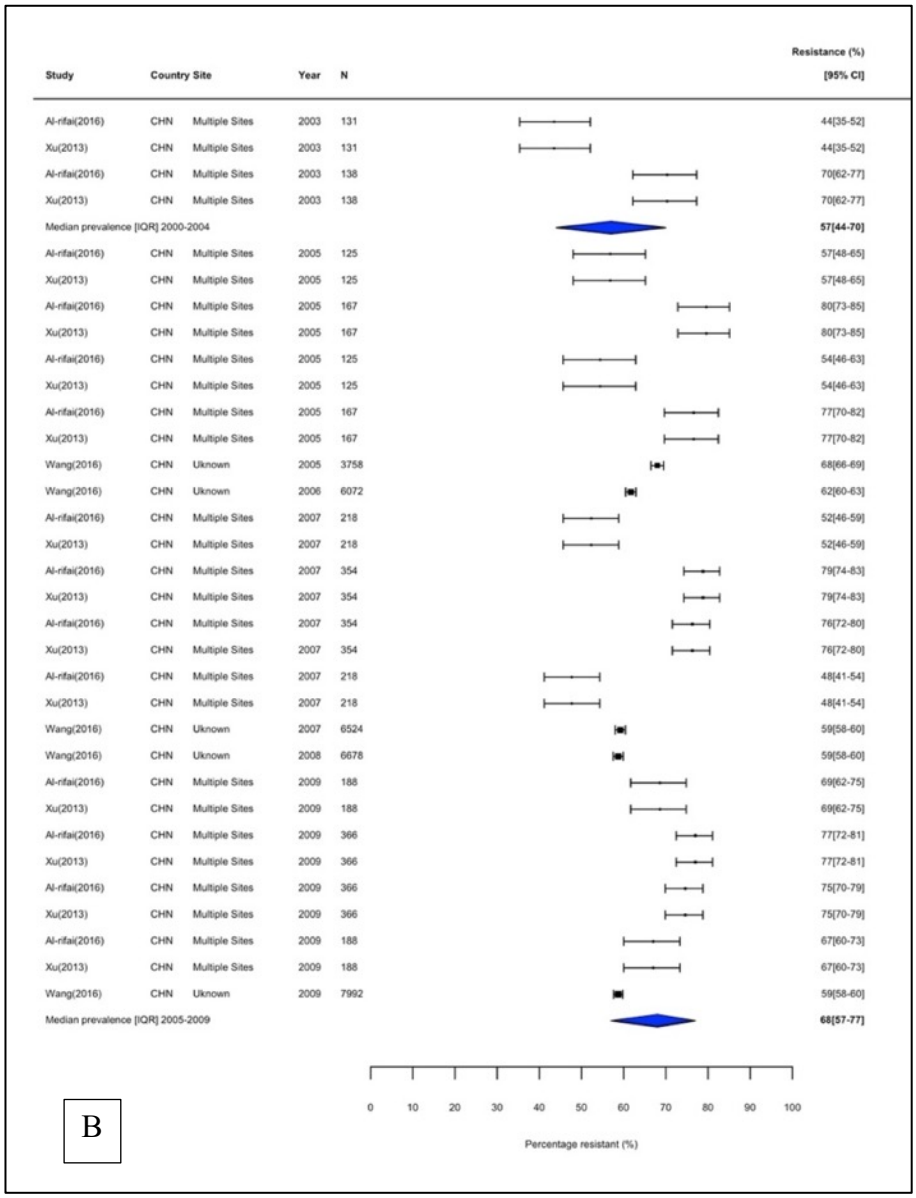


Figure C.1. Forest plot of fluoroquinolone resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Chang(2000) CHN Multiple Sites 1995 16354 13[13-14]
Chang(2000) CHN Multiple Sites 1996 23664 12[12-13]
Median prevalence [IQR] 1995-1999 13[13-13]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Al-rifai(2016) CHN Multiple Sites 2003 131 44[35-52]
Xu(2013) CHN Multiple Sites 2003 131 44[35-52]
Al-rifai(2016) CHN Multiple Sites 2003 138 70[62-77]
Xu(2013) CHN Multiple Sites 2003 138 70[62-77]
Median prevalence [IQR] 2000-2004 57[44-70]
Al-rifai(2016) CHN Multiple Sites 2005 125 57[48-65]
Xu(2013) CHN Multiple Sites 2005 125 57[48-65]
Al-rifai(2016) CHN Multiple Sites 2005 167 80[73-85]
Xu(2013) CHN Multiple Sites 2005 167 80[73-85]
Al-rifai(2016) CHN Multiple Sites 2005 125 54[46-63]
Xu(2013) CHN Multiple Sites 2005 125 54[46-63]
Al-rifai(2016) CHN Multiple Sites 2005 167 77[70-82]
Xu(2013) CHN Multiple Sites 2005 167 77[70-82]
Wang(2016) CHN Uknown 2005 3758 68[66-69]
Wang(2016) CHN Uknown 2006 6072 62[60-63]
Al-rifai(2016) CHN Multiple Sites 2007 218 52[46-59]
Xu(2013) CHN Multiple Sites 2007 218 52[46-59]
Al-rifai(2016) CHN Multiple Sites 2007 354 79[74-83]
Xu(2013) CHN Multiple Sites 2007 354 79[74-83]
Al-rifai(2016) CHN Multiple Sites 2007 354 76[72-80]
Xu(2013) CHN Multiple Sites 2007 354 76[72-80]
Al-rifai(2016) CHN Multiple Sites 2007 218 48[41-54]
Xu(2013) CHN Multiple Sites 2007 218 48[41-54]
Wang(2016) CHN Uknown 2007 6524 59[58-60]
Wang(2016) CHN Uknown 2008 6678 59[58-60]
Al-rifai(2016) CHN Multiple Sites 2009 188 69[62-75]
Xu(2013) CHN Multiple Sites 2009 188 69[62-75]
Al-rifai(2016) CHN Multiple Sites 2009 366 77[72-81]
Xu(2013) CHN Multiple Sites 2009 366 77[72-81]
Al-rifai(2016) CHN Multiple Sites 2009 366 75[70-79]
Xu(2013) CHN Multiple Sites 2009 366 75[70-79]
Al-rifai(2016) CHN Multiple Sites 2009 188 67[60-73]
Xu(2013) CHN Multiple Sites 2009 188 67[60-73]
Wang(2016) CHN Uknown 2009 7992 59[58-60]
Median prevalence [IQR] 2005-2009 68[57-77]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

B

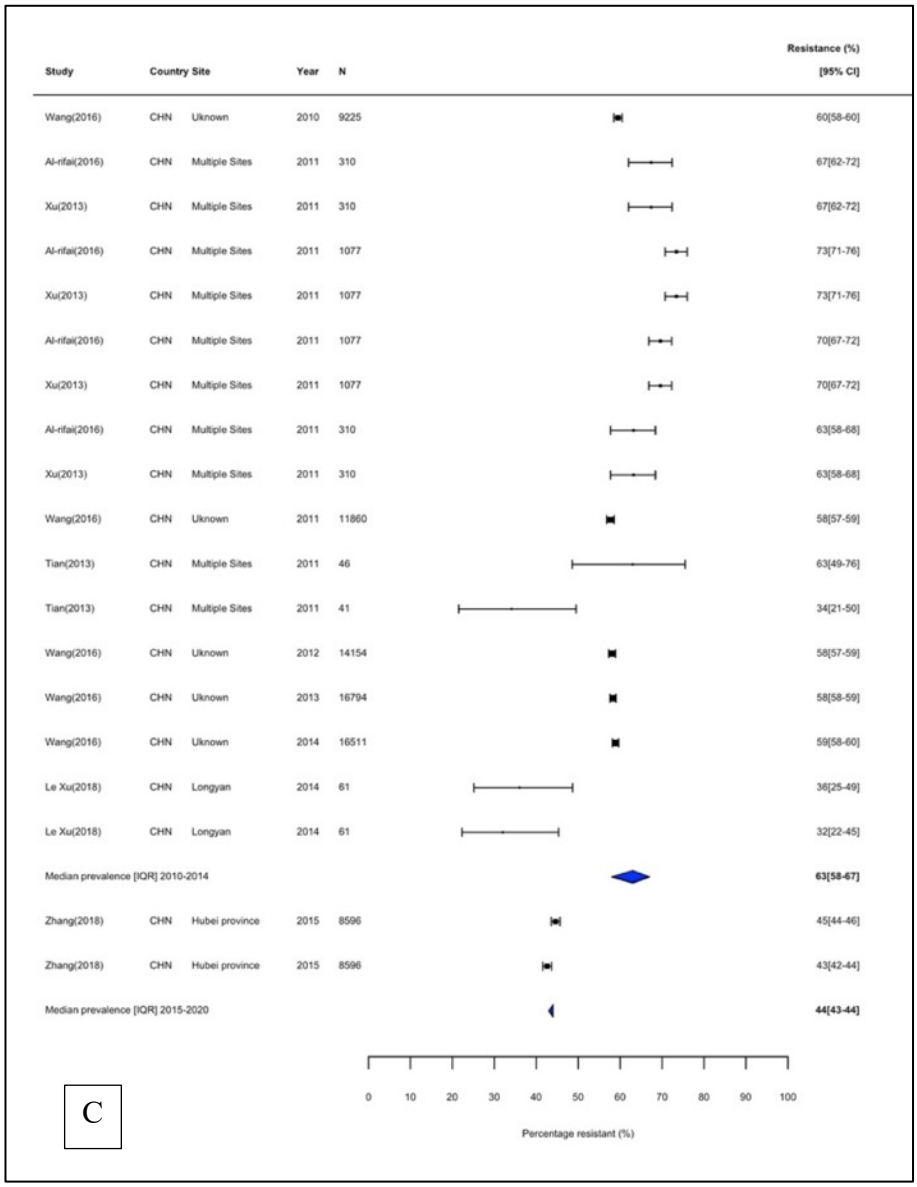


Figure C.2: Forest plot of fluoroquinolone resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2009, C: 2010-2018

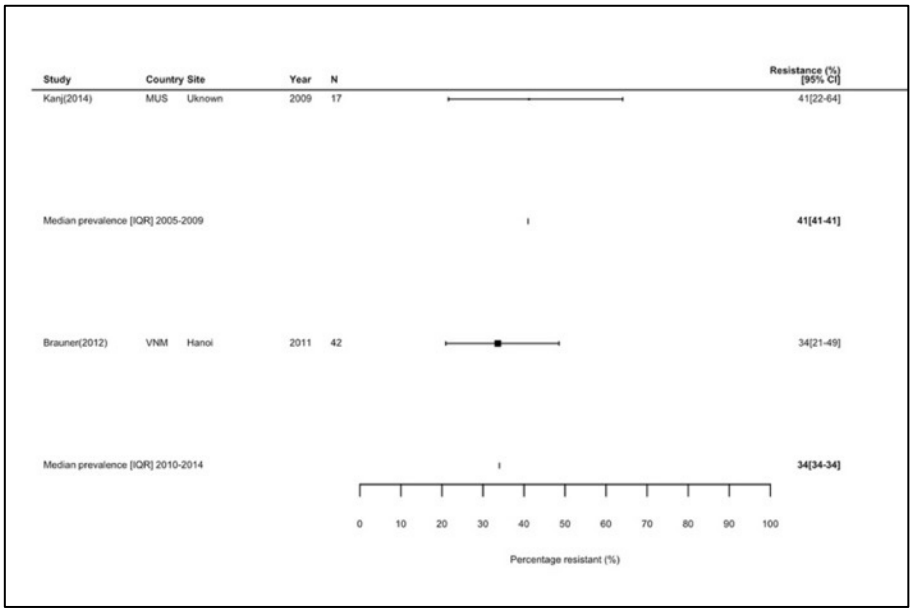


Figure C.3: Forest plot of fluoroquinolone resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

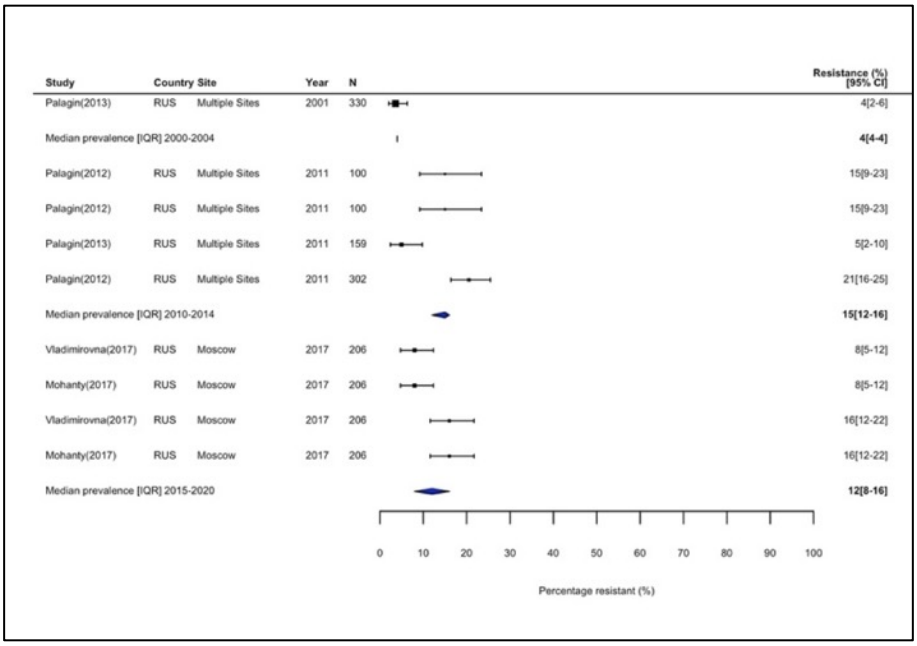


Figure C.4: Forest plot of fluoroquinolone resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup

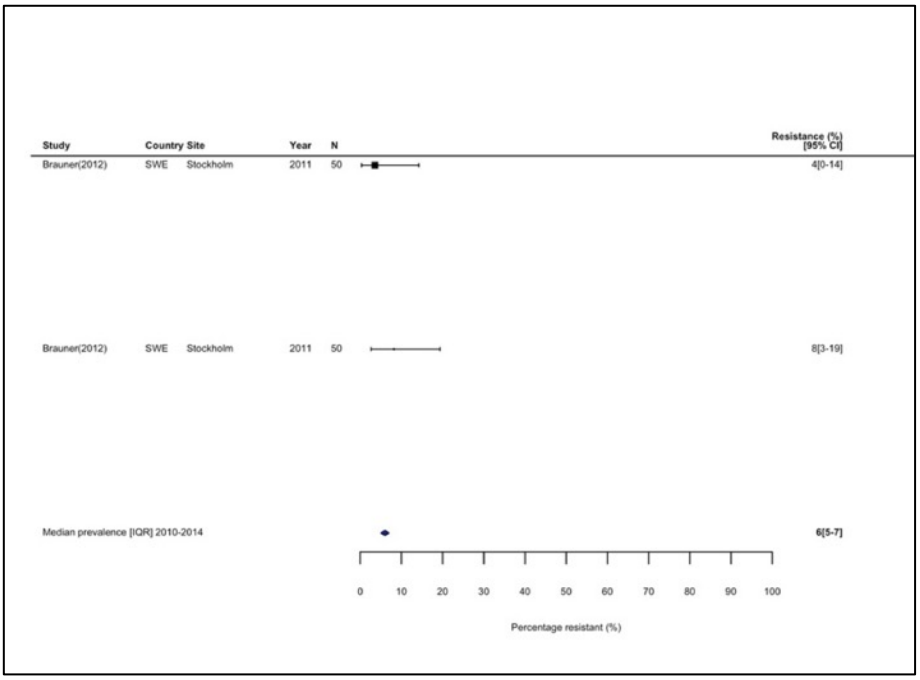


Figure C.5: Forest plot of fluoroquinolone resistance in Western Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup

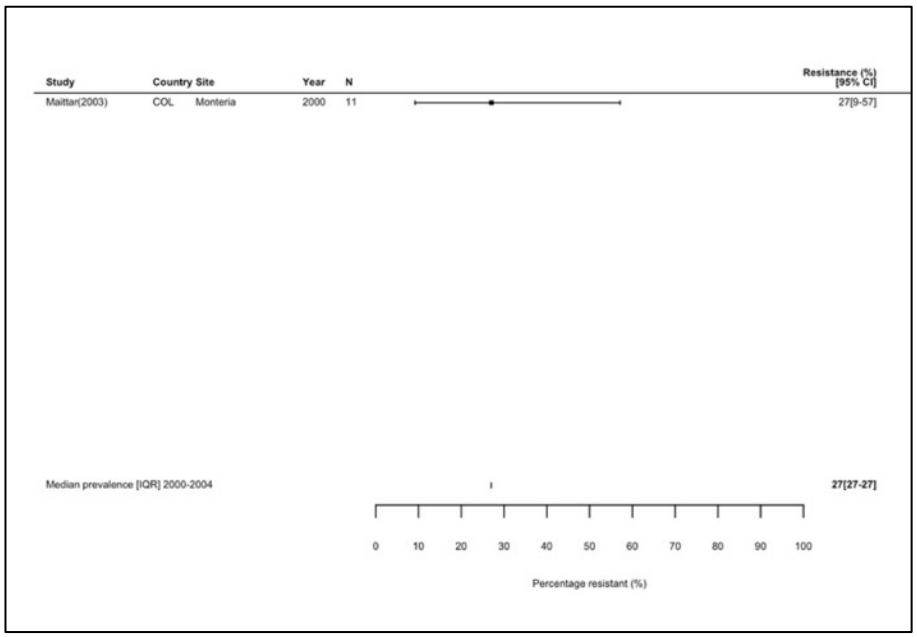


Figure C.6: Forest plot of fluoroquinolone resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup

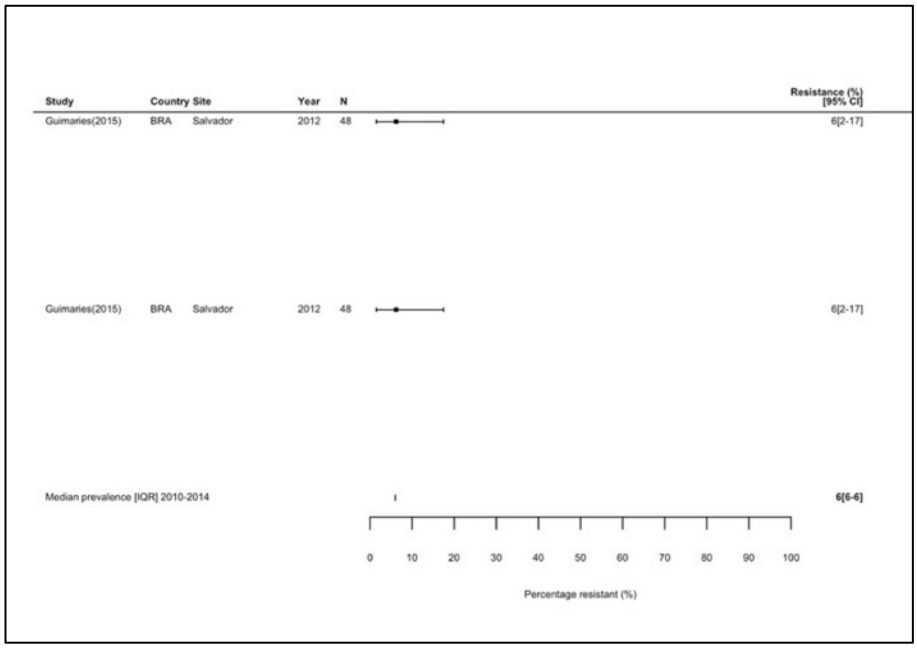


Figure C.7: Forest plot of fluoroquinolone resistance in Tropical Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

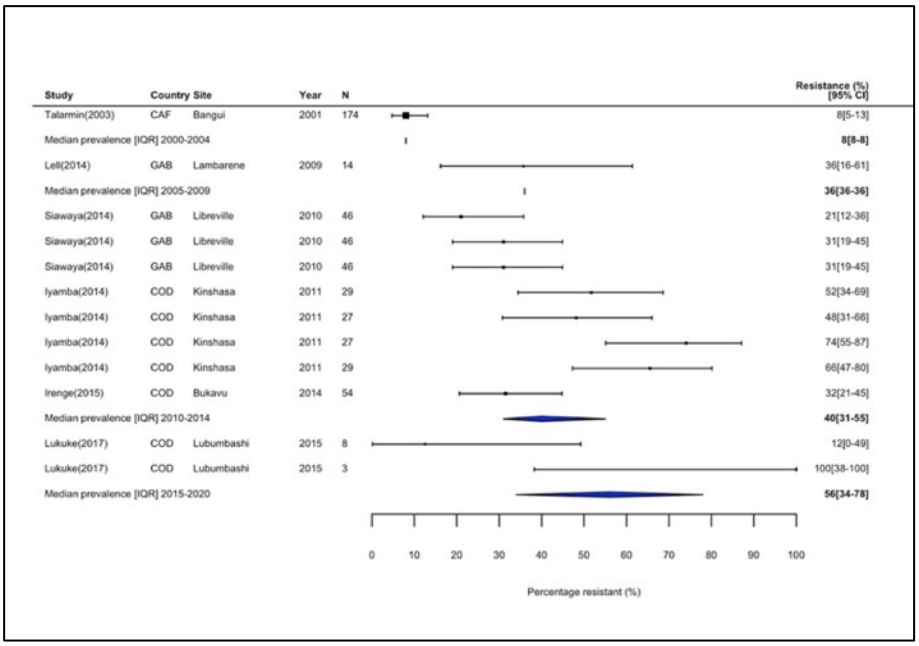
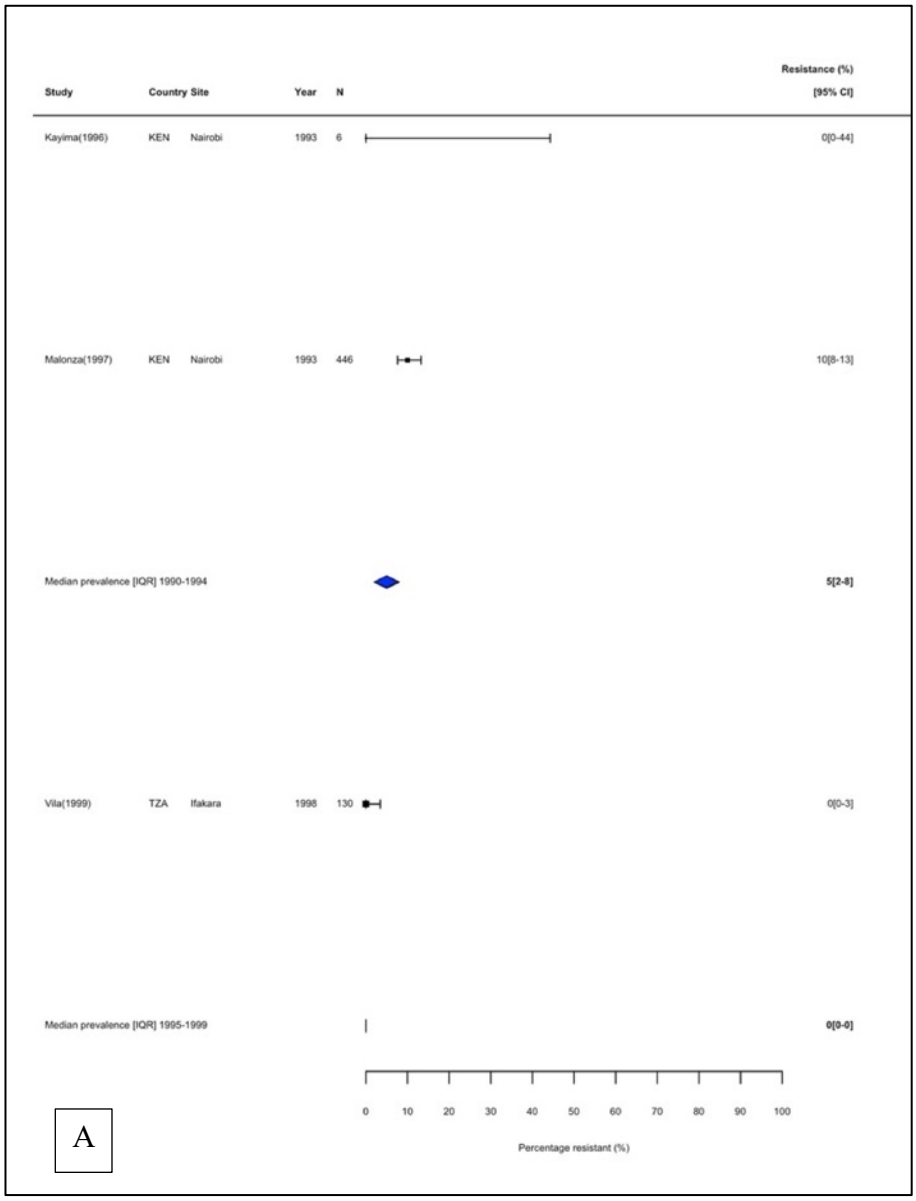
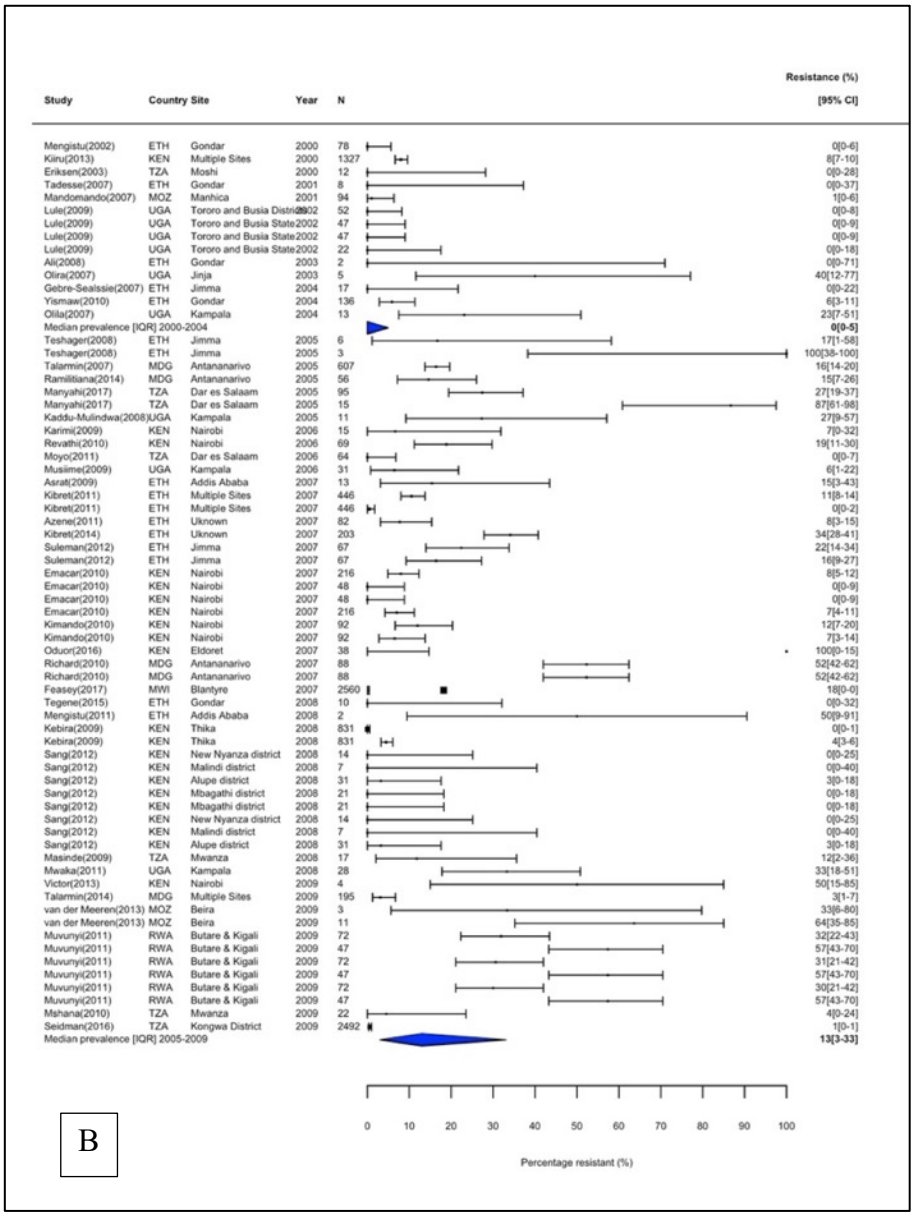
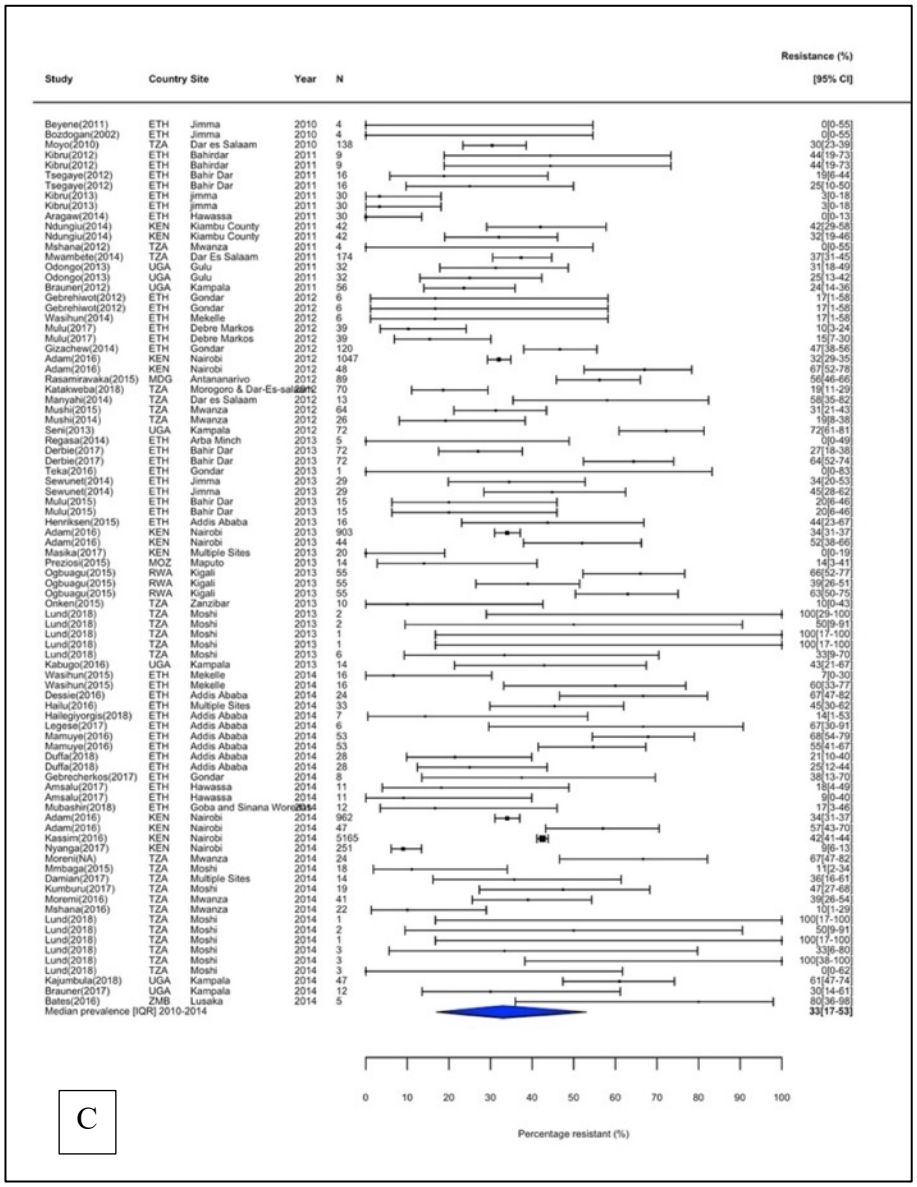


Figure C.8: Forest plot of fluoroquinolone resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Kayima(1996) KEN Nairobi 1993 6 0[0-44]
Malonza(1997) KEN Nairobi 1993 446 10[8-13]
Median prevalence [IQR] 1990-1994 5[2-8]
Vila(1999) TZA Ifakara 1998 130 0[0-3]
Median prevalence [IQR] 1995-1999 0[0-0]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Mengistu(2002) ETH Gondar 2000 78 0[0-6]
Kiiru(2013) KEN Multiple Sites 2000 1327 8[7-10]
Eriksen(2003) TZA Moshi 2000 12 0[0-28]
Tadesse(2007) ETH Gondar 2001 8 0[0-37]
Mandomando(2007) MOZ Manhica 2001 94 1[0-6]
Lule(2009) UGA Tororo and Busia Distric 2002 52 0[0-8]
Lule(2009) UGA Tororo and Busia State 2002 47 0[0-9]
Lule(2009) UGA Tororo and Busia State 2002 47 0[0-9]
Lule(2009) UGA Tororo and Busia State 2002 22 0[0-18]
Ali(2008) ETH Gondar 2003 2 0[0-71]
Olira(2007) UGA Jinja 2003 5 40[12-77]
Gebre-Sealssie(2007) ETH Jimma 2004 17 0[0-22]
Yismaw(2010) ETH Gondar 2004 136 6[3-11]
Olila(2007) UGA Kampala 2004 13 23[7-51]
Median prevalence [IQR] 2000-2004 0[0-5]
Teshager(2008) ETH Jimma 2005 6 17[1-58]
Teshager(2008) ETH Jimma 2005 3 100[38-100]
Talarmin(2007) MDG Antananarivo 2005 607 16[14-20]
Ramilitiana(2014) MDG Antananarivo 2005 56 15[7-26]
Manyahi(2017) TZA Dar es Salaam 2005 95 27[19-37]
Manyahi(2017) TZA Dar es Salaam 2005 15 87[61-98]
Kaddu-Mulindwa(2008) UGA Kampala 2005 11 27[9-57]
Karimi(2009) KEN Nairobi 2006 15 7[0-32]
Revathi(2010) KEN Nairobi 2006 69 19[11-30]
Moyo(2011) TZA Dar es Salaam 2006 64 0[0-7]
Musiime(2009) UGA Kampala 2006 31 6[1-22]
Asrat(2009) ETH Addis Ababa 2007 13 15[3-43]
Kibret(2011) ETH Multiple Sites 2007 446 11[8-14]
Kibret(2011) ETH Multiple Sites 2007 446 0[0-2]
Azene(2011) ETH Uknown 2007 82 8[3-15]
Kibret(2014) ETH Uknown 2007 203 34[28-41]
Suleman(2012) ETH Jimma 2007 67 22[14-34]
Suleman(2012) ETH Jimma 2007 67 16[9-27]
Emacar(2010) KEN Nairobi 2007 216 8[5-12]
Emacar(2010) KEN Nairobi 2007 48 0[0-9]
Emacar(2010) KEN Nairobi 2007 48 0[0-9]
Emacar(2010) KEN Nairobi 2007 216 7[4-11]
Kimando(2010) KEN Nairobi 2007 92 12[7-20]
Kimando(2010) KEN Nairobi 2007 92 7[3-14]
Oduor(2016) KEN Eldoret 2007 38 100[0-15]
Richard(2010) MDG Antananarivo 2007 88 52[42-62]
Richard(2010) MDG Antananarivo 2007 88 52[42-62]
Feasey(2017) MWI Blantyre 2007 2560 18[0-0]
Tegene(2015) ETH Gondar 2008 10 0[0-32]
Mengistu(2011) ETH Addis Ababa 2008 2 50[9-91]
Kebira(2009) KEN Thika 2008 831 0[0-1]
Kebira(2009) KEN Thika 2008 831 4[3-6]
Sang(2012) KEN New Nyanza district 2008 14 0[0-25]
Sang(2012) KEN Malindi district 2008 7 0[0-40]
Sang(2012) KEN Alupe district 2008 31 3[0-18]
Sang(2012) KEN Mbagathi district 2008 21 0[0-18]
Sang(2012) KEN Mbagathi district 2008 21 0[0-18]
Sang(2012) KEN New Nyanza district 2008 14 0[0-25]
Sang(2012) KEN Malindi district 2008 7 0[0-40]
Sang(2012) KEN Alupe district 2008 31 3[0-18]
Masinde(2009) TZA Mwanza 2008 17 12[2-36]
Mwaka(2011) UGA Kampala 2008 28 33[18-51]
Victor(2013) KEN Nairobi 2009 4 50[15-85]
Talarmin(2014) MDG Multiple Sites 2009 195 3[1-7]
van der Meeren(2013) MOZ Beira 2009 3 33[6-80]
van der Meeren(2013) MOZ Beira 2009 11 64[35-85]
Muvunyi(2011) RWA Butare & Kigali 2009 72 32[22-43]
Muvunyi(2011) RWA Butare & Kigali 2009 47 57[43-70]
Muvunyi(2011) RWA Butare & Kigali 2009 72 31[21-42]
Muvunyi(2011) RWA Butare & Kigali 2009 47 57[43-70]
Muvunyi(2011) RWA Butare & Kigali 2009 72 30[21-42]
Muvunyi(2011) RWA Butare & Kigali 2009 47 57[43-70]
Mshana(2010) TZA Mwanza 2009 22 4[0-24]
Seidman(2016) TZA Kongwa District 2009 2492 1[0-1]
Median prevalence [IQR] 2005-2009 13[3-33]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Beyene(2011) ETH Jimma 2010 4 0[0-55]
Bozdogan(2002) ETH Jimma 2010 4 0[0-55]
Moyo(2010) TZA Dar es Salaam 2010 138 30[23-39]
Kibru(2012) ETH Bahirdar 2011 9 44[19-73]
Kibru(2012) ETH Bahirdar 2011 9 44[19-73]
Tsegaye(2012) ETH Bahir Dar 2011 16 19[6-44]
Tsegaye(2012) ETH Bahir Dar 2011 16 25[10-50]
Kibru(2013) ETH jimma 2011 30 3[0-18]
Kibru(2013) ETH jimma 2011 30 3[0-18]
Aragaw(2014) ETH Hawassa 2011 30 0[0-13]
Ndungiu(2014) KEN Kiambu County 2011 42 42[29-58]
Ndungiu(2014) KEN Kiambu County 2011 42 32[19-46]
Mshana(2012) TZA Mwanza 2011 4 0[0-55]
Mwambete(2014) TZA Dar Es Salaam 2011 174 37[31-45]
Odongo(2013) UGA Gulu 2011 32 31[18-49]
Odongo(2013) UGA Gulu 2011 32 25[13-42]
Brauner(2012) UGA Kampala 2011 56 24[14-36]
Gebrehiwot(2012) ETH Gondar 2012 6 17[1-58]
Gebrehiwot(2012) ETH Gondar 2012 6 17[1-58]
Wasihun(2014) ETH Mekelle 2012 6 17[1-58]
Mulu(2017) ETH Debre Markos 2012 39 10[3-24]
Mulu(2017) ETH Debre Markos 2012 39 15[7-30]
Gizachew(2014) ETH Gondar 2012 120 47[38-56]
Adam(2016) KEN Nairobi 2012 1047 32[29-35]
Adam(2016) KEN Nairobi 2012 48 67[52-78]
Rasamiravaka(2015) MDG Antananarivo 2012 89 56[46-66]
Katakweba(2018) TZA Morogoro & Dar-Es-salaam 2012 70 19[11-29]
Manyahi(2014) TZA Dar es Salaam 2012 13 58[35-82]
Mushi(2015) TZA Mwanza 2012 64 31[21-43]
Mushi(2014) TZA Mwanza 2012 26 19[8-38]
Seni(2013) UGA Kampala 2012 72 72[61-81]
Regasa(2014) ETH Arba Minch 2013 5 0[0-49]
Derbie(2017) ETH Bahir Dar 2013 72 27[18-38]
Derbie(2017) ETH Bahir Dar 2013 72 64[52-74]
Teka(2016) ETH Gondar 2013 1 0[0-83]
Sewunet(2014) ETH Jimma 2013 29 34[20-53]
Sewunet(2014) ETH Jimma 2013 29 45[28-62]
Mulu(2015) ETH Bahir Dar 2013 15 20[6-46]
Mulu(2015) ETH Bahir Dar 2013 15 20[6-46]
Henriksen(2015) ETH Addis Ababa 2013 16 44[23-67]
Adam(2016) KEN Nairobi 2013 903 34[31-37]
Adam(2016) KEN Nairobi 2013 44 52[38-66]
Masika(2017) KEN Multiple Sites 2013 20 0[0-19]
Preziosi(2015) MOZ Maputo 2013 14 14[3-41]
Ogbuagu(2015) RWA Kigali 2013 55 66[52-77]
Ogbuagu(2015) RWA Kigali 2013 55 39[26-51]
Ogbuagu(2015) RWA Kigali 2013 55 63[50-75]
Oriken(2015) TZA Zanzibar 2013 10 10[0-43]
Lund(2018) TZA Moshi 2013 2 100[29-100]
Lund(2018) TZA Moshi 2013 2 50[9-91]
Lund(2018) TZA Moshi 2013 1 100[17-100]
Lund(2018) TZA Moshi 2013 1 100[17-100]
Lund(2018) TZA Moshi 2013 6 33[9-70]
Kabugo(2016) UGA Kampala 2013 14 43[21-67]
Wasihun(2015) ETH Mekelle 2014 16 7[0-30]
Wasihun(2015) ETH Mekelle 2014 16 60[33-77]
Dessie(2016) ETH Addis Ababa 2014 24 67[47-82]
Hailu(2016) ETH Multiple Sites 2014 33 45[30-62]
Haileyiyorgis(2018) ETH Addis Ababa 2014 7 14[1-53]
Legese(2017) ETH Addis Ababa 2014 6 67[30-91]
Mamuye(2016) ETH Addis Ababa 2014 53 68[54-79]
Mamuye(2016) ETH Addis Ababa 2014 53 55[41-67]
Dufla(2018) ETH Addis Ababa 2014 28 21[10-40]
Dufla(2018) ETH Addis Ababa 2014 28 25[12-44]
Gebrecherkos(2017) ETH Gondar 2014 8 38[13-70]
Amsalu(2017) ETH Hawassa 2014 11 18[4-49]
Amsalu(2017) ETH Hawassa 2014 11 9[0-40]
Mubashir(2018) ETH Goba and Sinana Woreda 2014 12 17[3-46]
Adam(2016) KEN Nairobi 2014 962 34[31-37]
Adam(2016) KEN Nairobi 2014 47 57[43-70]
Kassim(2016) KEN Nairobi 2014 5165 42[41-44]
Nyanga(2017) KEN Nairobi 2014 251 9[6-13]
Moreni(NA) TZA Mwanza 2014 24 67[47-82]
Mmbaga(2015) TZA Moshi 2014 18 11[2-34]
Damian(2017) TZA Multiple Sites 2014 14 36[16-61]
Kumburu(2017) TZA Moshi 2014 19 47[27-68]
Moremi(2016) TZA Mwanza 2014 41 39[26-54]
Mshana(2016) TZA Mwanza 2014 22 10[1-29]
Lund(2018) TZA Moshi 2014 1 100[17-100]
Lund(2018) TZA Moshi 2014 2 50[9-91]
Lund(2018) TZA Moshi 2014 1 100[17-100]
Lund(2018) TZA Moshi 2014 3 33[6-80]
Lund(2018) TZA Moshi 2014 3 100[38-100]
Lund(2018) TZA Moshi 2014 3 0[0-62]
Kajumbula(2018) UGA Kampala 2014 47 61[47-74]
Brauner(2017) UGA Kampala 2014 12 30[14-61]
Bates(2016) ZMB Lusaka 2014 5 80[36-98]
Median prevalence [IQR] 2010-2014 33[17-53]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

C

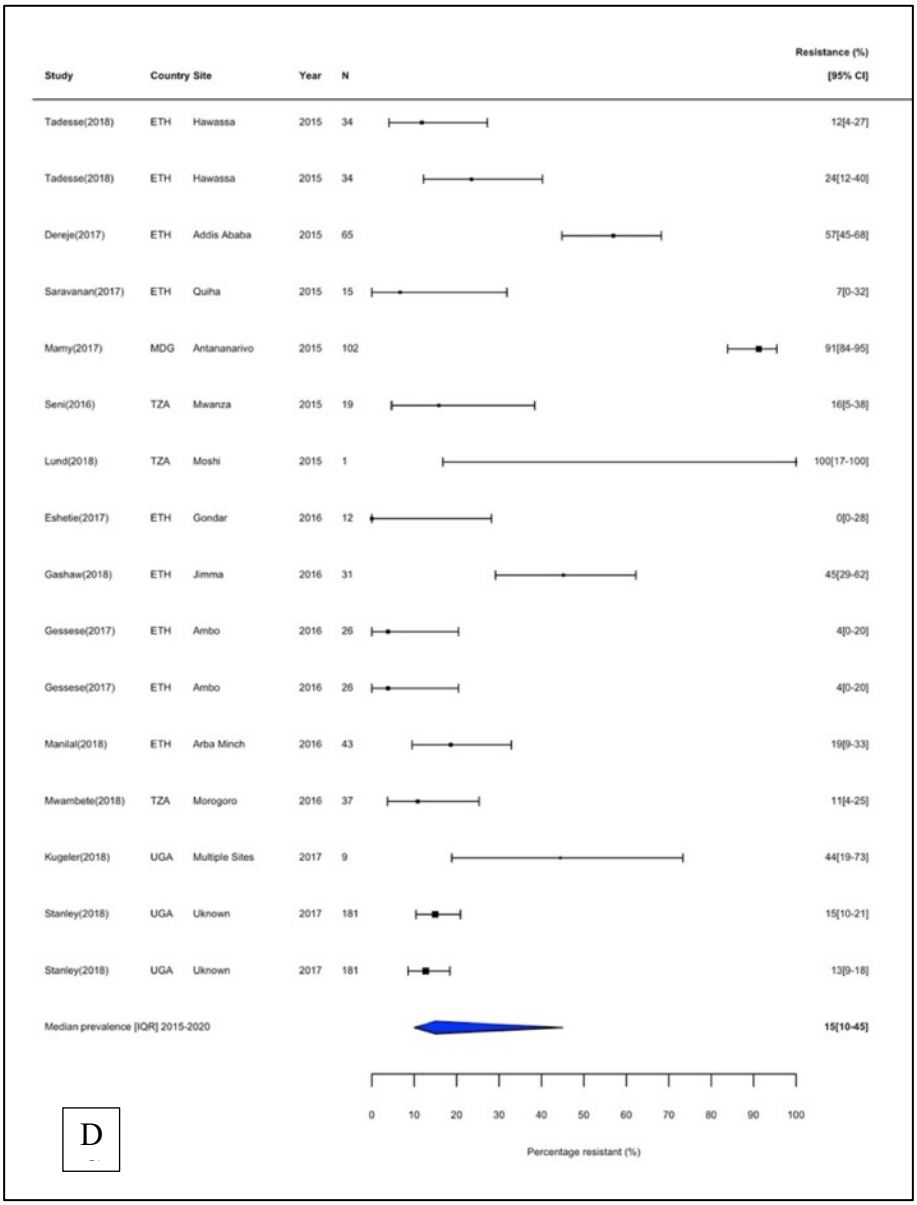
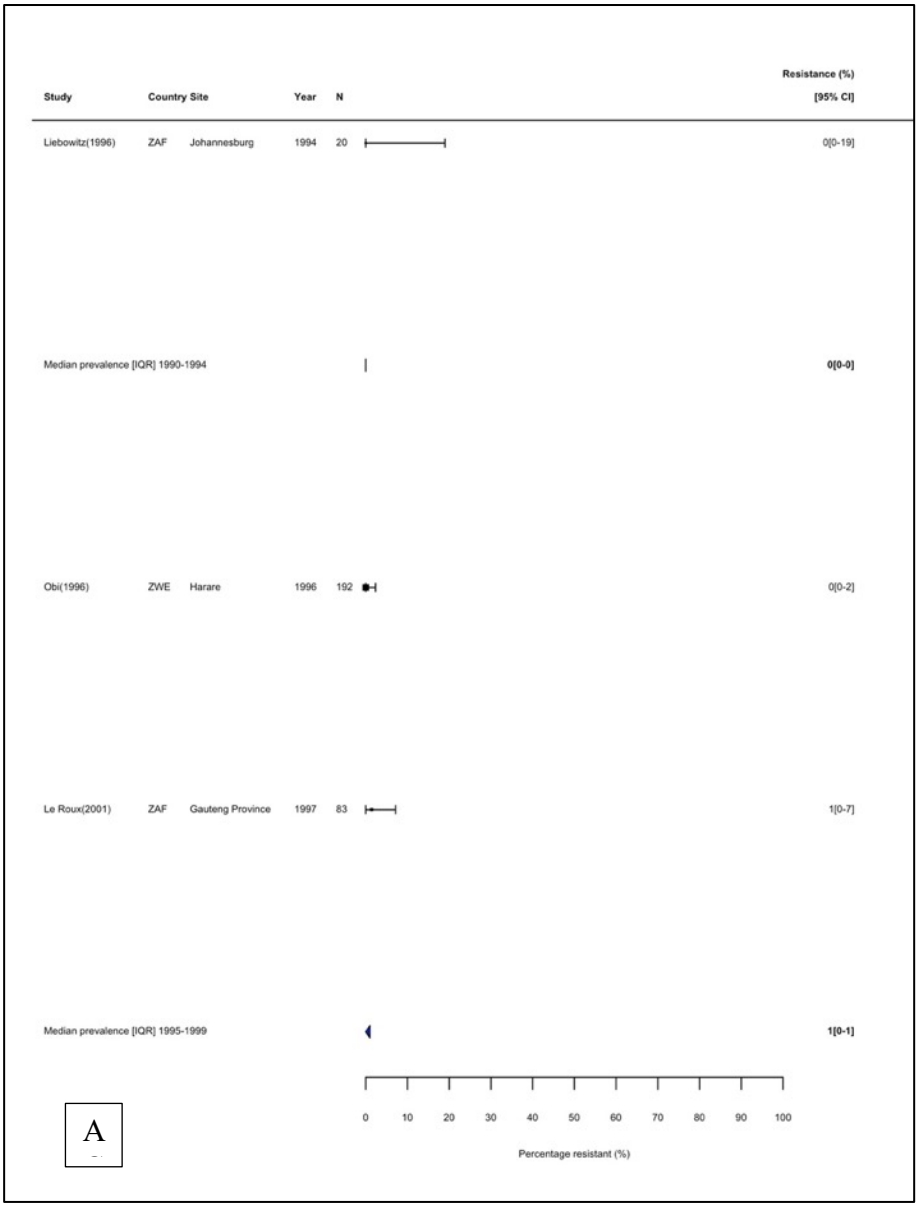
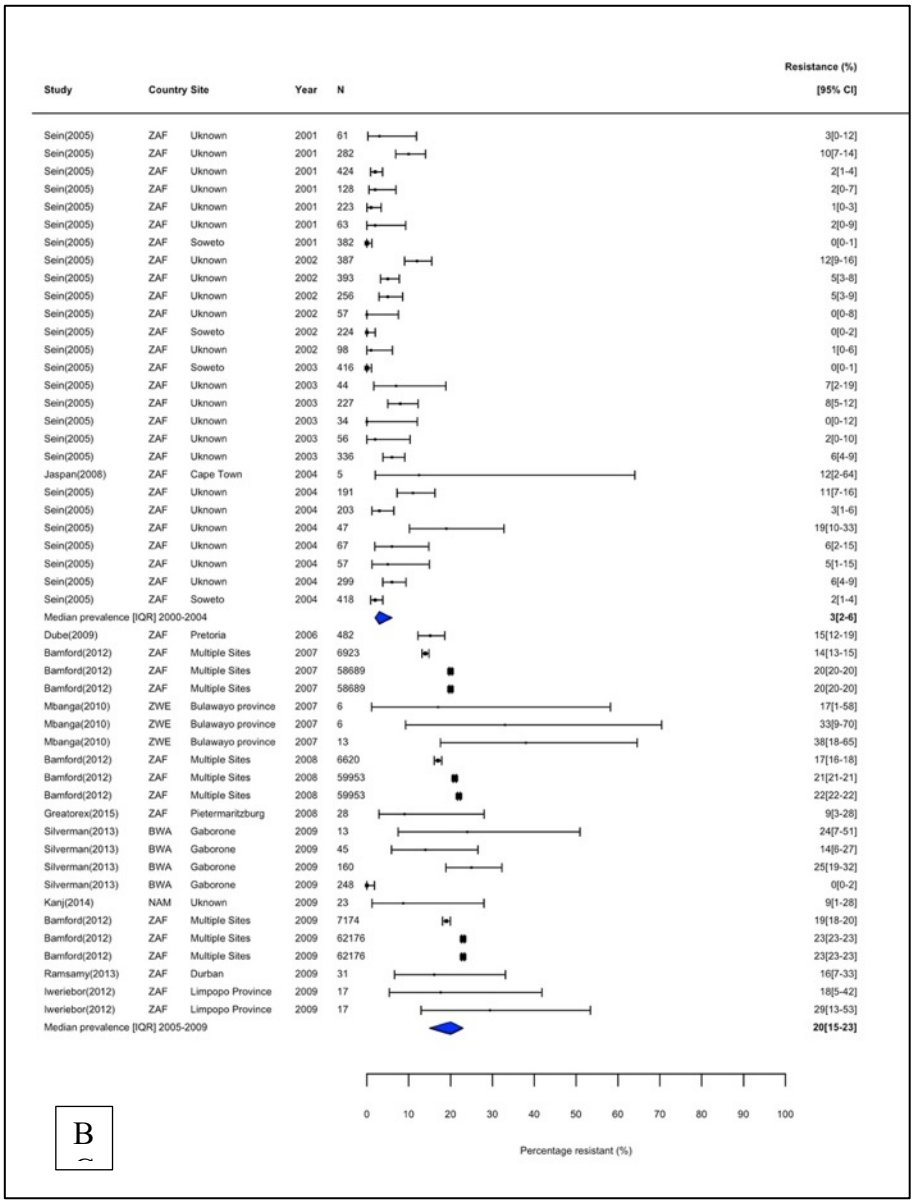


Figure C.9: Forest plot of fluoroquinolone resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2009, C: 2010-2014, D: 2015-2018.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Liebowitz(1996) ZAF Johannesburg 1994 20 0[0-19]
Median prevalence [IQR] 1990-1994 0[0-0]
Obi(1996) ZWE Harare 1996 192 0[0-2]
Le Roux(2001) ZAF Gauteng Province 1997 83 1[0-7]
Median prevalence [IQR] 1995-1999 1[0-1]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Sein(2005) ZAF Uknown 2001 61 3[0-12]
Sein(2005) ZAF Uknown 2001 282 10[7-14]
Sein(2005) ZAF Uknown 2001 424 2[1-4]
Sein(2005) ZAF Uknown 2001 128 2[0-7]
Sein(2005) ZAF Uknown 2001 223 1[0-3]
Sein(2005) ZAF Uknown 2001 63 2[0-9]
Sein(2005) ZAF Soweto 2001 382 0[0-1]
Sein(2005) ZAF Uknown 2002 387 12[9-16]
Sein(2005) ZAF Uknown 2002 393 5[3-8]
Sein(2005) ZAF Uknown 2002 256 5[3-9]
Sein(2005) ZAF Uknown 2002 57 0[0-8]
Sein(2005) ZAF Soweto 2002 224 0[0-2]
Sein(2005) ZAF Uknown 2002 98 1[0-6]
Sein(2005) ZAF Soweto 2003 416 0[0-1]
Sein(2005) ZAF Uknown 2003 44 7[2-19]
Sein(2005) ZAF Uknown 2003 227 8[5-12]
Sein(2005) ZAF Uknown 2003 34 0[0-12]
Sein(2005) ZAF Uknown 2003 56 2[0-10]
Sein(2005) ZAF Uknown 2003 336 6[4-9]
Jaspan(2008) ZAF Cape Town 2004 5 12[2-64]
Sein(2005) ZAF Uknown 2004 191 11[7-16]
Sein(2005) ZAF Uknown 2004 203 3[1-6]
Sein(2005) ZAF Uknown 2004 47 19[10-33]
Sein(2005) ZAF Uknown 2004 67 6[2-15]
Sein(2005) ZAF Uknown 2004 57 5[1-15]
Sein(2005) ZAF Uknown 2004 299 6[4-9]
Sein(2005) ZAF Soweto 2004 418 2[1-4]
Median prevalence [IQR] 2000-2004 3[2-6]
Dube(2009) ZAF Pretoria 2006 482 15[12-19]
Bamford(2012) ZAF Multiple Sites 2007 6923 14[13-15]
Bamford(2012) ZAF Multiple Sites 2007 58689 20[20-20]
Bamford(2012) ZAF Multiple Sites 2007 58689 20[20-20]
Mbanga(2010) ZWE Bulawayo province 2007 6 17[1-58]
Mbanga(2010) ZWE Bulawayo province 2007 6 33[9-70]
Mbanga(2010) ZWE Bulawayo province 2007 13 38[18-65]
Bamford(2012) ZAF Multiple Sites 2008 6620 17[16-18]
Bamford(2012) ZAF Multiple Sites 2008 59953 21[21-21]
Bamford(2012) ZAF Multiple Sites 2008 59953 22[22-22]
Greatorex(2015) ZAF Pietermaritzburg 2008 28 9[3-28]
Silverman(2013) BWA Gaborone 2009 13 24[7-51]
Silverman(2013) BWA Gaborone 2009 45 14[6-27]
Silverman(2013) BWA Gaborone 2009 160 25[19-32]
Silverman(2013) BWA Gaborone 2009 248 0[0-2]
Kanj(2014) NAM Uknown 2009 23 9[1-28]
Bamford(2012) ZAF Multiple Sites 2009 7174 19[18-20]
Bamford(2012) ZAF Multiple Sites 2009 62176 23[23-23]
Bamford(2012) ZAF Multiple Sites 2009 62176 23[23-23]
Ramsamy(2013) ZAF Durban 2009 31 16[7-33]
Iweriebor(2012) ZAF Limpopo Province 2009 17 18[5-42]
Iweriebor(2012) ZAF Limpopo Province 2009 17 29[13-53]
Median prevalence [IQR] 2005-2009 20[15-23]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B

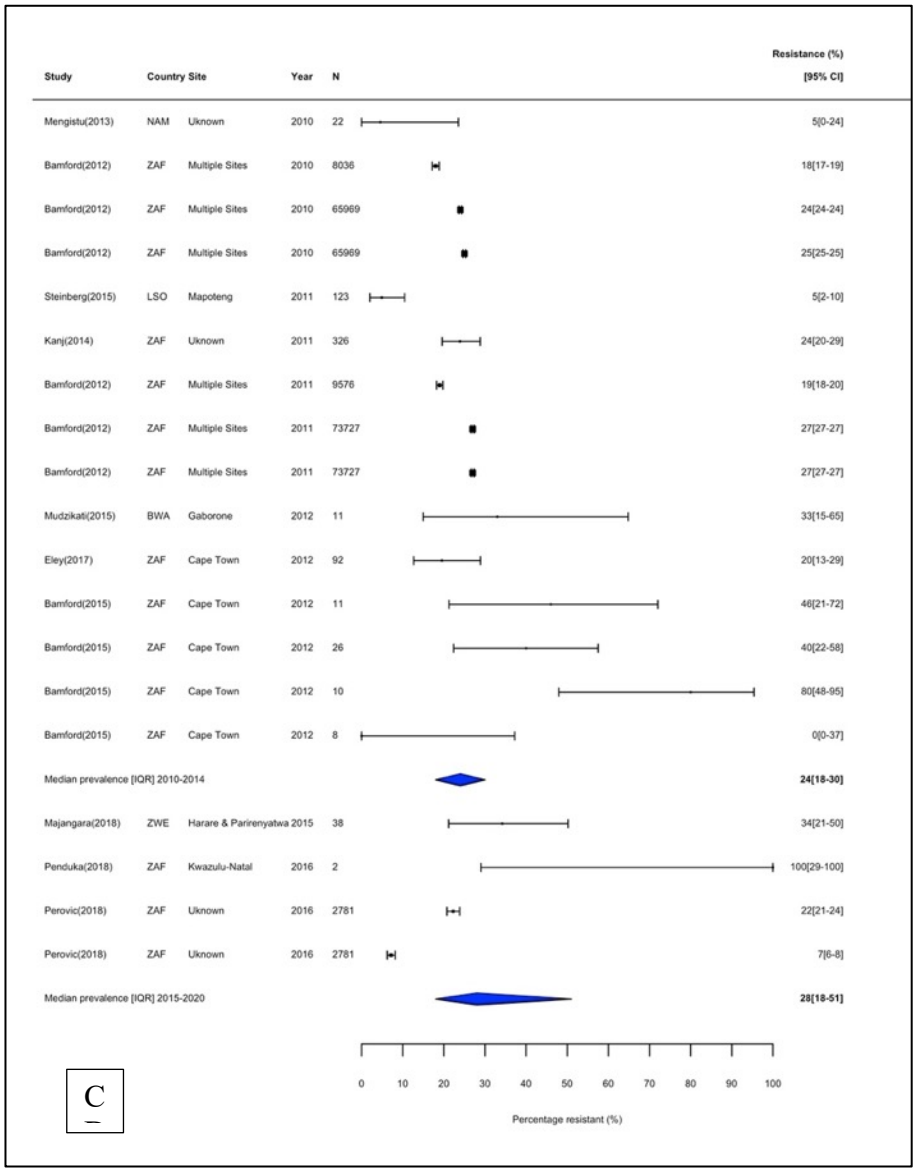
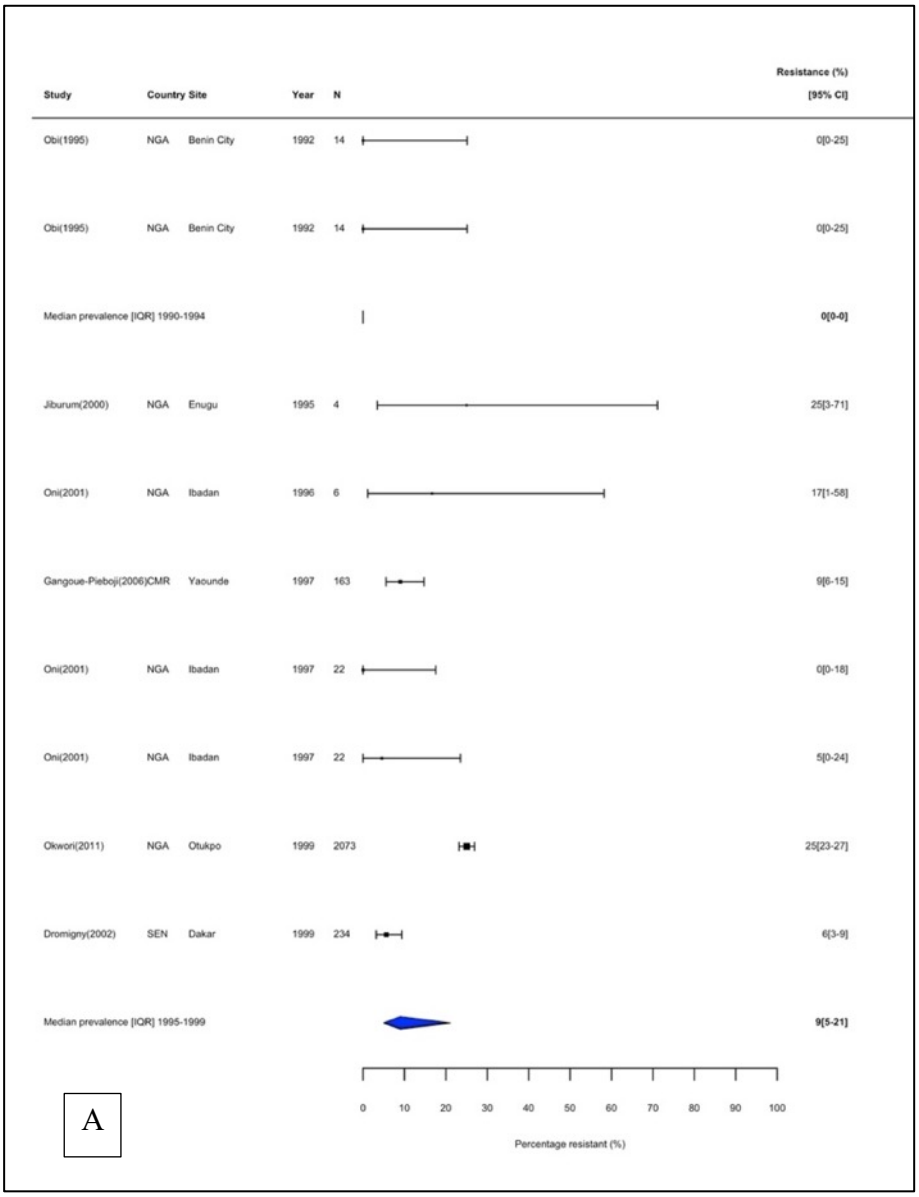
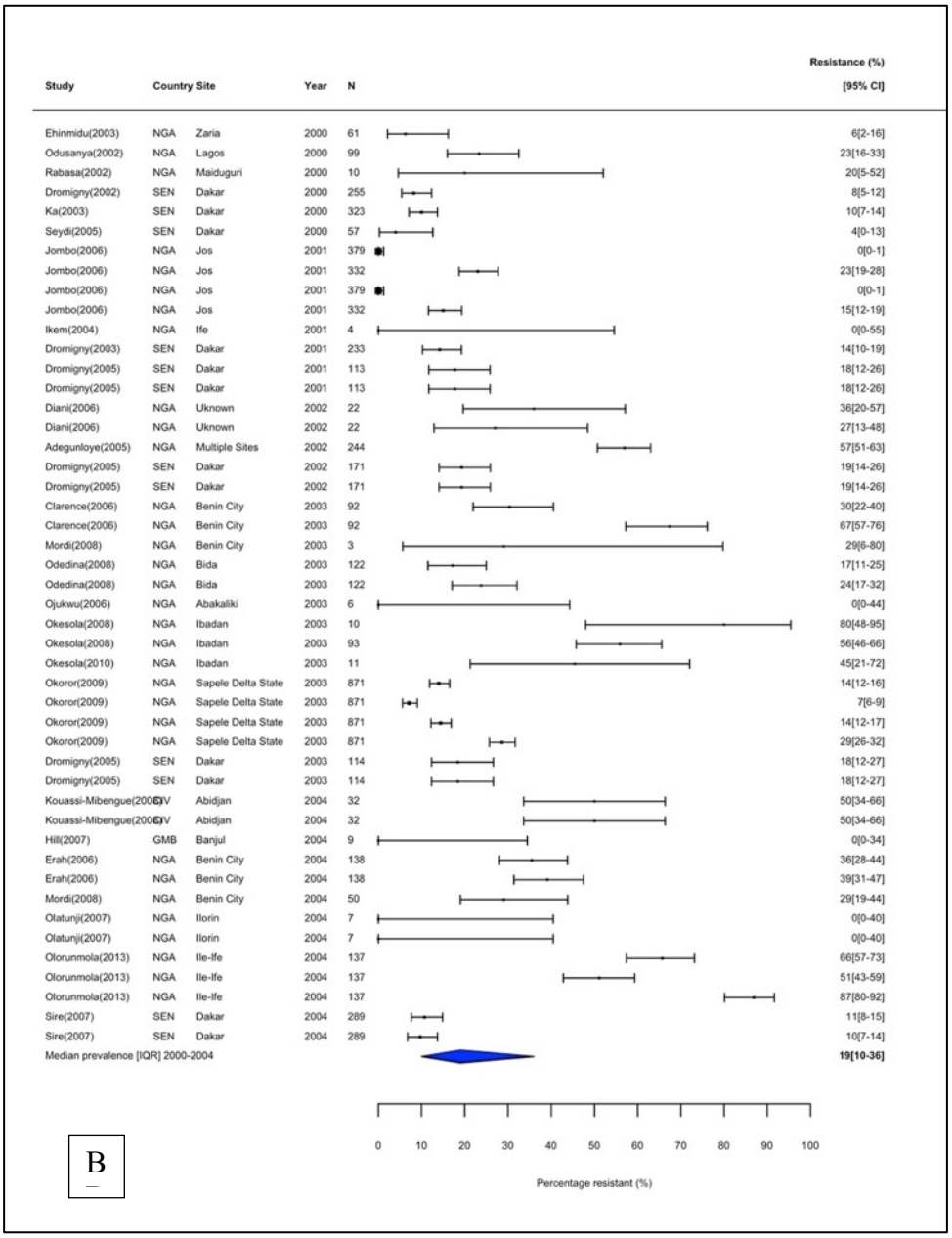
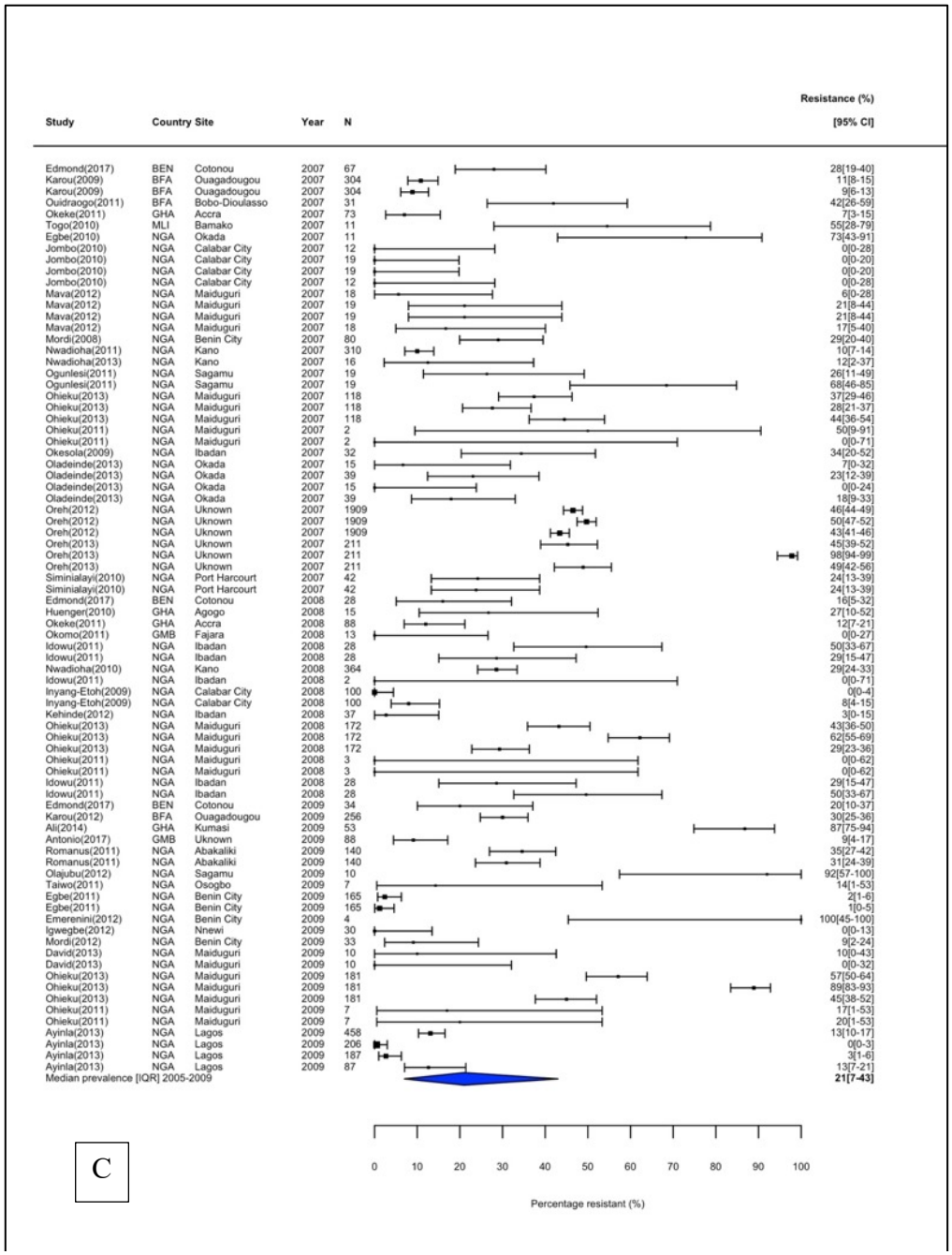


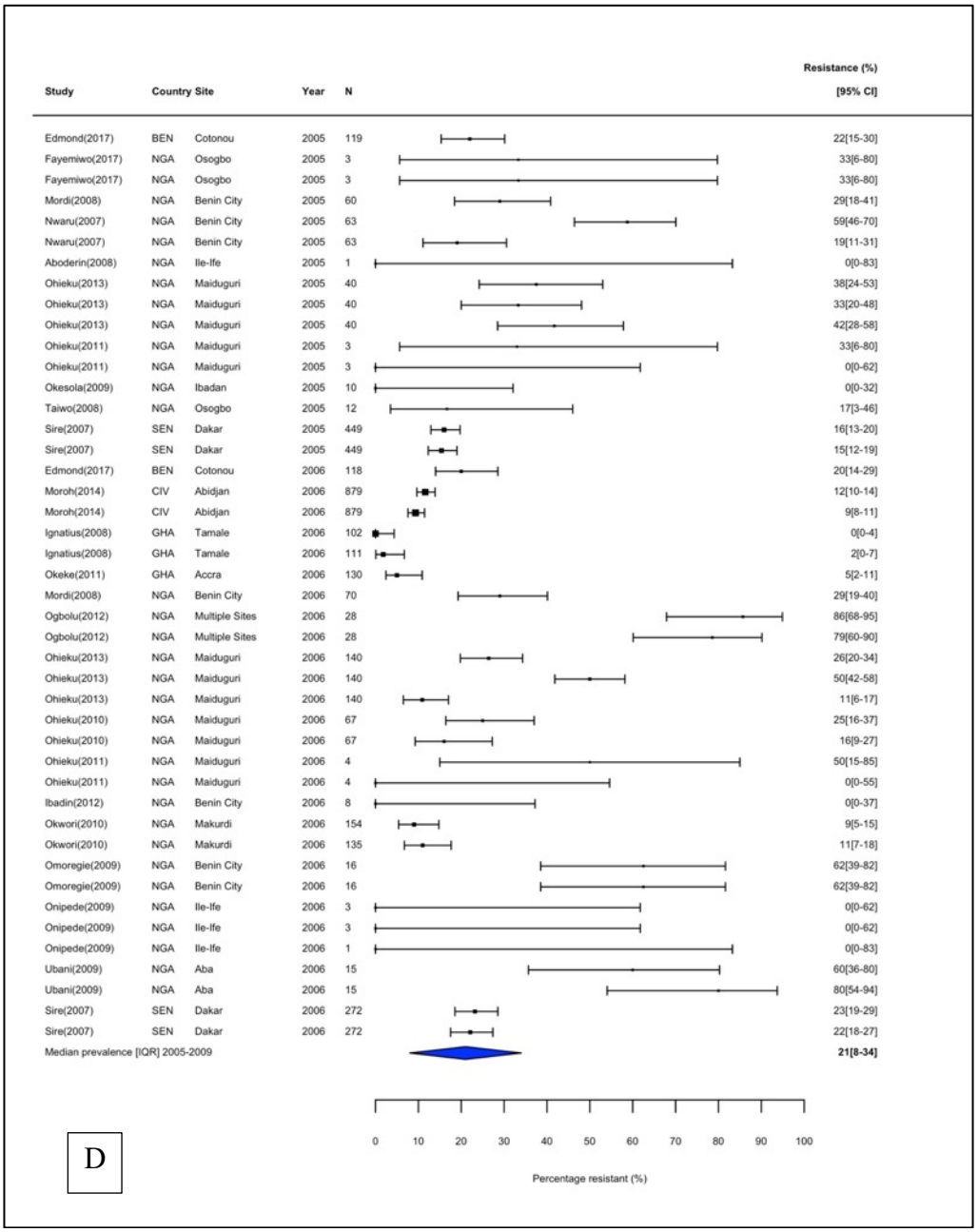
Figure C.10: Forest plot of fluoroquinolone resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2009, C: 2010-2018.


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Obi(1995) NGA Benin City 1992 14 0[0-25]
Obi(1995) NGA Benin City 1992 14 0[0-25]
Median prevalence [IQR] 1990-1994 0[0-0]
Jiburum(2000) NGA Enugu 1995 4 25[3-71]
Oni(2001) NGA Ibadan 1996 6 17[1-58]
Gangoue-Pieboji(2006)CMR Yaounde 1997 163 9[6-15]
Oni(2001) NGA Ibadan 1997 22 0[0-18]
Oni(2001) NGA Ibadan 1997 22 5[0-24]
Okwori(2011) NGA Otukpo 1999 2073 25[23-27]
Dromigny(2002) SEN Dakar 1999 234 6[3-9]
Median prevalence [IQR] 1995-1999 9[5-21]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A

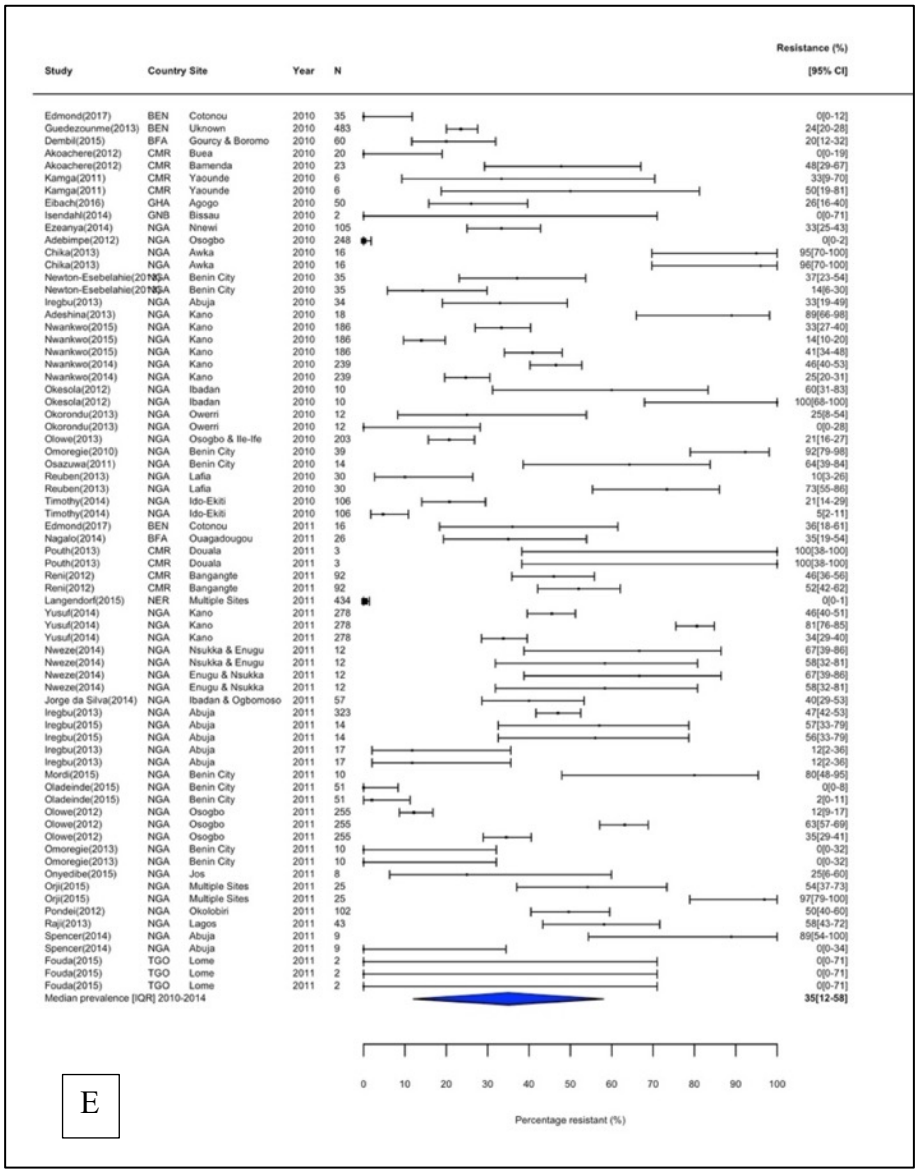

Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Ehinmidu(2003) NGA Zaria 2000 61 6[2-16]
Odusanya(2002) NGA Lagos 2000 99 23[16-33]
Rabasa(2002) NGA Maiduguri 2000 10 20[5-52]
Dromigny(2002) SEN Dakar 2000 255 8[5-12]
Ka(2003) SEN Dakar 2000 323 10[7-14]
Seydi(2005) SEN Dakar 2000 57 4[0-13]
Jombo(2006) NGA Jos 2001 379 0[0-1]
Jombo(2006) NGA Jos 2001 332 23[19-28]
Jombo(2006) NGA Jos 2001 379 0[0-1]
Jombo(2006) NGA Jos 2001 332 15[12-19]
Ikem(2004) NGA Ife 2001 4 0[0-55]
Dromigny(2003) SEN Dakar 2001 233 14[10-19]
Dromigny(2005) SEN Dakar 2001 113 18[12-26]
Dromigny(2005) SEN Dakar 2001 113 18[12-26]
Diani(2006) NGA Uknown 2002 22 36[20-57]
Diani(2006) NGA Uknown 2002 22 27[13-48]
Adegunloye(2005) NGA Multiple Sites 2002 244 57[51-63]
Dromigny(2005) SEN Dakar 2002 171 19[14-26]
Dromigny(2005) SEN Dakar 2002 171 19[14-26]
Clarence(2006) NGA Benin City 2003 92 30[22-40]
Clarence(2006) NGA Benin City 2003 92 67[57-76]
Mordi(2008) NGA Benin City 2003 3 29[6-80]
Odedina(2008) NGA Bida 2003 122 17[11-25]
Odedina(2008) NGA Bida 2003 122 24[17-32]
Ojukwu(2006) NGA Abakaliki 2003 6 0[0-44]
Okesola(2008) NGA Ibadan 2003 10 80[48-95]
Okesola(2008) NGA Ibadan 2003 93 56[46-66]
Okesola(2010) NGA Ibadan 2003 11 45[21-72]
Okoror(2009) NGA Sapele Delta State 2003 871 14[12-16]
Okoror(2009) NGA Sapele Delta State 2003 871 7[6-9]
Okoror(2009) NGA Sapele Delta State 2003 871 14[12-17]
Okoror(2009) NGA Sapele Delta State 2003 871 29[26-32]
Dromigny(2005) SEN Dakar 2003 114 18[12-27]
Dromigny(2005) SEN Dakar 2003 114 18[12-27]
Kouassi-Mibengue(2006) CIV Abidjan 2004 32 50[34-66]
Kouassi-Mibengue(2006) CIV Abidjan 2004 32 50[34-66]
Hill(2007) GMB Banjul 2004 9 0[0-34]
Erah(2006) NGA Benin City 2004 138 36[28-44]
Erah(2006) NGA Benin City 2004 138 39[31-47]
Mordi(2008) NGA Benin City 2004 50 29[19-44]
Olatunji(2007) NGA Ilorin 2004 7 0[0-40]
Olatunji(2007) NGA Ilorin 2004 7 0[0-40]
Olorunmola(2013) NGA Ile-Ife 2004 137 66[57-73]
Olorunmola(2013) NGA Ile-Ife 2004 137 51[43-59]
Olorunmola(2013) NGA Ile-Ife 2004 137 87[80-92]
Sire(2007) SEN Dakar 2004 289 11[8-15]
Sire(2007) SEN Dakar 2004 289 10[7-14]
Median prevalence [IQR] 2000-2004 19[10-36]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2007 67 28[19-40]
Karou(2009) BFA Ouagadougou 2007 304 11[8-15]
Karou(2009) BFA Ouagadougou 2007 304 9[6-13]
Ouidraogo(2011) BFA Bobo-Dioulasso 2007 31 42[26-59]
Okeke(2011) GHA Accra 2007 73 7[3-15]
Togo(2010) MLI Bamako 2007 11 55[28-79]
Egbe(2010) NGA Okada 2007 11 73[43-91]
Jombo(2010) NGA Calabar City 2007 12 0[0-28]
Jombo(2010) NGA Calabar City 2007 19 0[0-20]
Jombo(2010) NGA Calabar City 2007 19 0[0-20]
Jombo(2010) NGA Calabar City 2007 12 0[0-28]
Mava(2012) NGA Maiduguri 2007 18 6[0-28]
Mava(2012) NGA Maiduguri 2007 19 21[8-44]
Mava(2012) NGA Maiduguri 2007 19 21[8-44]
Mava(2012) NGA Maiduguri 2007 18 17[5-40]
Mordi(2008) NGA Benin City 2007 80 29[20-40]
Nwadioha(2011) NGA Kano 2007 310 10[7-14]
Nwadioha(2013) NGA Kano 2007 16 12[2-37]
Ogunlesi(2011) NGA Sagamu 2007 19 26[11-49]
Ogunlesi(2011) NGA Sagamu 2007 19 68[46-85]
Ohieku(2013) NGA Maiduguri 2007 118 37[29-46]
Ohieku(2013) NGA Maiduguri 2007 118 28[21-37]
Ohieku(2013) NGA Maiduguri 2007 118 44[36-54]
Ohieku(2011) NGA Maiduguri 2007 2 50[9-91]
Ohieku(2011) NGA Maiduguri 2007 2 0[0-71]
Okesola(2009) NGA Ibadan 2007 32 34[20-52]
Oladeinde(2013) NGA Okada 2007 15 7[0-32]
Oladeinde(2013) NGA Okada 2007 39 23[12-39]
Oladeinde(2013) NGA Okada 2007 15 0[0-24]
Oladeinde(2013) NGA Okada 2007 39 18[9-33]
Oreh(2012) NGA Uknown 2007 1909 46[44-49]
Oreh(2012) NGA Uknown 2007 1909 50[47-52]
Oreh(2012) NGA Uknown 2007 1909 43[41-46]
Oreh(2013) NGA Uknown 2007 211 45[39-52]
Oreh(2013) NGA Uknown 2007 211 98[94-99]
Oreh(2013) NGA Uknown 2007 211 49[42-56]
Siminialayi(2010) NGA Port Harcourt 2007 42 24[13-39]
Siminialayi(2010) NGA Port Harcourt 2007 42 24[13-39]
Edmond(2017) BEN Cotonou 2008 28 16[5-32]
Huenger(2010) GHA Agogo 2008 15 27[10-52]
Okeke(2011) GHA Accra 2008 88 12[7-21]
Okomo(2011) GMB Fajara 2008 13 0[0-27]
Idowu(2011) NGA Ibadan 2008 28 50[33-67]
Idowu(2011) NGA Ibadan 2008 28 29[15-47]
Nwadioha(2010) NGA Kano 2008 364 29[24-33]
Idowu(2011) NGA Ibadan 2008 2 0[0-71]
Inyang-Etoh(2009) NGA Calabar City 2008 100 0[0-4]
Inyang-Etoh(2009) NGA Calabar City 2008 100 8[4-15]
Kehinde(2012) NGA Ibadan 2008 37 3[0-15]
Ohieku(2013) NGA Maiduguri 2008 172 43[36-50]
Ohieku(2013) NGA Maiduguri 2008 172 62[55-69]
Ohieku(2013) NGA Maiduguri 2008 172 29[23-36]
Ohieku(2011) NGA Maiduguri 2008 3 0[0-62]
Ohieku(2011) NGA Maiduguri 2008 3 0[0-62]
Idowu(2011) NGA Ibadan 2008 28 29[15-47]
Idowu(2011) NGA Ibadan 2008 28 50[33-67]
Edmond(2017) BEN Cotonou 2009 34 20[10-37]
Karou(2012) BFA Ouagadougou 2009 256 30[25-36]
Ali(2014) GHA Kumasi 2009 53 87[75-94]
Antonio(2017) GMB Uknown 2009 88 9[4-17]
Romanus(2011) NGA Abakaliki 2009 140 35[27-42]
Romanus(2011) NGA Abakaliki 2009 140 31[24-39]
Olajubu(2012) NGA Sagamu 2009 10 92[57-100]
Taiwo(2011) NGA Osogbo 2009 7 14[1-53]
Egbe(2011) NGA Benin City 2009 165 2[1-6]
Egbe(2011) NGA Benin City 2009 165 1[0-5]
Emerenini(2012) NGA Benin City 2009 4 100[45-100]
Igwegbe(2012) NGA Nnewi 2009 30 0[0-13]
Mordi(2012) NGA Benin City 2009 33 9[2-24]
David(2013) NGA Maiduguri 2009 10 10[0-43]
David(2013) NGA Maiduguri 2009 10 0[0-32]
Ohieku(2013) NGA Maiduguri 2009 181 57[50-64]
Ohieku(2013) NGA Maiduguri 2009 181 89[83-93]
Ohieku(2013) NGA Maiduguri 2009 181 45[38-52]
Ohieku(2011) NGA Maiduguri 2009 7 17[1-53]
Ohieku(2011) NGA Maiduguri 2009 7 20[1-53]
Ayinla(2013) NGA Lagos 2009 458 13[10-17]
Ayinla(2013) NGA Lagos 2009 206 0[0-3]
Ayinla(2013) NGA Lagos 2009 187 3[1-6]
Ayinla(2013) NGA Lagos 2009 87 13[7-21]
Median prevalence [IQR] 2005-2009 21[7-43]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

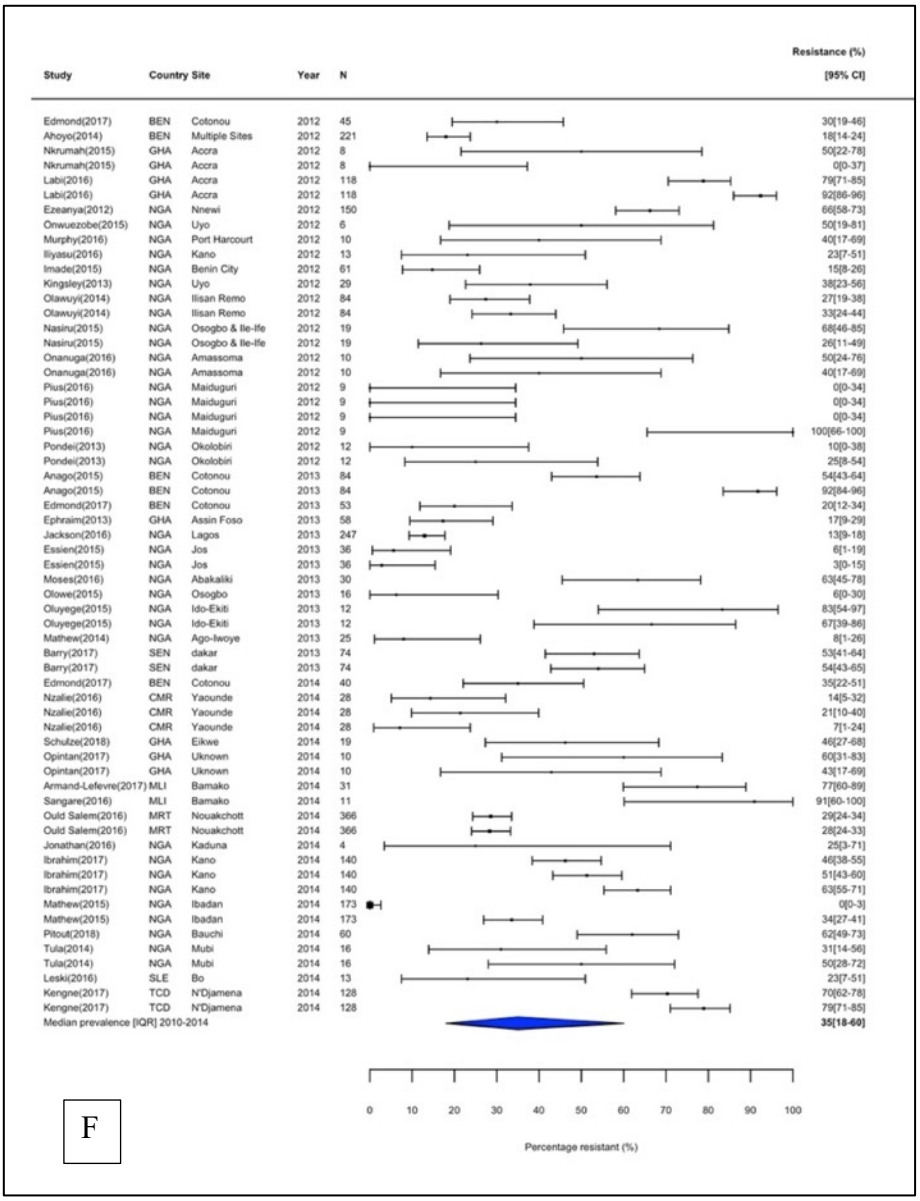
C


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2005 119 22[15-30]
Fayemiwo(2017) NGA Osogbo 2005 3 33[6-80]
Fayemiwo(2017) NGA Osogbo 2005 3 33[6-80]
Mordi(2008) NGA Benin City 2005 60 29[18-41]
Nwaru(2007) NGA Benin City 2005 63 59[46-70]
Nwaru(2007) NGA Benin City 2005 63 19[11-31]
Aboderin(2008) NGA Ile-Ife 2005 1 0[0-83]
Ohieku(2013) NGA Maiduguri 2005 40 38[24-53]
Ohieku(2013) NGA Maiduguri 2005 40 33[20-48]
Ohieku(2013) NGA Maiduguri 2005 40 42[28-58]
Ohieku(2011) NGA Maiduguri 2005 3 33[6-80]
Ohieku(2011) NGA Maiduguri 2005 3 0[0-62]
Okesola(2009) NGA Ibadan 2005 10 0[0-32]
Taiwo(2008) NGA Osogbo 2005 12 17[3-46]
Sire(2007) SEN Dakar 2005 449 16[13-20]
Sire(2007) SEN Dakar 2005 449 15[12-19]
Edmond(2017) BEN Cotonou 2006 118 20[14-29]
Moroh(2014) CIV Abidjan 2006 879 12[10-14]
Moroh(2014) CIV Abidjan 2006 879 9[8-11]
Ignatius(2008) GHA Tamale 2006 102 0[0-4]
Ignatius(2008) GHA Tamale 2006 111 2[0-7]
Okeke(2011) GHA Accra 2006 130 5[2-11]
Mordi(2008) NGA Benin City 2006 70 29[19-40]
Ogbolu(2012) NGA Multiple Sites 2006 28 86[68-95]
Ogbolu(2012) NGA Multiple Sites 2006 28 79[60-90]
Ohieku(2013) NGA Maiduguri 2006 140 26[20-34]
Ohieku(2013) NGA Maiduguri 2006 140 50[42-58]
Ohieku(2013) NGA Maiduguri 2006 140 11[6-17]
Ohieku(2010) NGA Maiduguri 2006 67 25[16-37]
Ohieku(2010) NGA Maiduguri 2006 67 16[9-27]
Ohieku(2011) NGA Maiduguri 2006 4 50[15-85]
Ohieku(2011) NGA Maiduguri 2006 4 0[0-55]
Ibadin(2012) NGA Benin City 2006 8 0[0-37]
Okwori(2010) NGA Makurdi 2006 154 9[5-15]
Okwori(2010) NGA Makurdi 2006 135 11[7-18]
Omoregie(2009) NGA Benin City 2006 16 62[39-82]
Omoregie(2009) NGA Benin City 2006 16 62[39-82]
Onipede(2009) NGA Ile-Ife 2006 3 0[0-62]
Onipede(2009) NGA Ile-Ife 2006 3 0[0-62]
Onipede(2009) NGA Ile-Ife 2006 1 0[0-83]
Ubani(2009) NGA Aba 2006 15 60[36-80]
Ubani(2009) NGA Aba 2006 15 80[54-94]
Sire(2007) SEN Dakar 2006 272 23[19-29]
Sire(2007) SEN Dakar 2006 272 22[18-27]
Median prevalence [IQR] 2005-2009 21[8-34]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

D


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2010 35 0[0-12]
Guedezounme(2013) BEN Uknown 2010 483 24[20-28]
Dembi(2015) BFA Gourcy & Boromo 2010 60 20[12-32]
Akoachere(2012) CMR Buea 2010 20 0[0-19]
Akoachere(2012) CMR Bamenda 2010 23 48[29-67]
Kamga(2011) CMR Yaounde 2010 6 33[9-70]
Kamga(2011) CMR Yaounde 2010 6 50[19-81]
Eibach(2016) GHA Agogo 2010 50 26[16-40]
Isendahl(2014) GNB Bissau 2010 2 0[0-71]
Ezeanya(2014) NGA Nnewi 2010 105 33[25-43]
Adebimpe(2012) NGA Osogbo 2010 248 0[0-2]
Chika(2013) NGA Awka 2010 16 95[70-100]
Chika(2013) NGA Awka 2010 16 96[70-100]
Newton-Esebelahie(2013) NGA Benin City 2010 35 37[23-54]
Newton-Esebelahie(2013) NGA Benin City 2010 35 14[6-30]
Iregbu(2013) NGA Abuja 2010 34 33[19-49]
Adeshina(2013) NGA Kano 2010 18 89[66-98]
Nwankwo(2015) NGA Kano 2010 186 33[27-40]
Nwankwo(2015) NGA Kano 2010 186 14[10-20]
Nwankwo(2015) NGA Kano 2010 186 41[34-48]
Nwankwo(2014) NGA Kano 2010 239 46[40-53]
Nwankwo(2014) NGA Kano 2010 239 25[20-31]
Okesola(2012) NGA Ibadan 2010 10 60[31-83]
Okesola(2012) NGA Ibadan 2010 10 100[68-100]
Okorondu(2013) NGA Owerri 2010 12 25[8-54]
Okorondu(2013) NGA Owerri 2010 12 0[0-28]
Olowe(2013) NGA Osogbo & Ile-Ife 2010 203 21[16-27]
Omoregie(2010) NGA Benin City 2010 39 92[79-98]
Osazuwa(2011) NGA Benin City 2010 14 64[39-84]
Reuben(2013) NGA Lafia 2010 30 10[3-26]
Reuben(2013) NGA Lafia 2010 30 73[55-86]
Timothy(2014) NGA Ido-Ekiti 2010 106 21[14-29]
Timothy(2014) NGA Ido-Ekiti 2010 106 5[2-11]
Edmond(2017) BEN Cotonou 2011 16 36[18-61]
Nagalo(2014) BFA Ouagadougou 2011 26 35[19-54]
Pouth(2013) CMR Douala 2011 3 100[38-100]
Pouth(2013) CMR Douala 2011 3 100[38-100]
Reni(2012) CMR Bangangte 2011 92 46[36-56]
Reni(2012) CMR Bangangte 2011 92 52[42-62]
Langendorf(2015) NER Multiple Sites 2011 434 0[0-1]
Yusuf(2014) NGA Kano 2011 278 46[40-51]
Yusuf(2014) NGA Kano 2011 278 81[76-85]
Yusuf(2014) NGA Kano 2011 278 34[29-40]
Nweze(2014) NGA Nsukka & Enugu 2011 12 67[39-86]
Nweze(2014) NGA Nsukka & Enugu 2011 12 58[32-81]
Nweze(2014) NGA Enugu & Nsukka 2011 12 67[39-86]
Nweze(2014) NGA Enugu & Nsukka 2011 12 58[32-81]
Jorge da Silva(2014) NGA Ibadan & Ogbomoso 2011 57 40[29-53]
Iregbu(2013) NGA Abuja 2011 323 47[42-53]
Iregbu(2015) NGA Abuja 2011 14 57[33-79]
Iregbu(2015) NGA Abuja 2011 14 56[33-79]
Iregbu(2013) NGA Abuja 2011 17 12[2-36]
Iregbu(2013) NGA Abuja 2011 17 12[2-36]
Mordi(2015) NGA Benin City 2011 10 80[48-95]
Oladeinde(2015) NGA Benin City 2011 51 0[0-8]
Oladeinde(2015) NGA Benin City 2011 51 2[0-11]
Olowe(2012) NGA Osogbo 2011 255 12[9-17]
Olowe(2012) NGA Osogbo 2011 255 63[57-69]
Olowe(2012) NGA Osogbo 2011 255 35[29-41]
Omoregie(2013) NGA Benin City 2011 10 0[0-32]
Omoregie(2013) NGA Benin City 2011 10 0[0-32]
Onyedibe(2015) NGA Jos 2011 8 25[6-60]
Orji(2015) NGA Multiple Sites 2011 25 54[37-73]
Orji(2015) NGA Multiple Sites 2011 25 97[79-100]
Pondei(2012) NGA Okolobiri 2011 102 50[40-60]
Raji(2013) NGA Lagos 2011 43 58[43-72]
Spencer(2014) NGA Abuja 2011 9 89[54-100]
Spencer(2014) NGA Abuja 2011 9 0[0-34]
Fouda(2015) TGO Lome 2011 2 0[0-71]
Fouda(2015) TGO Lome 2011 2 0[0-71]
Fouda(2015) TGO Lome 2011 2 0[0-71]
Median prevalence [IQR] 2010-2014 35[12-58]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

E


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2012 45 30[19-46]
Ahoyo(2014) BEN Multiple Sites 2012 221 18[14-24]
Nkrumah(2015) GHA Accra 2012 8 50[22-78]
Nkrumah(2015) GHA Accra 2012 8 0[0-37]
Labi(2016) GHA Accra 2012 118 79[71-85]
Labi(2016) GHA Accra 2012 118 92[86-96]
Ezeanya(2012) NGA Nnewi 2012 150 66[58-73]
Onwuezobe(2015) NGA Uyo 2012 6 50[19-81]
Murphy(2016) NGA Port Harcourt 2012 10 40[17-69]
Iliyasu(2016) NGA Kano 2012 13 23[7-51]
Imade(2015) NGA Benin City 2012 61 15[8-26]
Kingsley(2013) NGA Uyo 2012 29 38[23-56]
Olawuyi(2014) NGA Ilisan Remo 2012 84 27[19-38]
Olawuyi(2014) NGA Ilisan Remo 2012 84 33[24-44]
Nasiru(2015) NGA Osogbo & Ile-Ife 2012 19 68[46-85]
Nasiru(2015) NGA Osogbo & Ile-Ife 2012 19 26[11-49]
Onanuga(2016) NGA Amassoma 2012 10 50[24-76]
Onanuga(2016) NGA Amassoma 2012 10 40[17-69]
Pius(2016) NGA Maiduguri 2012 9 0[0-34]
Pius(2016) NGA Maiduguri 2012 9 0[0-34]
Pius(2016) NGA Maiduguri 2012 9 0[0-34]
Pius(2016) NGA Maiduguri 2012 9 100[66-100]
Pondei(2013) NGA Okolobiri 2012 12 10[0-38]
Pondei(2013) NGA Okolobiri 2012 12 25[8-54]
Anago(2015) BEN Cotonou 2013 84 54[43-64]
Anago(2015) BEN Cotonou 2013 84 92[84-96]
Edmond(2017) BEN Cotonou 2013 53 20[12-34]
Ephraim(2013) GHA Assin Foso 2013 58 17[9-29]
Jackson(2016) NGA Lagos 2013 247 13[9-18]
Essien(2015) NGA Jos 2013 36 6[1-19]
Essien(2015) NGA Jos 2013 36 3[0-15]
Moses(2016) NGA Abakaliki 2013 30 63[45-78]
Olowe(2015) NGA Osogbo 2013 16 6[0-30]
Oluyege(2015) NGA Ido-Ekiti 2013 12 83[54-97]
Oluyege(2015) NGA Ido-Ekiti 2013 12 67[39-86]
Mathew(2014) NGA Ago-Iwoye 2013 25 8[1-26]
Barry(2017) SEN dakar 2013 74 53[41-64]
Barry(2017) SEN dakar 2013 74 54[43-65]
Edmond(2017) BEN Cotonou 2014 40 35[22-51]
Nzalie(2016) CMR Yaounde 2014 28 14[5-32]
Nzalie(2016) CMR Yaounde 2014 28 21[10-40]
Nzalie(2016) CMR Yaounde 2014 28 7[1-24]
Schulze(2018) GHA Eikwe 2014 19 46[27-68]
Opintan(2017) GHA Uknown 2014 10 60[31-83]
Opintan(2017) GHA Uknown 2014 10 43[17-69]
Armand-Lefevre(2017) MLI Bamako 2014 31 77[60-89]
Sangare(2016) MLI Bamako 2014 11 91[60-100]
Ould Salem(2016) MRT Nouakchott 2014 366 29[24-34]
Ould Salem(2016) MRT Nouakchott 2014 366 28[24-33]
Jonathan(2016) NGA Kaduna 2014 4 25[3-71]
Ibrahim(2017) NGA Kano 2014 140 46[38-55]
Ibrahim(2017) NGA Kano 2014 140 51[43-60]
Ibrahim(2017) NGA Kano 2014 140 63[55-71]
Mathew(2015) NGA Ibadan 2014 173 0[0-3]
Mathew(2015) NGA Ibadan 2014 173 34[27-41]
Pitout(2018) NGA Bauchi 2014 60 62[49-73]
Tula(2014) NGA Mubi 2014 16 31[14-56]
Tula(2014) NGA Mubi 2014 16 50[28-72]
Leski(2016) SLE Bo 2014 13 23[7-51]
Kengne(2017) TCD N'Djamena 2014 128 70[62-78]
Kengne(2017) TCD N'Djamena 2014 128 79[71-85]
Median prevalence [IQR] 2010-2014 35[18-60]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

F

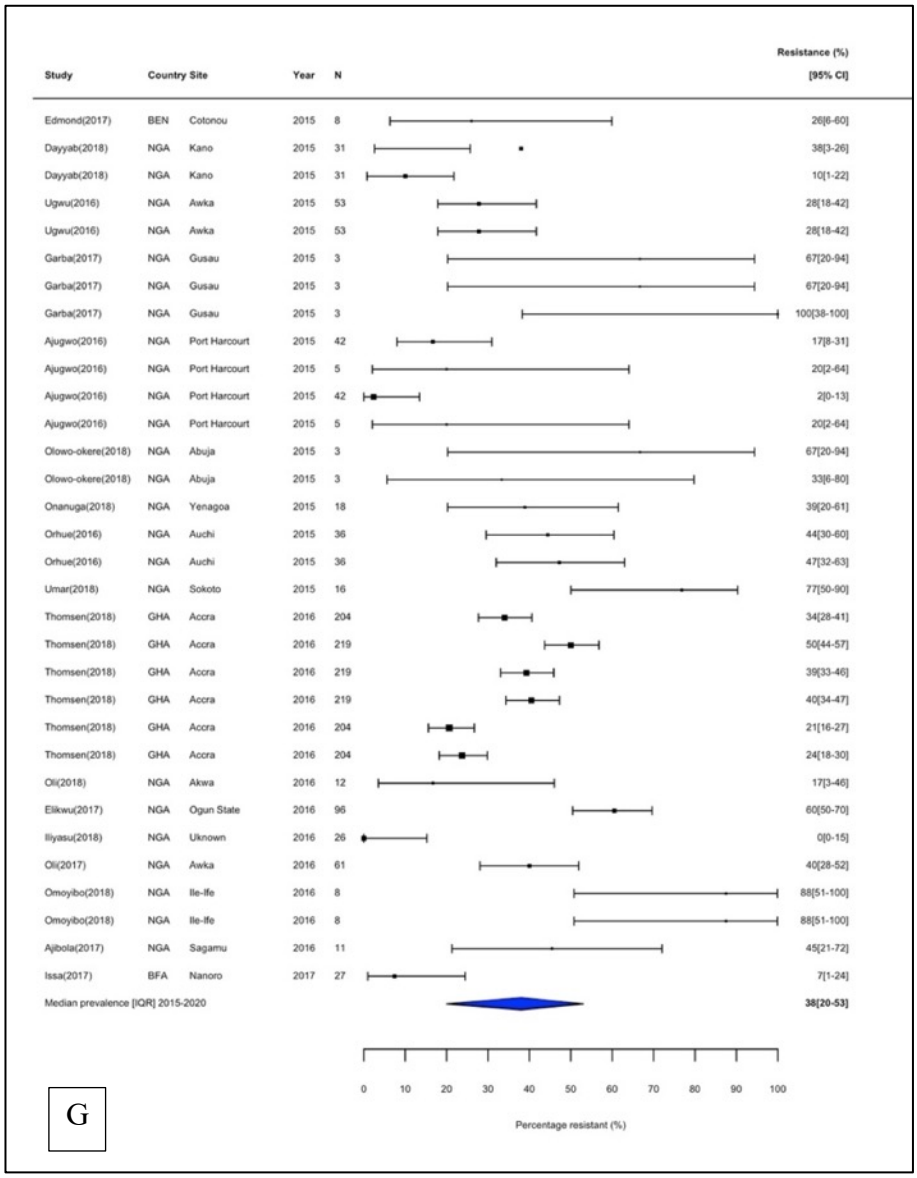


Figure C.11: Forest plot of fluoroquinolone resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2004, C:2005-2007, D:2007-2009, E: 2010-2011, F: 2012-2014, G: 2015-2018

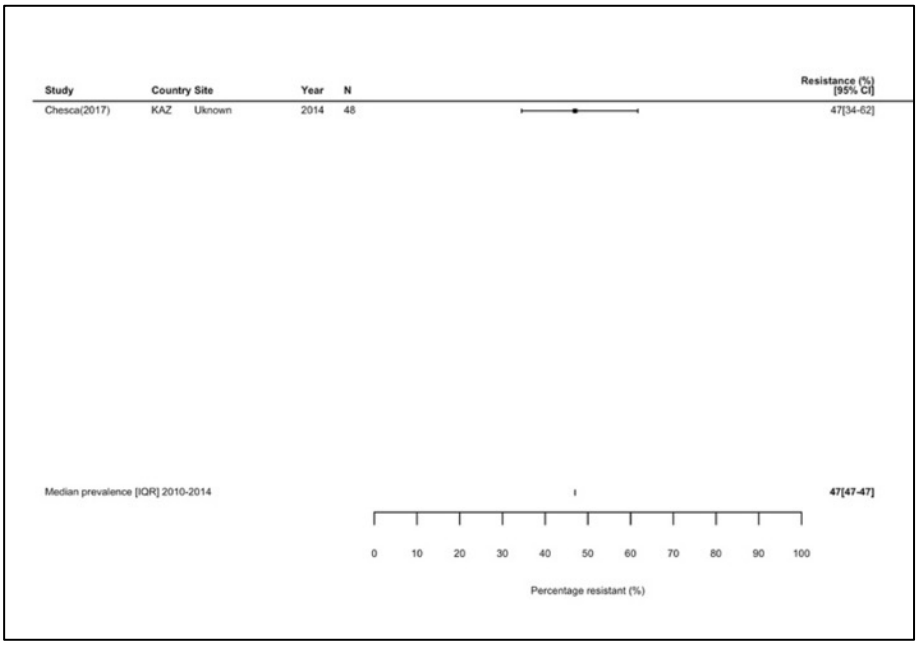


Figure C.12: Forest plot of penicillin resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

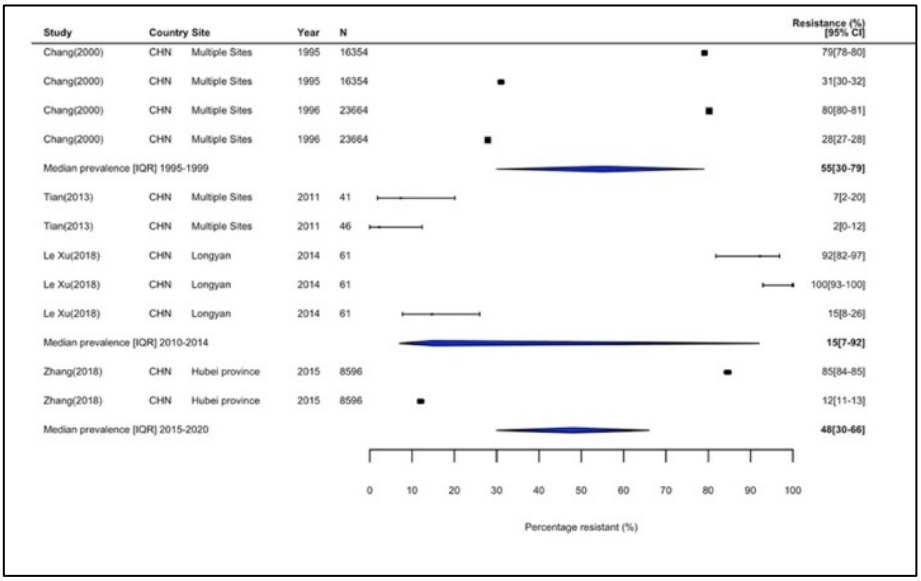


Figure C.13: Forest plot of penicillin resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

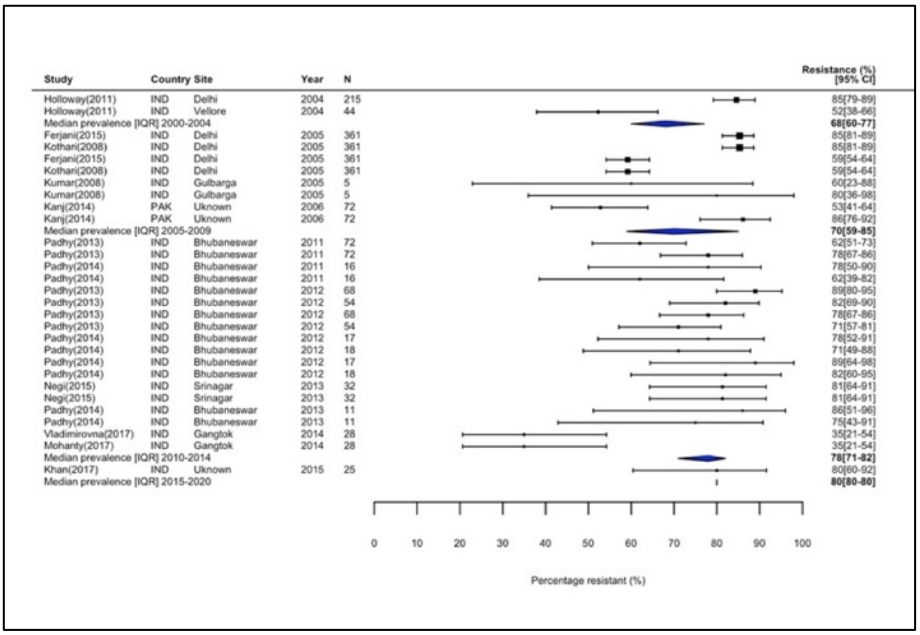


Figure C.14: Forest plot of penicillin resistance in South Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

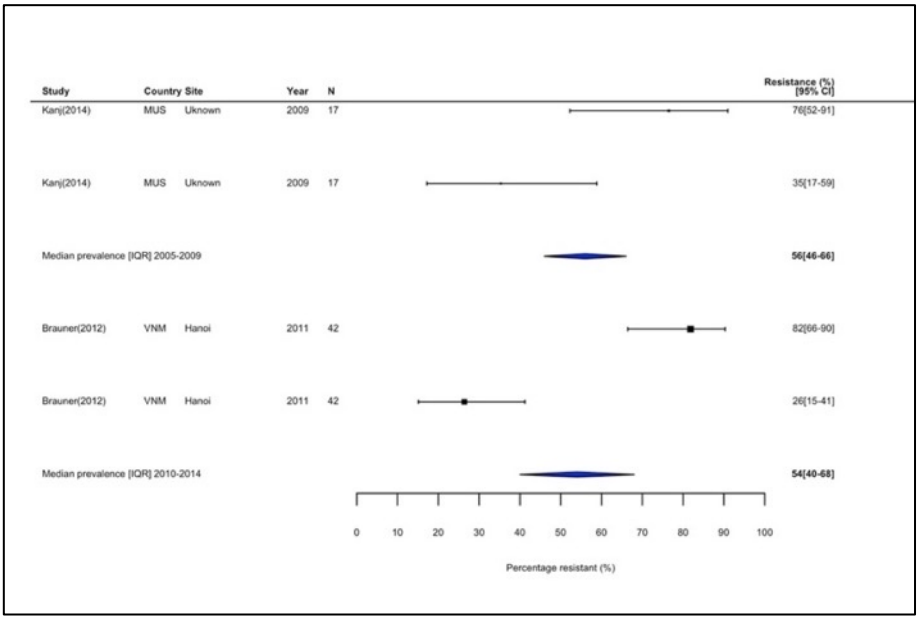


Figure C.15: Forest plot of penicillin resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

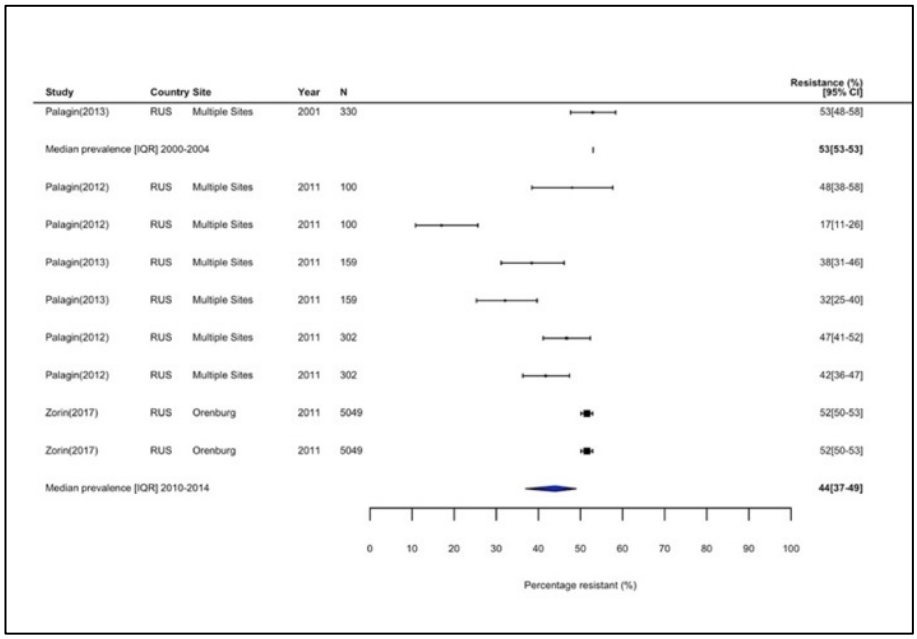


Figure C.16: Forest plot of penicillin resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

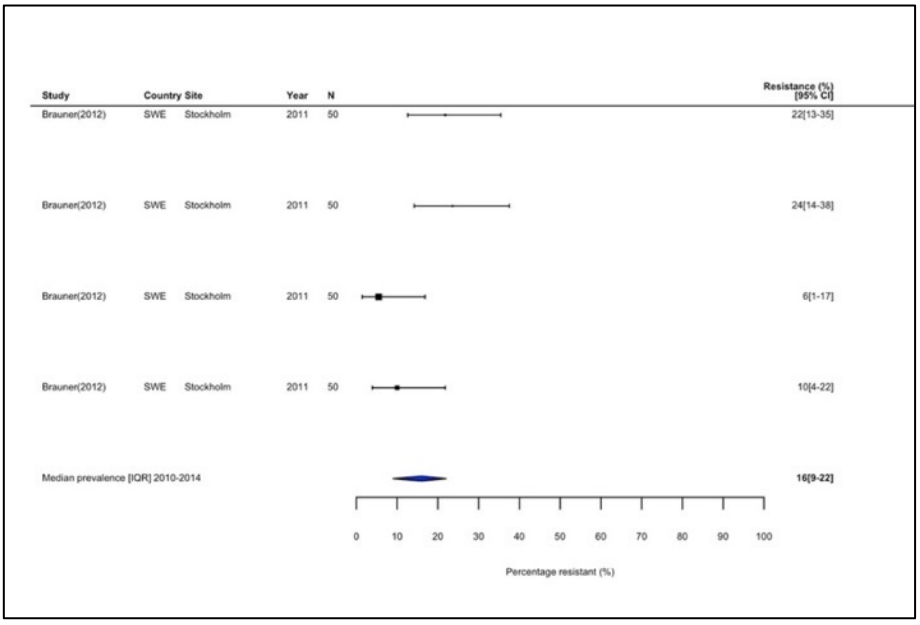


Figure C.17: Forest plot of penicillin resistance in Western Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

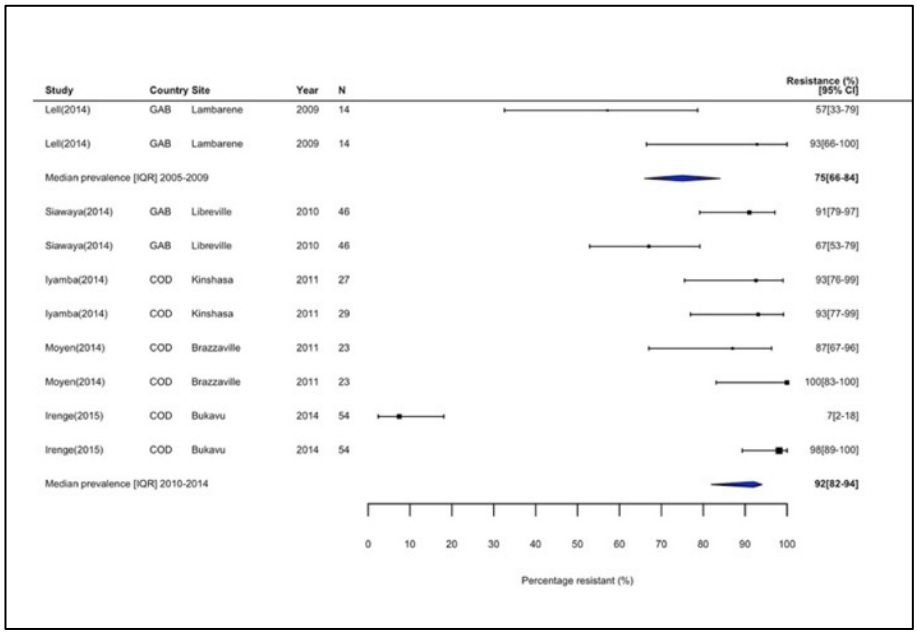
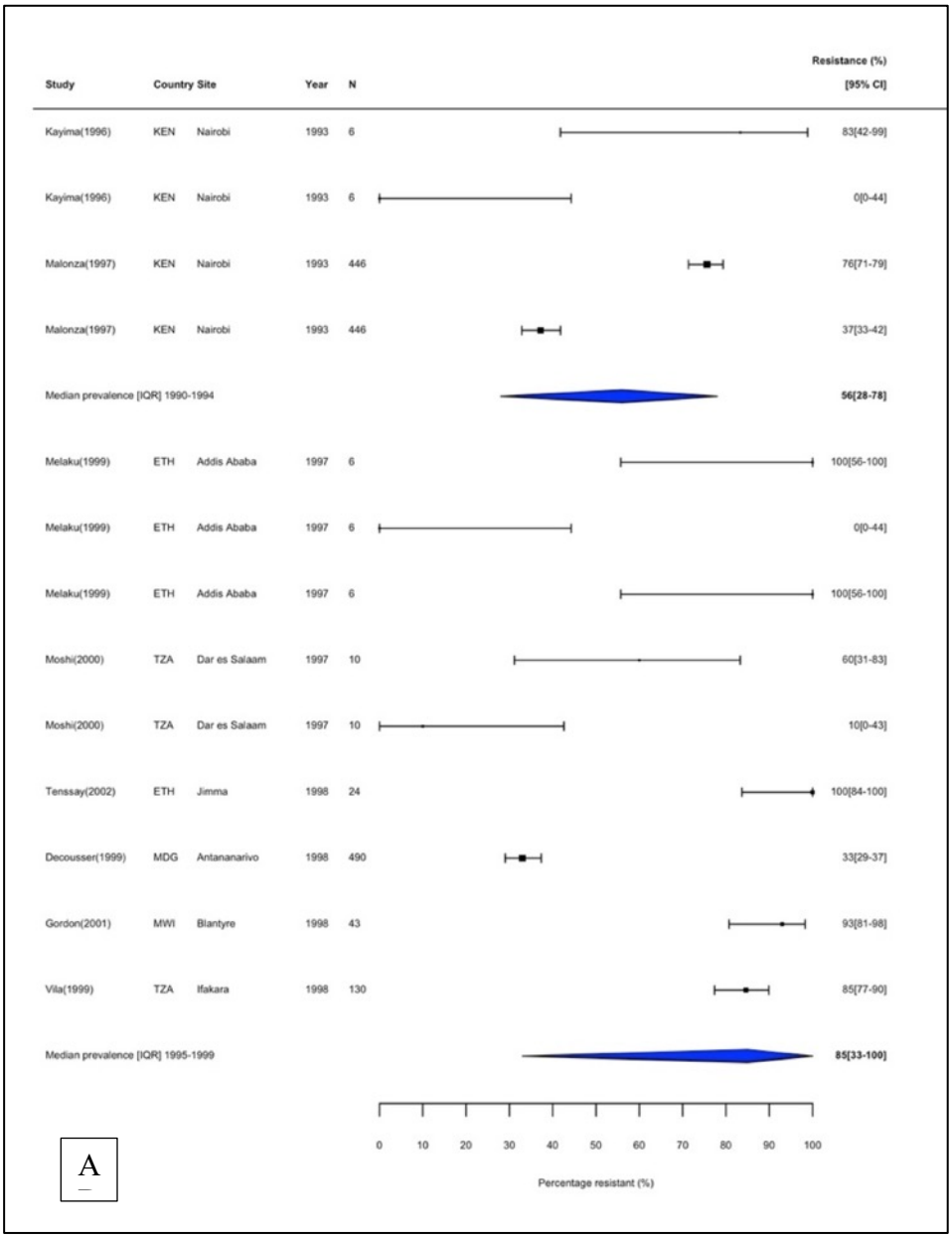
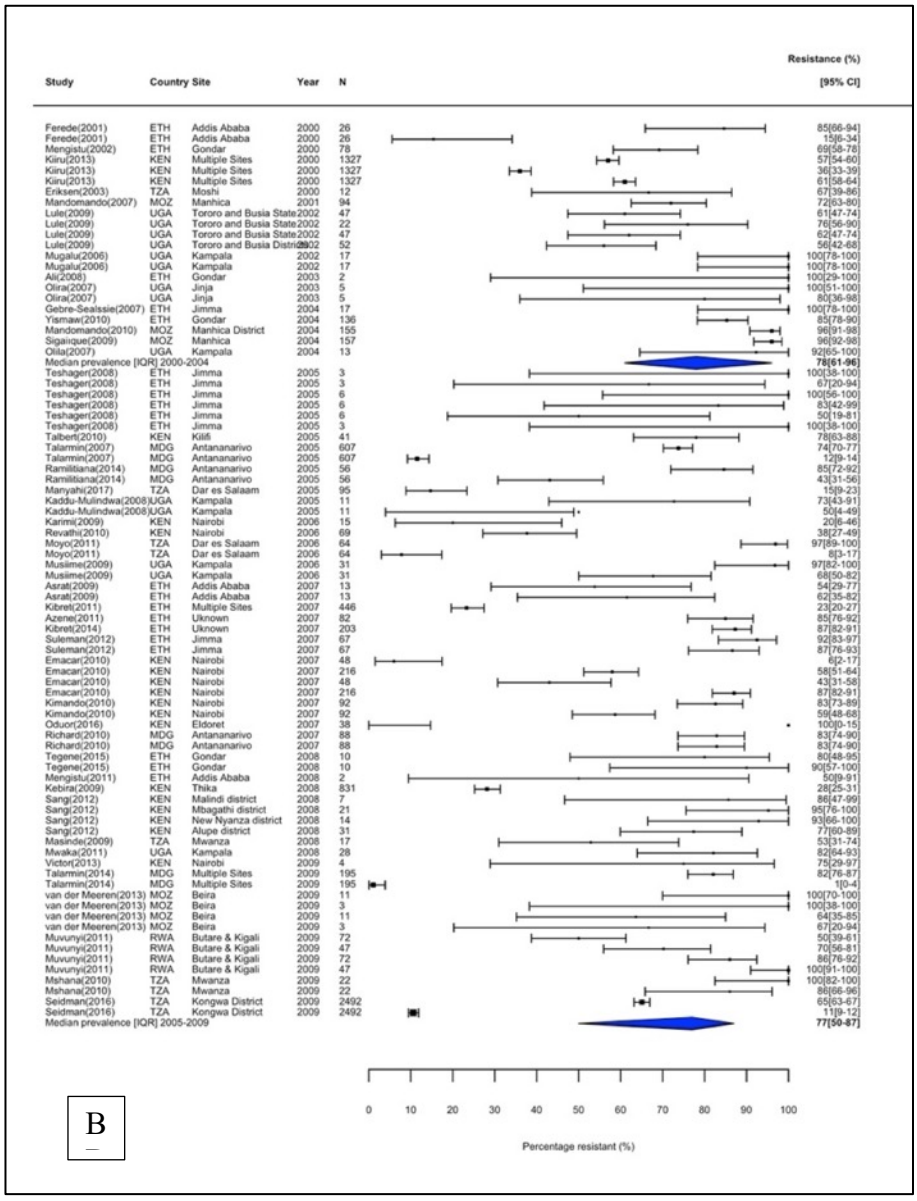
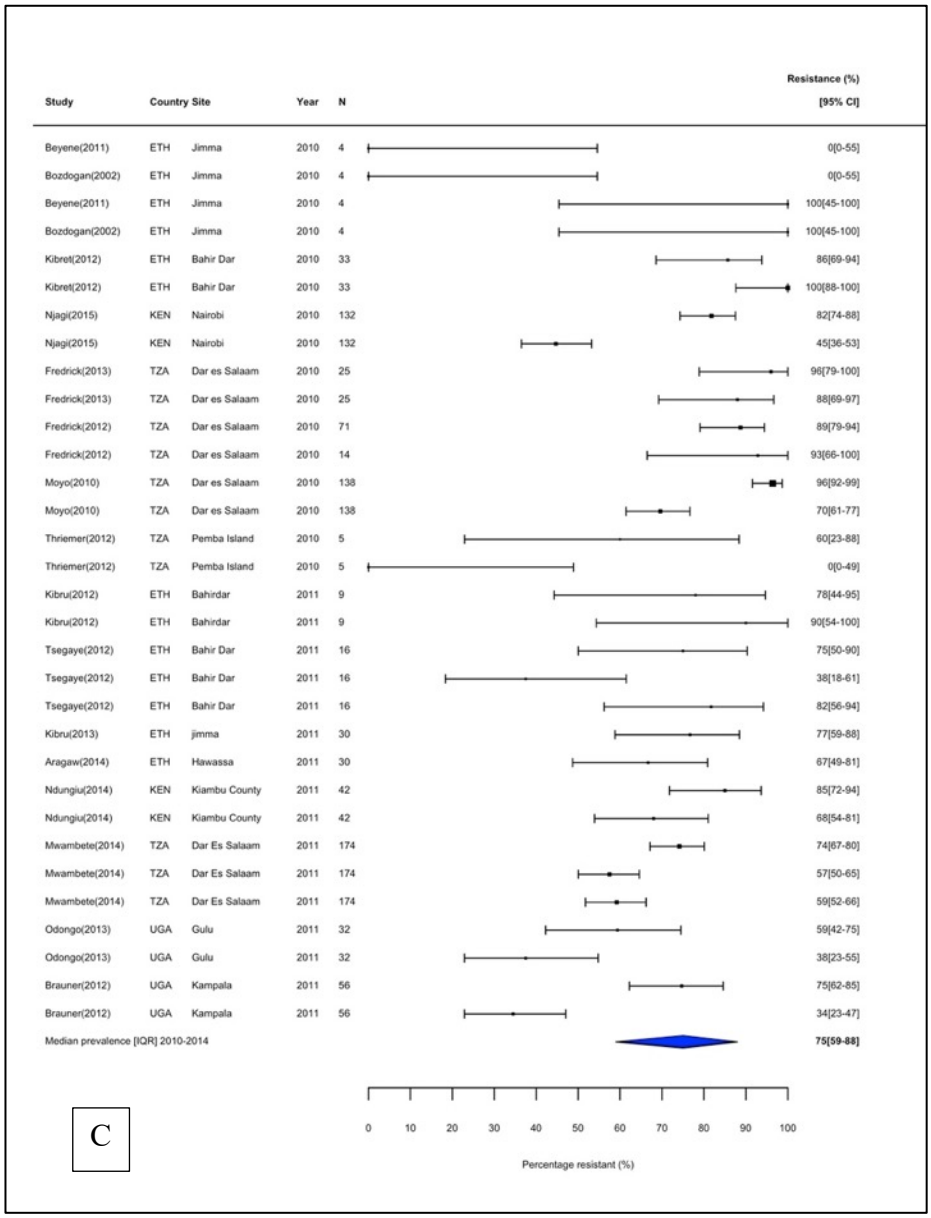
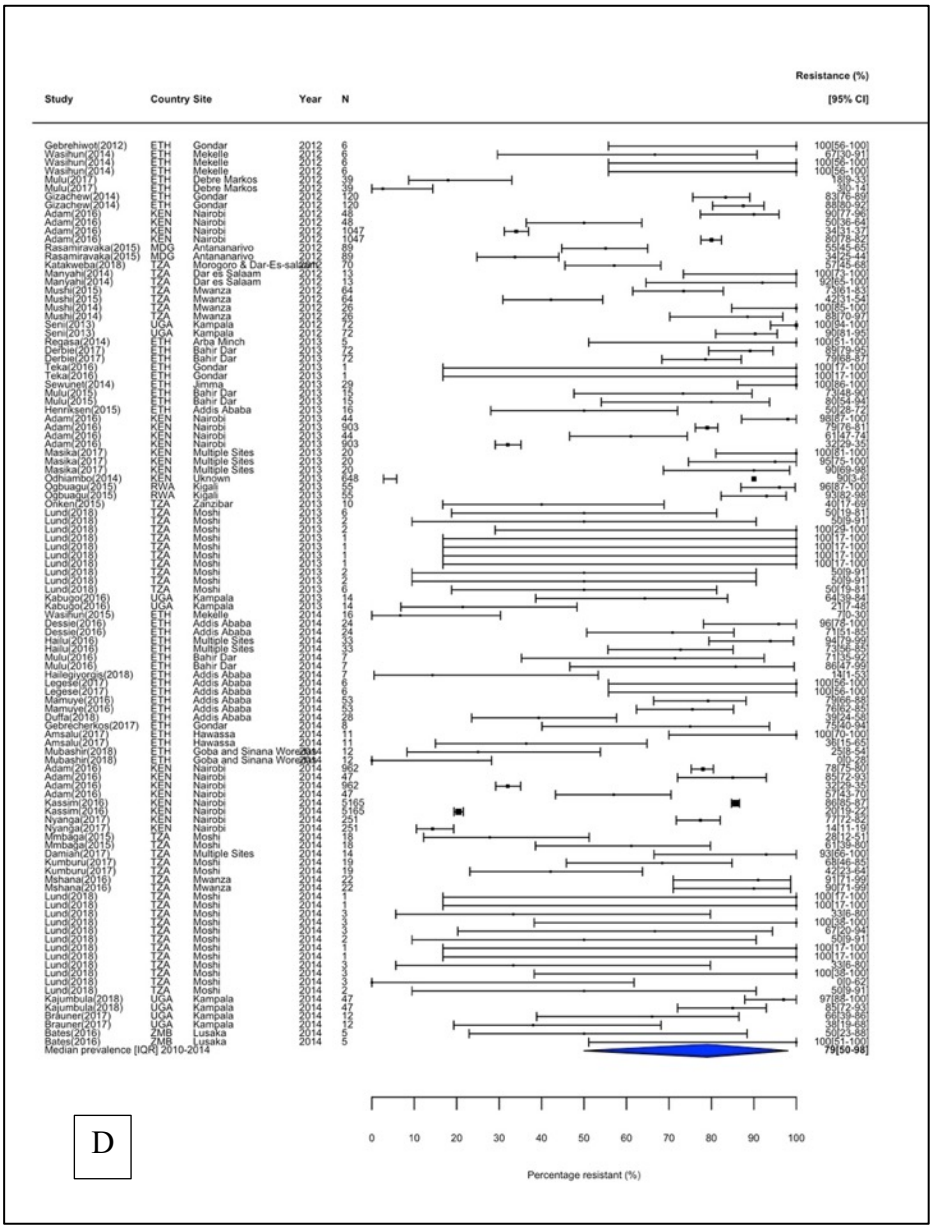


Figure C.18: Forest plot of penicillin resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Kayima(1996) KEN Nairobi 1993 6 83[42-99]
Kayima(1996) KEN Nairobi 1993 6 0[0-44]
Malonza(1997) KEN Nairobi 1993 446 76[71-79]
Malonza(1997) KEN Nairobi 1993 446 37[33-42]
Median prevalence [IQR] 1990-1994 56[28-78]
Melaku(1999) ETH Addis Ababa 1997 6 100[56-100]
Melaku(1999) ETH Addis Ababa 1997 6 0[0-44]
Melaku(1999) ETH Addis Ababa 1997 6 100[56-100]
Moshi(2000) TZA Dar es Salaam 1997 10 60[31-83]
Moshi(2000) TZA Dar es Salaam 1997 10 10[0-43]
Tenssay(2002) ETH Jimma 1998 24 100[84-100]
Decousser(1999) MDG Antananarivo 1998 490 33[29-37]
Gordon(2001) MWI Blantyre 1998 43 93[81-98]
Vila(1999) TZA Ifakara 1998 130 85[77-90]
Median prevalence [IQR] 1995-1999 85[33-100]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Ferede(2001) ETH Addis Ababa 2000 26 85[66-94]
Ferede(2001) ETH Addis Ababa 2000 26 15[6-34]
Mengistu(2002) ETH Gondar 2000 78 69[58-78]
Kiiru(2013) KEN Multiple Sites 2000 1327 57[54-60]
Kiiru(2013) KEN Multiple Sites 2000 1327 36[33-39]
Kiiru(2013) KEN Multiple Sites 2000 1327 61[58-64]
Eriksen(2003) TZA Moshi 2000 12 67[39-86]
Mandomando(2007) MOZ Manhica 2001 94 72[63-80]
Lule(2009) UGA Tororo and Busia State 2002 47 61[47-74]
Lule(2009) UGA Tororo and Busia State 2002 22 76[56-90]
Lule(2009) UGA Tororo and Busia State 2002 47 62[47-74]
Lule(2009) UGA Tororo and Busia District 2002 52 56[42-68]
Mugalu(2006) UGA Kampala 2002 17 100[78-100]
Mugalu(2006) UGA Kampala 2002 17 100[78-100]
Ali(2008) ETH Gondar 2003 2 100[29-100]
Olira(2007) UGA Jinja 2003 5 100[51-100]
Olira(2007) UGA Jinja 2003 5 80[36-98]
Gebre-Sealssie(2007) ETH Jimma 2004 17 100[78-100]
Yismaw(2010) ETH Gondar 2004 136 85[78-90]
Mandomando(2010) MOZ Manhica District 2004 155 96[91-98]
Sigaique(2009) MOZ Manhica 2004 157 96[92-98]
Olila(2007) UGA Kampala 2004 13 92[65-100]
Median prevalence [IQR] 2000-2004 78[61-96]
Teshager(2008) ETH Jimma 2005 3 100[38-100]
Teshager(2008) ETH Jimma 2005 3 67[20-94]
Teshager(2008) ETH Jimma 2005 6 100[56-100]
Teshager(2008) ETH Jimma 2005 6 83[42-99]
Teshager(2008) ETH Jimma 2005 6 50[19-81]
Teshager(2008) ETH Jimma 2005 3 100[38-100]
Talbert(2010) KEN Kilifi 2005 41 78[63-88]
Talarmin(2007) MDG Antananarivo 2005 607 74[70-77]
Talarmin(2007) MDG Antananarivo 2005 607 12[9-14]
Ramilitiana(2014) MDG Antananarivo 2005 56 85[72-92]
Ramilitiana(2014) MDG Antananarivo 2005 56 43[31-56]
Manyahi(2017) TZA Dar es Salaam 2005 95 15[9-23]
Kaddu-Mulindwa(2008) UGA Kampala 2005 11 73[43-91]
Kaddu-Mulindwa(2008) UGA Kampala 2005 11 50[4-49]
Karimi(2009) KEN Nairobi 2006 15 20[8-46]
Revathi(2010) KEN Nairobi 2006 69 38[27-49]
Moyo(2011) TZA Dar es Salaam 2006 64 97[89-100]
Moyo(2011) TZA Dar es Salaam 2006 64 8[3-17]
Musiime(2009) UGA Kampala 2006 31 97[82-100]
Musiime(2009) UGA Kampala 2006 31 68[50-82]
Asrat(2009) ETH Addis Ababa 2007 13 54[29-77]
Asrat(2009) ETH Addis Ababa 2007 13 62[35-82]
Kibret(2011) ETH Multiple Sites 2007 446 23[20-27]
Azene(2011) ETH Uknown 2007 82 85[76-92]
Kibret(2014) ETH Uknown 2007 203 87[82-91]
Suleman(2012) ETH Jimma 2007 67 92[83-97]
Suleman(2012) ETH Jimma 2007 67 87[76-93]
Emacar(2010) KEN Nairobi 2007 48 8[2-17]
Emacar(2010) KEN Nairobi 2007 216 58[51-64]
Emacar(2010) KEN Nairobi 2007 48 43[31-58]
Emacar(2010) KEN Nairobi 2007 216 87[82-91]
Kimando(2010) KEN Nairobi 2007 92 83[73-89]
Kimando(2010) KEN Nairobi 2007 92 59[48-68]
Oduor(2016) KEN Eldoret 2007 38 100[0-15]
Richard(2010) MDG Antananarivo 2007 88 83[74-90]
Richard(2010) MDG Antananarivo 2007 88 83[74-90]
Tegene(2015) ETH Gondar 2008 10 80[48-95]
Tegene(2015) ETH Gondar 2008 10 90[57-100]
Mengistu(2011) ETH Addis Ababa 2008 2 50[9-91]
Kebira(2009) KEN Thika 2008 831 28[25-31]
Sang(2012) KEN Malindi district 2008 7 86[47-99]
Sang(2012) KEN Mbagathi district 2008 21 95[76-100]
Sang(2012) KEN New Nyanza district 2008 14 93[66-100]
Sang(2012) KEN Alupe district 2008 31 77[60-89]
Masinde(2009) TZA Mwanza 2008 17 53[31-74]
Mwaka(2011) UGA Kampala 2008 28 82[64-93]
Victor(2013) KEN Nairobi 2009 4 75[29-97]
Talarmin(2014) MDG Multiple Sites 2009 195 82[76-87]
Talarmin(2014) MDG Multiple Sites 2009 195 1[0-4]
van der Meeren(2013) MOZ Beira 2009 11 100[70-100]
van der Meeren(2013) MOZ Beira 2009 3 100[38-100]
van der Meeren(2013) MOZ Beira 2009 11 64[35-85]
van der Meeren(2013) MOZ Beira 2009 3 67[20-94]
Muvunyi(2011) RWA Butare & Kigali 2009 72 50[39-61]
Muvunyi(2011) RWA Butare & Kigali 2009 47 70[56-81]
Muvunyi(2011) RWA Butare & Kigali 2009 72 86[76-92]
Muvunyi(2011) RWA Butare & Kigali 2009 47 100[91-100]
Mshana(2010) TZA Mwanza 2009 22 100[82-100]
Mshana(2010) TZA Mwanza 2009 22 86[66-96]
Seidman(2016) TZA Kongwa District 2009 2492 65[63-67]
Seidman(2016) TZA Kongwa District 2009 2492 11[9-12]
Median prevalence [IQR] 2005-2009 77[50-87]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Beyene(2011) ETH Jimma 2010 4 0[0-55]
Bozdogan(2002) ETH Jimma 2010 4 0[0-55]
Beyene(2011) ETH Jimma 2010 4 100[45-100]
Bozdogan(2002) ETH Jimma 2010 4 100[45-100]
Kibret(2012) ETH Bahir Dar 2010 33 86[69-94]
Kibret(2012) ETH Bahir Dar 2010 33 100[88-100]
Njagi(2015) KEN Nairobi 2010 132 82[74-88]
Njagi(2015) KEN Nairobi 2010 132 45[36-53]
Fredrick(2013) TZA Dar es Salaam 2010 25 96[79-100]
Fredrick(2013) TZA Dar es Salaam 2010 25 88[69-97]
Fredrick(2012) TZA Dar es Salaam 2010 71 89[79-94]
Fredrick(2012) TZA Dar es Salaam 2010 14 93[66-100]
Moyo(2010) TZA Dar es Salaam 2010 138 96[92-99]
Moyo(2010) TZA Dar es Salaam 2010 138 70[61-77]
Thriemer(2012) TZA Pemba Island 2010 5 60[23-88]
Thriemer(2012) TZA Pemba Island 2010 5 0[0-49]
Kibru(2012) ETH Bahirdar 2011 9 78[44-95]
Kibru(2012) ETH Bahirdar 2011 9 90[54-100]
Tsegaye(2012) ETH Bahir Dar 2011 16 75[50-90]
Tsegaye(2012) ETH Bahir Dar 2011 16 38[18-61]
Tsegaye(2012) ETH Bahir Dar 2011 16 82[56-94]
Kibru(2013) ETH jimma 2011 30 77[59-88]
Aragaw(2014) ETH Hawassa 2011 30 67[49-81]
Ndungiu(2014) KEN Kiambu County 2011 42 85[72-94]
Ndungiu(2014) KEN Kiambu County 2011 42 68[54-81]
Mwambete(2014) TZA Dar Es Salaam 2011 174 74[67-80]
Mwambete(2014) TZA Dar Es Salaam 2011 174 57[50-65]
Mwambete(2014) TZA Dar Es Salaam 2011 174 59[52-66]
Odongo(2013) UGA Gulu 2011 32 59[42-75]
Odongo(2013) UGA Gulu 2011 32 38[23-55]
Brauner(2012) UGA Kampala 2011 56 75[62-85]
Brauner(2012) UGA Kampala 2011 56 34[23-47]
Median prevalence [IQR] 2010-2014 75[59-88]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
C


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2010-2014
79[50-98]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

D

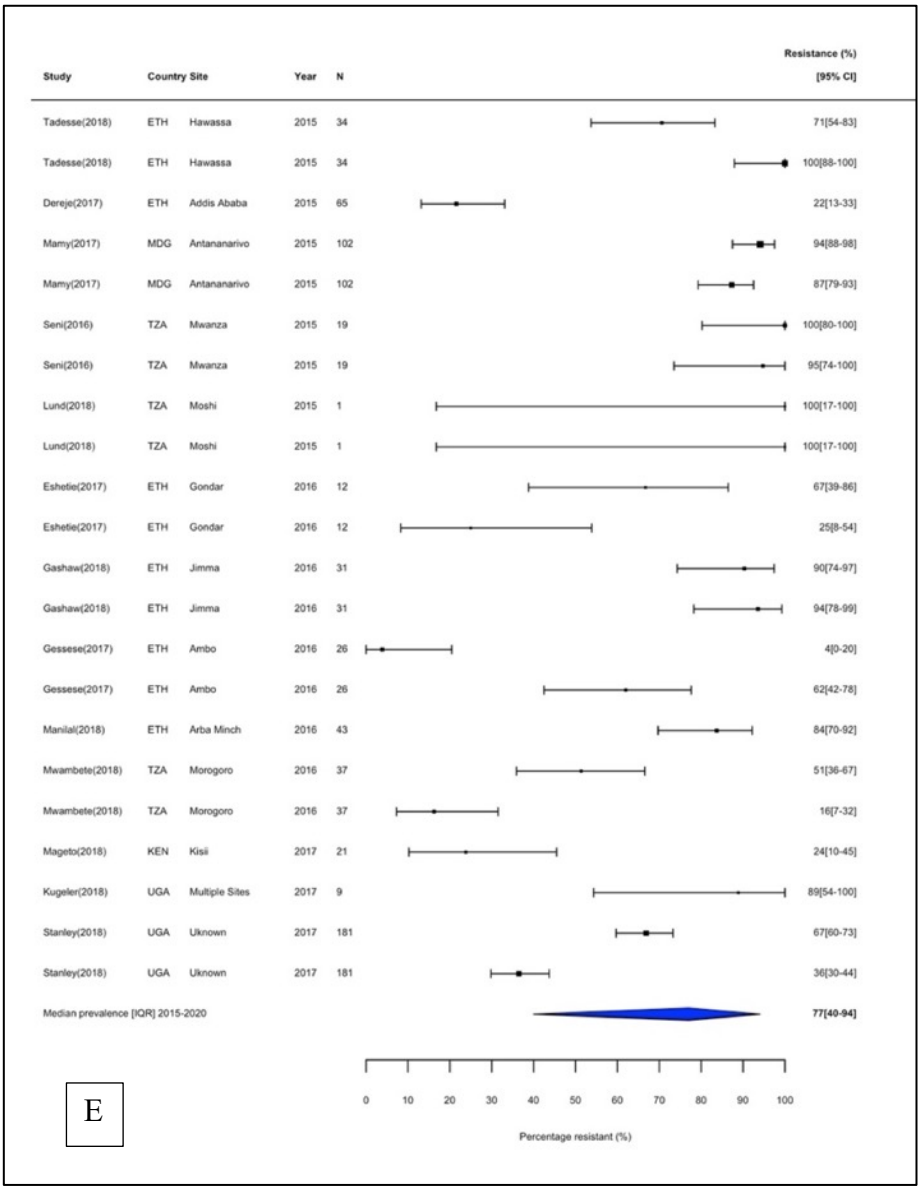
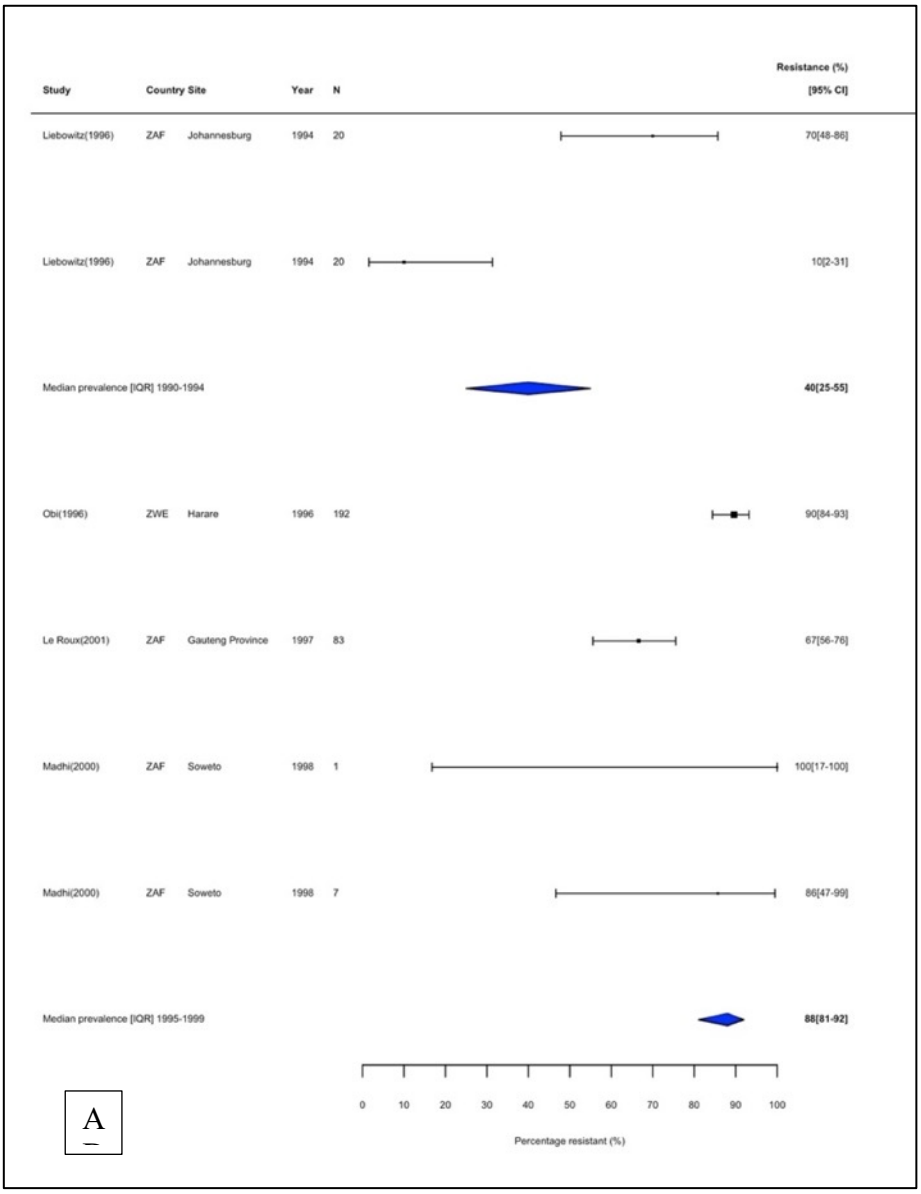
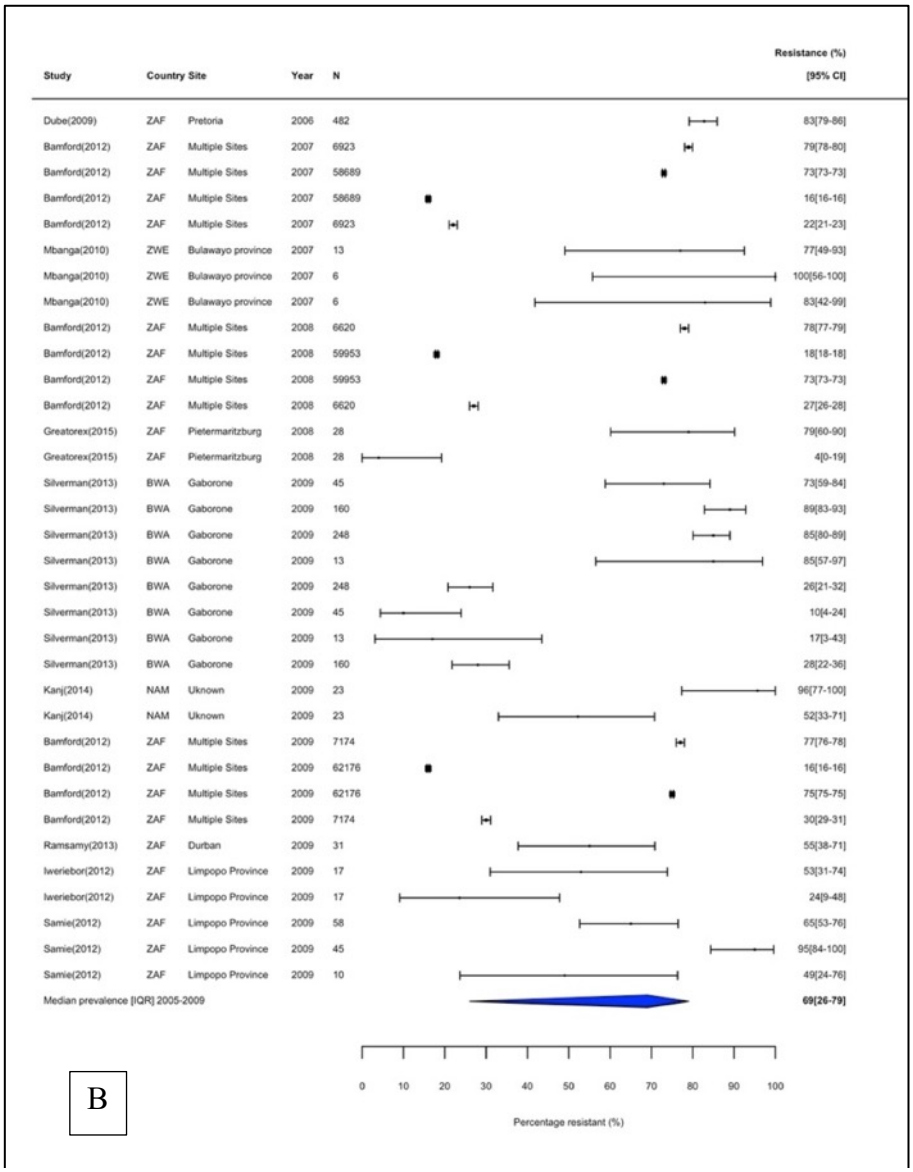
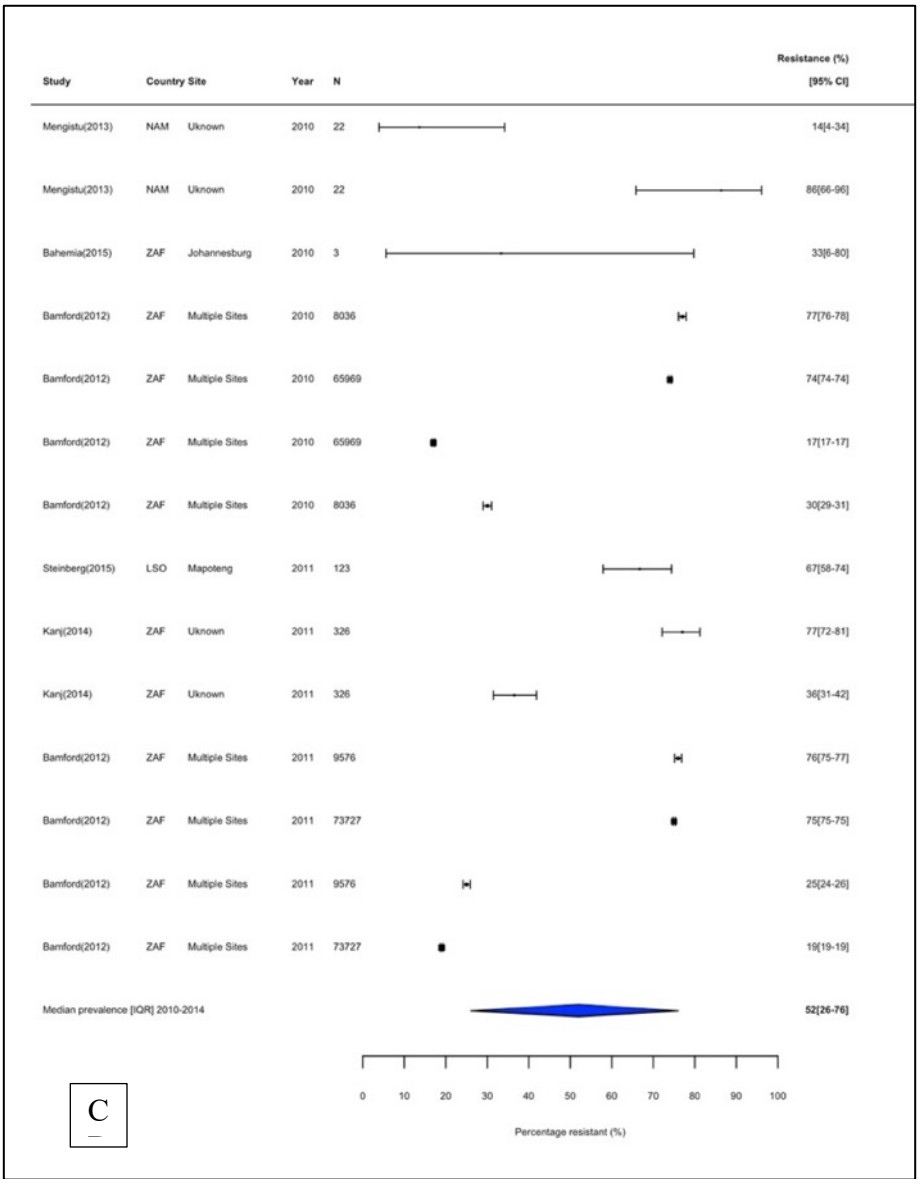


Figure C.19: Forest plot of penicillin resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2009, C: 2010-2011, D: 2012-2014, E:2015-2018.

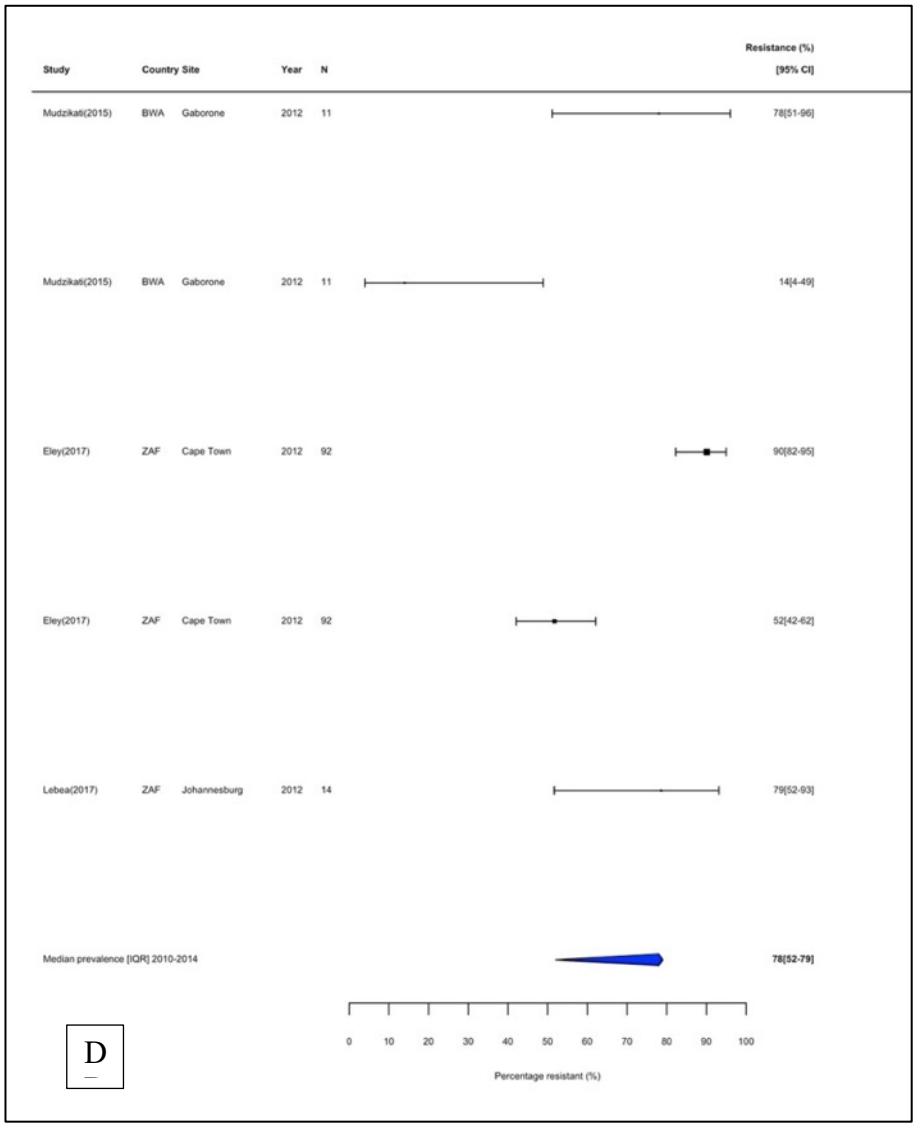

Study
Country
Site
Year
N
Resistance (%) [95% CI]
Liebowitz(1996) ZAF Johannesburg 1994 20 70[48-86]
Liebowitz(1996) ZAF Johannesburg 1994 20 10[2-31]
Median prevalence [IQR] 1990-1994 40[25-55]
Obi(1996) ZWE Harare 1996 192 90[84-93]
Le Roux(2001) ZAF Gauteng Province 1997 83 67[56-76]
Madhi(2000) ZAF Soweto 1998 1 100[17-100]
Madhi(2000) ZAF Soweto 1998 7 86[47-99]
Median prevalence [IQR] 1995-1999 88[81-92]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Dube(2009) ZAF Pretoria 2006 482 83[79-86]
Bamford(2012) ZAF Multiple Sites 2007 6923 79[78-80]
Bamford(2012) ZAF Multiple Sites 2007 58689 73[73-73]
Bamford(2012) ZAF Multiple Sites 2007 58689 16[16-16]
Bamford(2012) ZAF Multiple Sites 2007 6923 22[21-23]
Mbanga(2010) ZWE Bulawayo province 2007 13 77[49-93]
Mbanga(2010) ZWE Bulawayo province 2007 6 100[56-100]
Mbanga(2010) ZWE Bulawayo province 2007 6 83[42-99]
Bamford(2012) ZAF Multiple Sites 2008 6620 78[77-79]
Bamford(2012) ZAF Multiple Sites 2008 59953 18[18-18]
Bamford(2012) ZAF Multiple Sites 2008 59953 73[73-73]
Bamford(2012) ZAF Multiple Sites 2008 6620 27[26-28]
Greatorex(2015) ZAF Pietermaritzburg 2008 28 79[60-90]
Greatorex(2015) ZAF Pietermaritzburg 2008 28 4[0-19]
Silverman(2013) BWA Gaborone 2009 45 73[59-84]
Silverman(2013) BWA Gaborone 2009 160 89[83-93]
Silverman(2013) BWA Gaborone 2009 248 85[80-89]
Silverman(2013) BWA Gaborone 2009 13 85[57-97]
Silverman(2013) BWA Gaborone 2009 248 26[21-32]
Silverman(2013) BWA Gaborone 2009 45 10[4-24]
Silverman(2013) BWA Gaborone 2009 13 17[3-43]
Silverman(2013) BWA Gaborone 2009 160 28[22-36]
Kanj(2014) NAM Uknown 2009 23 96[77-100]
Kanj(2014) NAM Uknown 2009 23 52[33-71]
Bamford(2012) ZAF Multiple Sites 2009 7174 77[76-78]
Bamford(2012) ZAF Multiple Sites 2009 62176 16[16-16]
Bamford(2012) ZAF Multiple Sites 2009 62176 75[75-75]
Bamford(2012) ZAF Multiple Sites 2009 7174 30[29-31]
Ramsamy(2013) ZAF Durban 2009 31 55[38-71]
Iweriebor(2012) ZAF Limpopo Province 2009 17 53[31-74]
Iweriebor(2012) ZAF Limpopo Province 2009 17 24[9-48]
Samie(2012) ZAF Limpopo Province 2009 58 65[53-76]
Samie(2012) ZAF Limpopo Province 2009 45 95[84-100]
Samie(2012) ZAF Limpopo Province 2009 10 49[24-76]
Median prevalence [IQR] 2005-2009 69[26-79]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Mengistu(2013) NAM Uknown 2010 22 14[4-34]
Mengistu(2013) NAM Uknown 2010 22 86[66-96]
Bahemia(2015) ZAF Johannesburg 2010 3 33[6-80]
Bamford(2012) ZAF Multiple Sites 2010 8036 77[76-78]
Bamford(2012) ZAF Multiple Sites 2010 65969 74[74-74]
Bamford(2012) ZAF Multiple Sites 2010 65969 17[17-17]
Bamford(2012) ZAF Multiple Sites 2010 8036 30[29-31]
Steinberg(2015) LSO Mapoteng 2011 123 67[58-74]
Karuj(2014) ZAF Uknown 2011 326 77[72-81]
Karuj(2014) ZAF Uknown 2011 326 36[31-42]
Bamford(2012) ZAF Multiple Sites 2011 9576 76[75-77]
Bamford(2012) ZAF Multiple Sites 2011 73727 75[75-75]
Bamford(2012) ZAF Multiple Sites 2011 9576 25[24-26]
Bamford(2012) ZAF Multiple Sites 2011 73727 19[19-19]
Median prevalence [IQR] 2010-2014 52[26-76]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

C


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Mudzikati(2015) BWA Gaborone 2012 11 78[51-96]
Mudzikati(2015) BWA Gaborone 2012 11 14[4-49]
Eley(2017) ZAF Cape Town 2012 92 90[82-95]
Eley(2017) ZAF Cape Town 2012 92 52[42-62]
Lebea(2017) ZAF Johannesburg 2012 14 79[52-93]
Median prevalence [IQR] 2010-2014 78[52-79]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
D

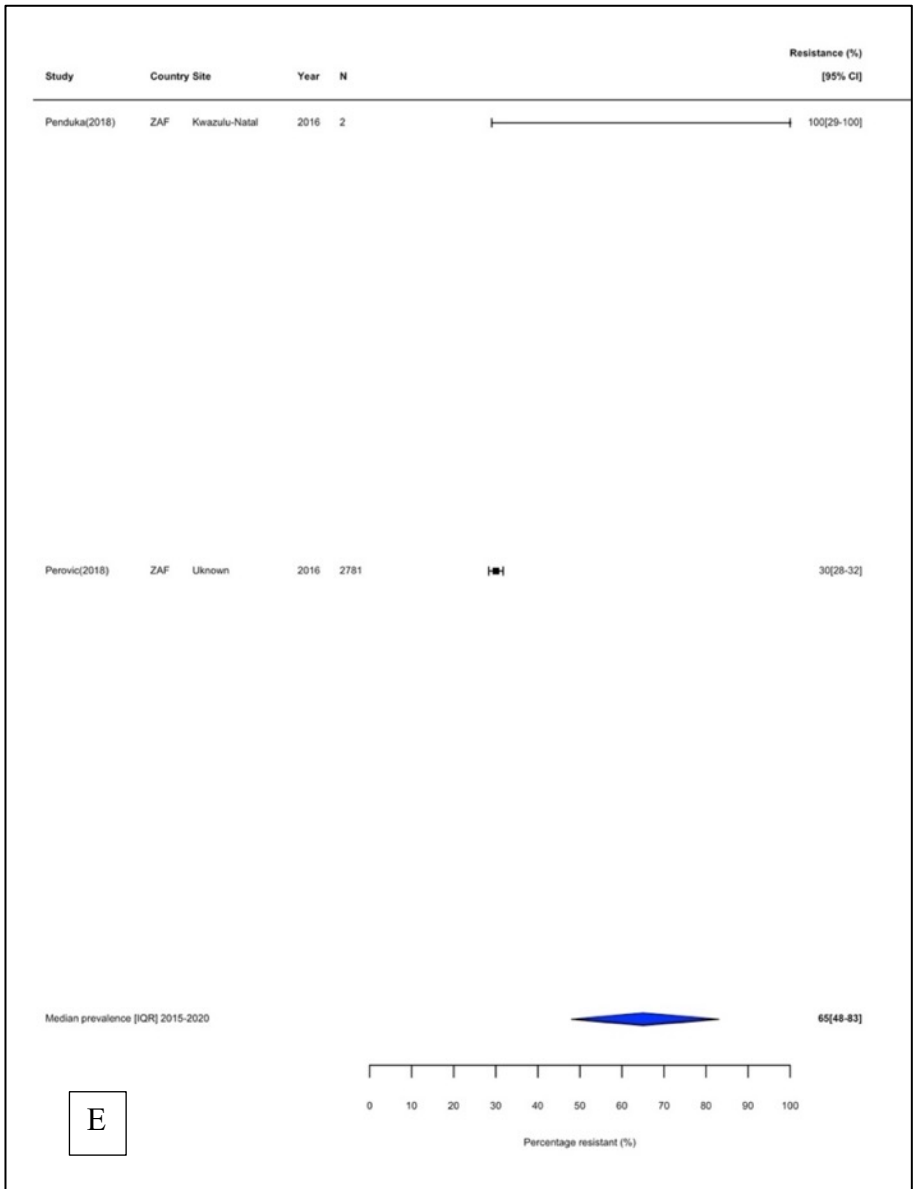
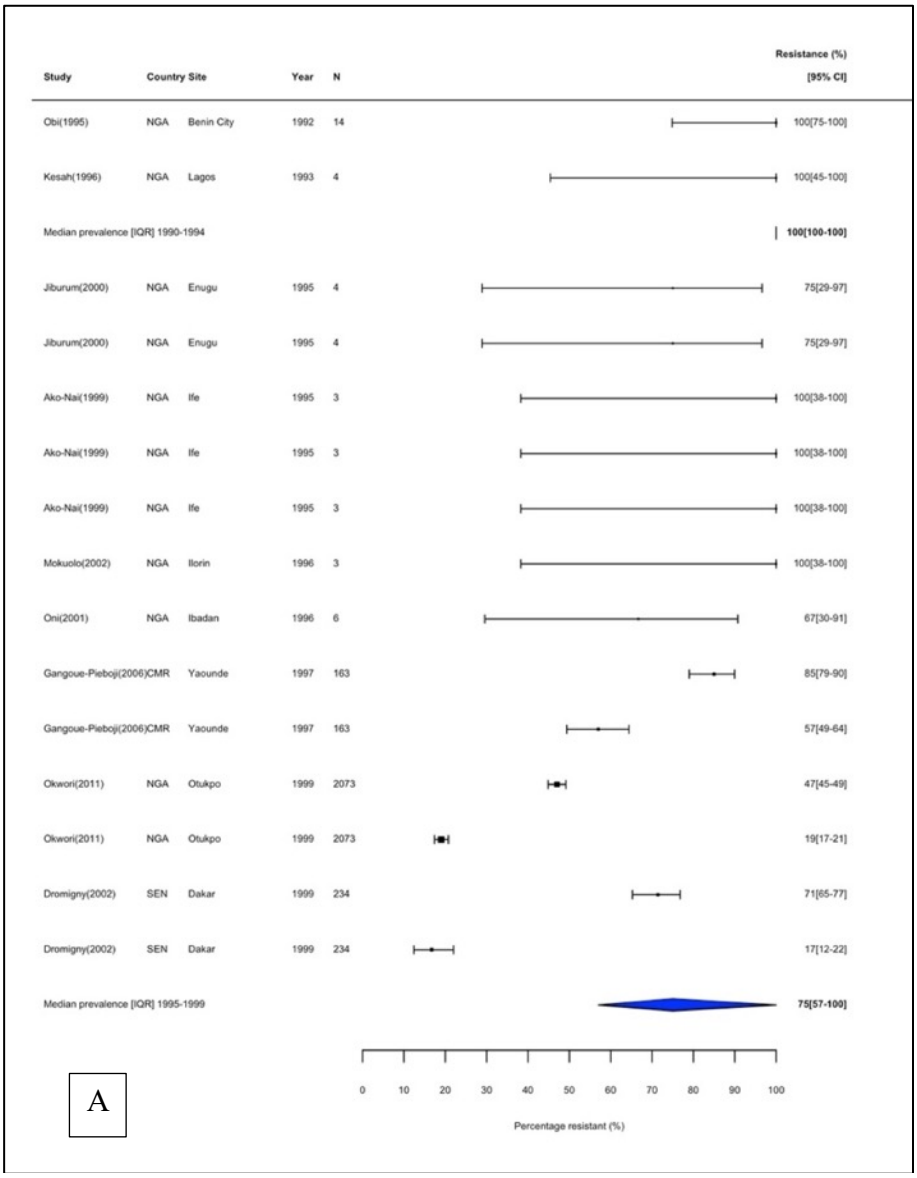
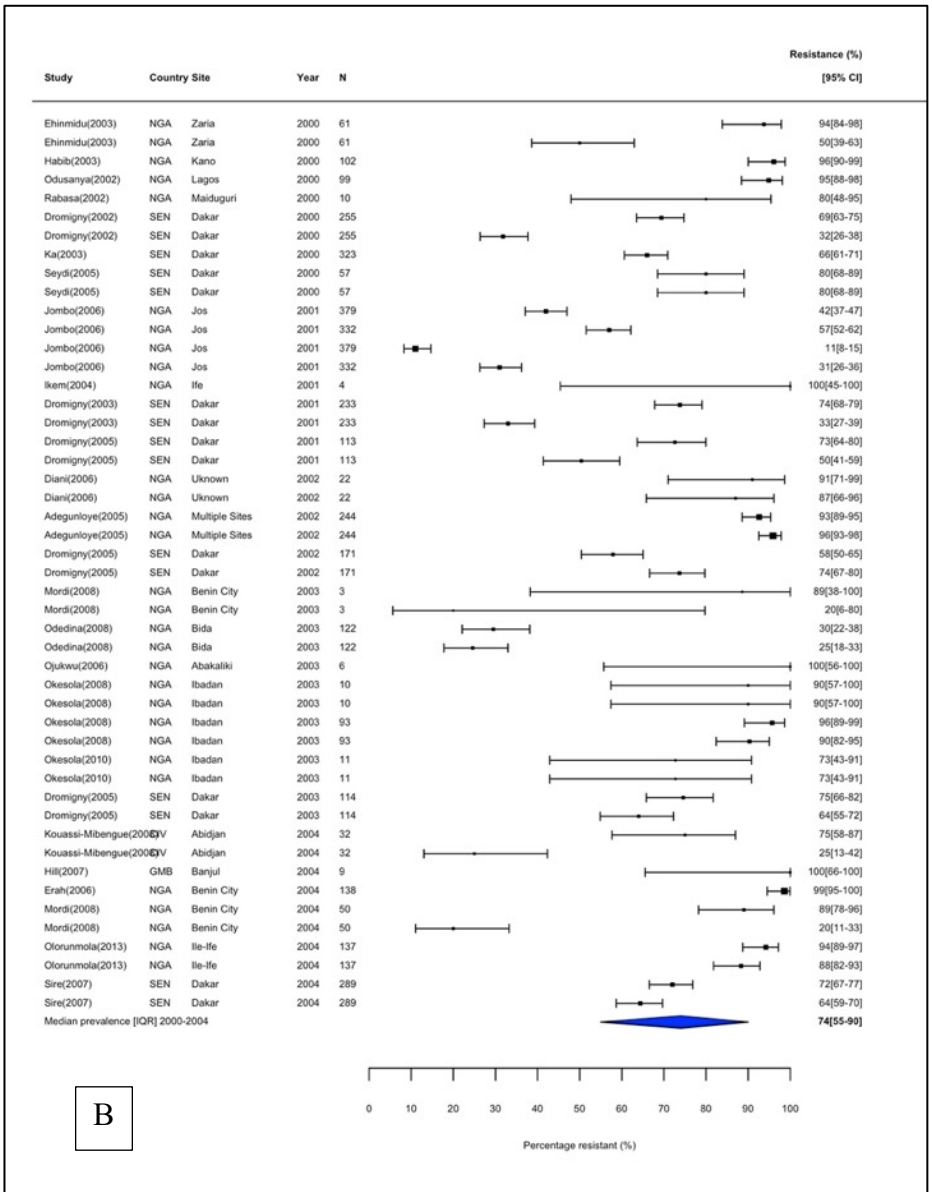
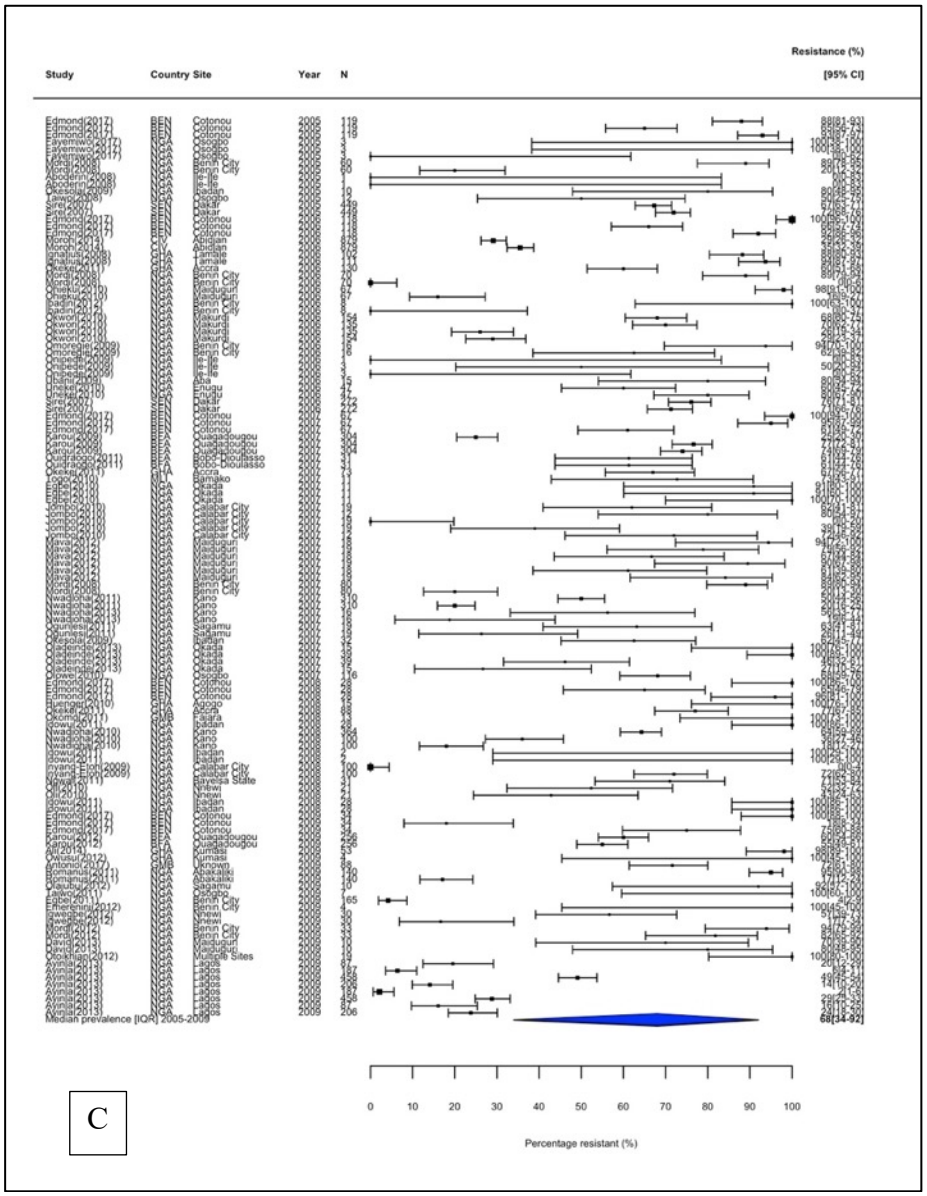


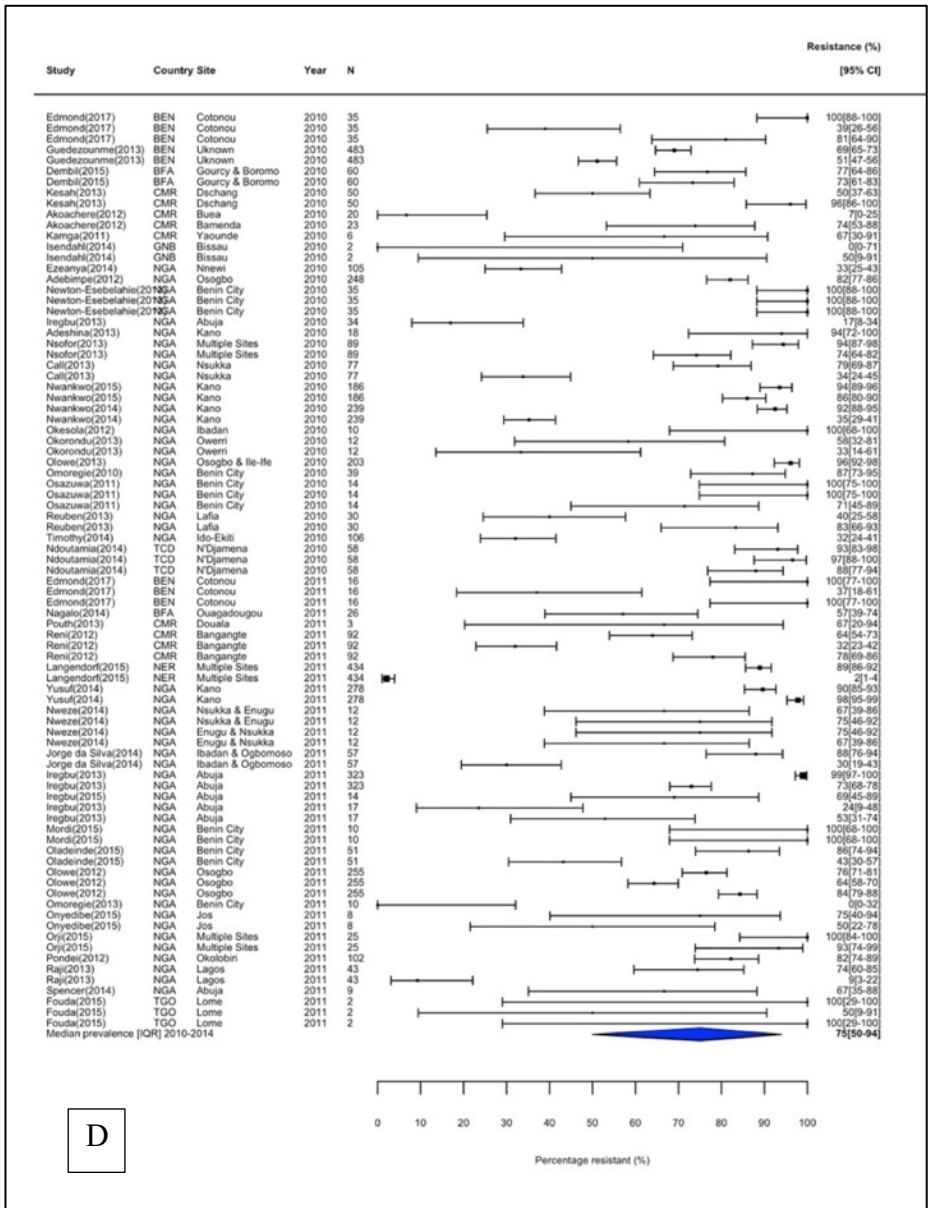
Figure C.20: Forest plot of penicillin resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2009, C: 2010-2012, D: 2013-2014, E: 2015-2018


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Obi(1995) NGA Benin City 1992 14 100[75-100]
Kesah(1996) NGA Lagos 1993 4 100[45-100]
Median prevalence [IQR] 1990-1994 100[100-100]
Jiburum(2000) NGA Enugu 1995 4 75[29-97]
Jiburum(2000) NGA Enugu 1995 4 75[29-97]
Ako-Nai(1999) NGA Ife 1995 3 100[38-100]
Ako-Nai(1999) NGA Ife 1995 3 100[38-100]
Ako-Nai(1999) NGA Ife 1995 3 100[38-100]
Mokuolo(2002) NGA Ilorin 1996 3 100[38-100]
Oni(2001) NGA Ibadan 1996 6 67[30-91]
Gangoue-Pieboji(2006) CMR Yaounde 1997 163 85[79-90]
Gangoue-Pieboji(2006) CMR Yaounde 1997 163 57[49-64]
Okwori(2011) NGA Otukpo 1999 2073 47[45-49]
Okwori(2011) NGA Otukpo 1999 2073 19[17-21]
Dromigny(2002) SEN Dakar 1999 234 71[65-77]
Dromigny(2002) SEN Dakar 1999 234 17[12-22]
Median prevalence [IQR] 1995-1999 75[57-100]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A

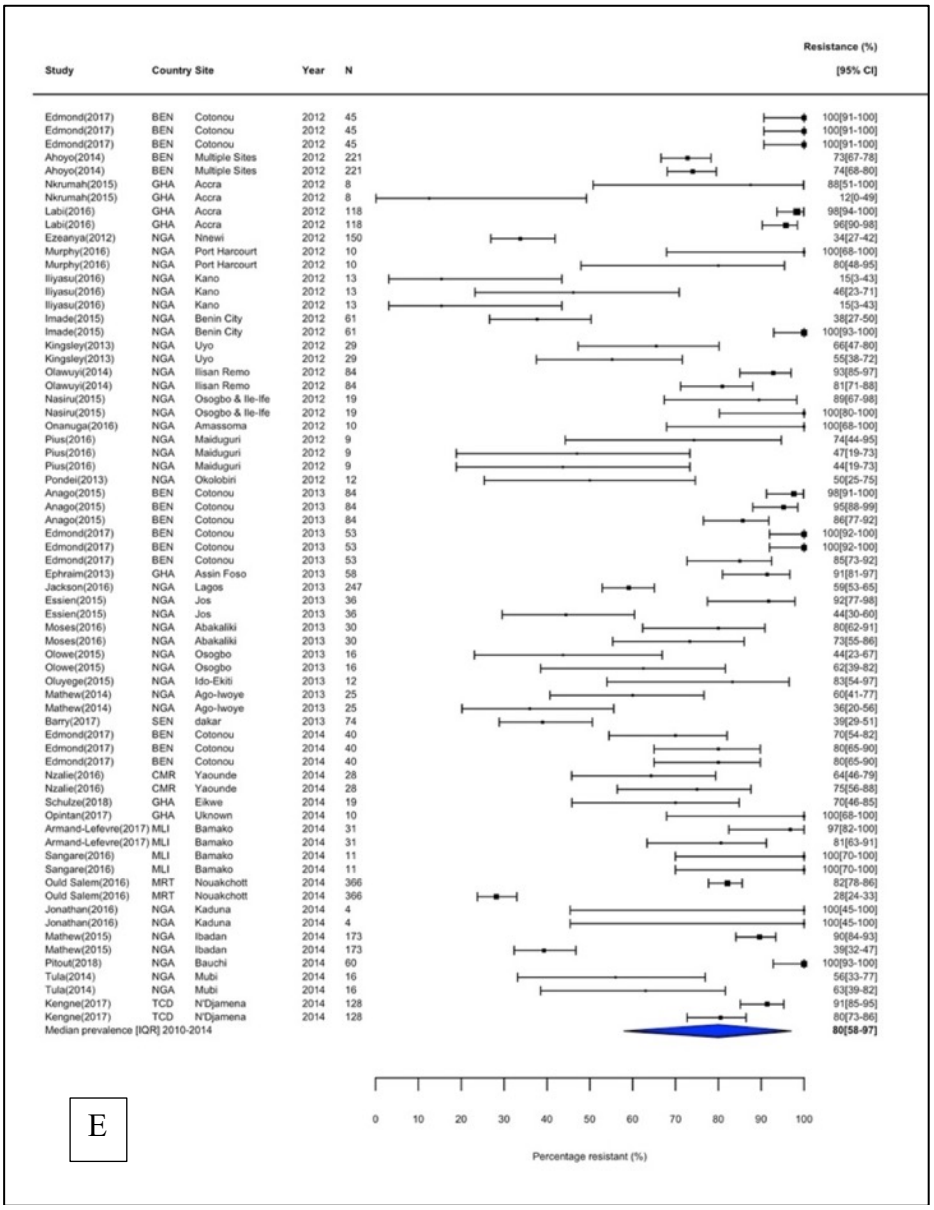

Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Ehinmidu(2003) NGA Zaria 2000 61 94[84-98]
Ehinmidu(2003) NGA Zaria 2000 61 50[39-63]
Habib(2003) NGA Kano 2000 102 96[90-99]
Odusanya(2002) NGA Lagos 2000 99 95[88-98]
Rabasa(2002) NGA Maiduguri 2000 10 80[48-95]
Dromigny(2002) SEN Dakar 2000 255 69[63-75]
Dromigny(2002) SEN Dakar 2000 255 32[26-38]
Ka(2003) SEN Dakar 2000 323 66[61-71]
Seydi(2005) SEN Dakar 2000 57 80[68-89]
Seydi(2005) SEN Dakar 2000 57 80[68-89]
Jombo(2006) NGA Jos 2001 379 42[37-47]
Jombo(2006) NGA Jos 2001 332 57[52-62]
Jombo(2006) NGA Jos 2001 379 11[8-15]
Jombo(2006) NGA Jos 2001 332 31[26-36]
Ikem(2004) NGA Ife 2001 4 100[45-100]
Dromigny(2003) SEN Dakar 2001 233 74[68-79]
Dromigny(2003) SEN Dakar 2001 233 33[27-39]
Dromigny(2005) SEN Dakar 2001 113 73[64-80]
Dromigny(2005) SEN Dakar 2001 113 50[41-59]
Diani(2006) NGA Uknown 2002 22 91[71-99]
Diani(2006) NGA Uknown 2002 22 87[66-96]
Adegunloye(2005) NGA Multiple Sites 2002 244 93[89-95]
Adegunloye(2005) NGA Multiple Sites 2002 244 96[93-98]
Dromigny(2005) SEN Dakar 2002 171 58[50-65]
Dromigny(2005) SEN Dakar 2002 171 74[67-80]
Mordi(2008) NGA Benin City 2003 3 89[38-100]
Mordi(2008) NGA Benin City 2003 3 20[6-80]
Odedina(2008) NGA Bida 2003 122 30[22-38]
Odedina(2008) NGA Bida 2003 122 25[18-33]
Ojukwu(2006) NGA Abakaliki 2003 6 100[56-100]
Okesola(2008) NGA Ibadan 2003 10 90[57-100]
Okesola(2008) NGA Ibadan 2003 10 90[57-100]
Okesola(2008) NGA Ibadan 2003 93 96[89-99]
Okesola(2008) NGA Ibadan 2003 93 90[82-95]
Okesola(2010) NGA Ibadan 2003 11 73[43-91]
Okesola(2010) NGA Ibadan 2003 11 73[43-91]
Dromigny(2005) SEN Dakar 2003 114 75[66-82]
Dromigny(2005) SEN Dakar 2003 114 64[55-72]
Kouassi-Mibengue(2008) CIV Abidjan 2004 32 75[58-87]
Kouassi-Mibengue(2008) CIV Abidjan 2004 32 25[13-42]
Hill(2007) GMB Banjul 2004 9 100[66-100]
Erah(2006) NGA Benin City 2004 138 99[95-100]
Mordi(2008) NGA Benin City 2004 50 89[78-96]
Mordi(2008) NGA Benin City 2004 50 20[11-33]
Olorunmola(2013) NGA Ile-Ife 2004 137 94[89-97]
Olorunmola(2013) NGA Ile-Ife 2004 137 88[82-93]
Sire(2007) SEN Dakar 2004 289 72[67-77]
Sire(2007) SEN Dakar 2004 289 64[59-70]
Median prevalence [IQR] 2000-2004 74[55-90]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2005-2009
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
C


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2010 35 100[88-100]
Edmond(2017) BEN Cotonou 2010 35 39[26-56]
Edmond(2017) BEN Cotonou 2010 35 81[64-90]
Guedezounme(2013) BEN Uknown 2010 483 69[65-73]
Guedezounme(2013) BEN Uknown 2010 483 51[47-56]
Dembil(2015) BFA Gourcy & Boromo 2010 60 77[64-86]
Dembil(2015) BFA Gourcy & Boromo 2010 60 73[61-83]
Kesah(2013) CMR Dschang 2010 50 50[37-63]
Kesah(2013) CMR Dschang 2010 50 96[86-100]
Akoachere(2012) CMR Buea 2010 20 7[0-25]
Akoachere(2012) CMR Bamenda 2010 23 74[53-88]
Kamga(2011) CMR Yaounde 2010 6 67[30-91]
Isendahl(2014) GNB Bissau 2010 2 0[0-71]
Isendahl(2014) GNB Bissau 2010 2 50[9-91]
Ezeanya(2014) NGA Nnewi 2010 105 33[25-43]
Adebimpe(2012) NGA Osogbo 2010 248 82[77-86]
Newton-Esebelahie(2013) NGA Benin City 2010 35 100[88-100]
Newton-Esebelahie(2013) NGA Benin City 2010 35 100[88-100]
Newton-Esebelahie(2013) NGA Benin City 2010 35 100[88-100]
Iregbu(2013) NGA Abuja 2010 34 17[8-34]
Adeshina(2013) NGA Kano 2010 18 94[72-100]
Nsofor(2013) NGA Multiple Sites 2010 89 94[87-98]
Nsofor(2013) NGA Multiple Sites 2010 89 74[64-82]
Call(2013) NGA Nsukka 2010 77 79[69-87]
Call(2013) NGA Nsukka 2010 77 34[24-45]
Nwankwo(2015) NGA Kano 2010 186 94[89-96]
Nwankwo(2015) NGA Kano 2010 186 86[80-90]
Nwankwo(2014) NGA Kano 2010 239 92[88-95]
Nwankwo(2014) NGA Kano 2010 239 35[29-41]
Okesola(2012) NGA Ibadan 2010 10 100[68-100]
Okorondu(2013) NGA Owerri 2010 12 58[32-81]
Okorondu(2013) NGA Owerri 2010 12 33[14-61]
Olowe(2013) NGA Osogbo & Ile-Ife 2010 203 96[92-98]
Omoregie(2010) NGA Benin City 2010 39 87[73-95]
Osazuwa(2011) NGA Benin City 2010 14 100[75-100]
Osazuwa(2011) NGA Benin City 2010 14 100[75-100]
Osazuwa(2011) NGA Benin City 2010 14 71[45-89]
Reuben(2013) NGA Lafia 2010 30 40[25-58]
Reuben(2013) NGA Lafia 2010 30 83[66-93]
Timothy(2014) NGA Ido-Ekiti 2010 106 32[24-41]
Ndoutamia(2014) TCD N'Djamena 2010 58 93[83-98]
Ndoutamia(2014) TCD N'Djamena 2010 58 97[88-100]
Ndoutamia(2014) TCD N'Djamena 2010 58 88[77-94]
Edmond(2017) BEN Cotonou 2011 16 100[77-100]
Edmond(2017) BEN Cotonou 2011 16 37[18-61]
Edmond(2017) BEN Cotonou 2011 16 100[7-100]
Nagalo(2014) BFA Ouagadougou 2011 26 57[39-74]
Pouth(2013) CMR Douala 2011 3 67[20-94]
Reni(2012) CMR Bangangte 2011 92 64[54-73]
Reni(2012) CMR Bangangte 2011 92 32[23-42]
Reni(2012) CMR Bangangte 2011 92 78[69-86]
Langendorf(2015) NER Multiple Sites 2011 434 89[86-92]
Langendorf(2015) NER Multiple Sites 2011 434 2[1-4]
Yusuf(2014) NGA Kano 2011 278 90[85-93]
Yusuf(2014) NGA Kano 2011 278 98[95-99]
Nweze(2014) NGA Nsukka & Enugu 2011 12 67[39-86]
Nweze(2014) NGA Nsukka & Enugu 2011 12 75[46-92]
Nweze(2014) NGA Enugu & Nsukka 2011 12 75[46-92]
Nweze(2014) NGA Enugu & Nsukka 2011 12 67[39-86]
Jorge da Silva(2014) NGA Ibadan & Ogbomoso 2011 57 88[76-94]
Jorge da Silva(2014) NGA Ibadan & Ogbomoso 2011 57 30[19-43]
Iregbu(2013) NGA Abuja 2011 323 99[97-100]
Iregbu(2013) NGA Abuja 2011 323 73[68-78]
Iregbu(2015) NGA Abuja 2011 14 69[45-89]
Iregbu(2013) NGA Abuja 2011 17 24[9-48]
Iregbu(2013) NGA Abuja 2011 17 53[31-74]
Mordi(2015) NGA Benin City 2011 10 100[68-100]
Mordi(2015) NGA Benin City 2011 10 100[68-100]
Oladeinde(2015) NGA Benin City 2011 51 86[74-94]
Oladeinde(2015) NGA Benin City 2011 51 43[30-57]
Olowe(2012) NGA Osogbo 2011 255 76[71-81]
Olowe(2012) NGA Osogbo 2011 255 64[58-70]
Olowe(2012) NGA Osogbo 2011 255 84[79-88]
Omoregie(2013) NGA Benin City 2011 10 0[0-32]
Onyedibe(2015) NGA Jos 2011 8 75[40-94]
Onyedibe(2015) NGA Jos 2011 8 50[22-78]
Orji(2015) NGA Multiple Sites 2011 25 100[84-100]
Orji(2015) NGA Multiple Sites 2011 25 93[74-99]
Pondei(2012) NGA Okolobiri 2011 102 82[74-89]
Raji(2013) NGA Lagos 2011 43 74[60-85]
Raji(2013) NGA Lagos 2011 43 9[3-22]
Spencer(2014) NGA Abuja 2011 9 67[35-88]
Fouda(2015) TGO Lome 2011 2 100[29-100]
Fouda(2015) TGO Lome 2011 2 50[9-91]
Fouda(2015) TGO Lome 2011 2 100[29-100]
Median prevalence [IQR] 2010-2014 75[50-94]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

D


Resistance (%)
Study
Country
Site
Year
N
[95% CI]
Edmond(2017) BEN Cotonou 2012 45 100[91-100]
Edmond(2017) BEN Cotonou 2012 45 100[91-100]
Edmond(2017) BEN Cotonou 2012 45 100[91-100]
Ahoyo(2014) BEN Multiple Sites 2012 221 73[67-78]
Ahoyo(2014) BEN Multiple Sites 2012 221 74[68-80]
Nkrumah(2015) GHA Accra 2012 8 88[51-100]
Nkrumah(2015) GHA Accra 2012 8 12[0-49]
Labi(2016) GHA Accra 2012 118 98[94-100]
Labi(2016) GHA Accra 2012 118 96[90-98]
Ezeanya(2012) NGA Nnewi 2012 150 34[27-42]
Murphy(2016) NGA Port Harcourt 2012 10 100[68-100]
Murphy(2016) NGA Port Harcourt 2012 10 80[48-95]
Iliyasu(2016) NGA Kano 2012 13 15[3-43]
Iliyasu(2016) NGA Kano 2012 13 46[23-71]
Iliyasu(2016) NGA Kano 2012 13 15[3-43]
Imade(2015) NGA Benin City 2012 61 38[27-50]
Imade(2015) NGA Benin City 2012 61 100[93-100]
Kingsley(2013) NGA Uyo 2012 29 66[47-80]
Kingsley(2013) NGA Uyo 2012 29 55[38-72]
Olawuyi(2014) NGA Ilisan Remo 2012 84 93[85-97]
Olawuyi(2014) NGA Ilisan Remo 2012 84 81[71-88]
Nasiru(2015) NGA Osogbo & Ile-Ife 2012 19 89[67-98]
Nasiru(2015) NGA Osogbo & Ile-Ife 2012 19 100[80-100]
Onanuga(2016) NGA Amassoma 2012 10 100[68-100]
Pius(2016) NGA Maiduguri 2012 9 74[44-95]
Pius(2016) NGA Maiduguri 2012 9 47[19-73]
Pius(2016) NGA Maiduguri 2012 9 44[19-73]
Pondei(2013) NGA Okolobiri 2012 12 50[25-75]
Anago(2015) BEN Cotonou 2013 84 98[91-100]
Anago(2015) BEN Cotonou 2013 84 95[88-99]
Anago(2015) BEN Cotonou 2013 84 86[77-92]
Edmond(2017) BEN Cotonou 2013 53 100[92-100]
Edmond(2017) BEN Cotonou 2013 53 100[92-100]
Edmond(2017) BEN Cotonou 2013 53 85[73-92]
Ephraim(2013) GHA Assin Foso 2013 58 91[81-97]
Jackson(2016) NGA Lagos 2013 247 59[53-65]
Essien(2015) NGA Jos 2013 36 92[77-98]
Essien(2015) NGA Jos 2013 36 44[30-60]
Moses(2016) NGA Abakaliki 2013 30 80[62-91]
Moses(2016) NGA Abakaliki 2013 30 73[55-86]
Olowe(2015) NGA Osogbo 2013 16 44[23-67]
Olowe(2015) NGA Osogbo 2013 16 62[39-82]
Oluyege(2015) NGA Ido-Ekiti 2013 12 83[54-97]
Mathew(2014) NGA Ago-Iwoye 2013 25 60[41-77]
Mathew(2014) NGA Ago-Iwoye 2013 25 36[20-56]
Barry(2017) SEN dakar 2013 74 39[29-51]
Edmond(2017) BEN Cotonou 2014 40 70[54-82]
Edmond(2017) BEN Cotonou 2014 40 80[65-90]
Edmond(2017) BEN Cotonou 2014 40 80[65-90]
Nzalie(2016) CMR Yaounde 2014 28 64[46-79]
Nzalie(2016) CMR Yaounde 2014 28 75[56-88]
Schulze(2018) GHA Eikwe 2014 19 70[46-85]
Opintan(2017) GHA Uknown 2014 10 100[68-100]
Armand-Lefevre(2017) MLI Bamako 2014 31 97[82-100]
Armand-Lefevre(2017) MLI Bamako 2014 31 81[63-91]
Sangare(2016) MLI Bamako 2014 11 100[70-100]
Sangare(2016) MLI Bamako 2014 11 100[70-100]
Ould Salem(2016) MRT Nouakchott 2014 366 82[78-86]
Ould Salem(2016) MRT Nouakchott 2014 366 28[24-33]
Jonathan(2016) NGA Kaduna 2014 4 100[45-100]
Jonathan(2016) NGA Kaduna 2014 4 100[45-100]
Mathew(2015) NGA Ibadan 2014 173 90[84-93]
Mathew(2015) NGA Ibadan 2014 173 39[32-47]
Pitout(2018) NGA Bauchi 2014 60 100[93-100]
Tula(2014) NGA Mubi 2014 16 56[33-77]
Tula(2014) NGA Mubi 2014 16 63[39-82]
Kengne(2017) TCD N'Djamena 2014 128 91[85-95]
Kengne(2017) TCD N'Djamena 2014 128 80[73-86]
Median prevalence [IQR] 2010-2014 80[58-97]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
E

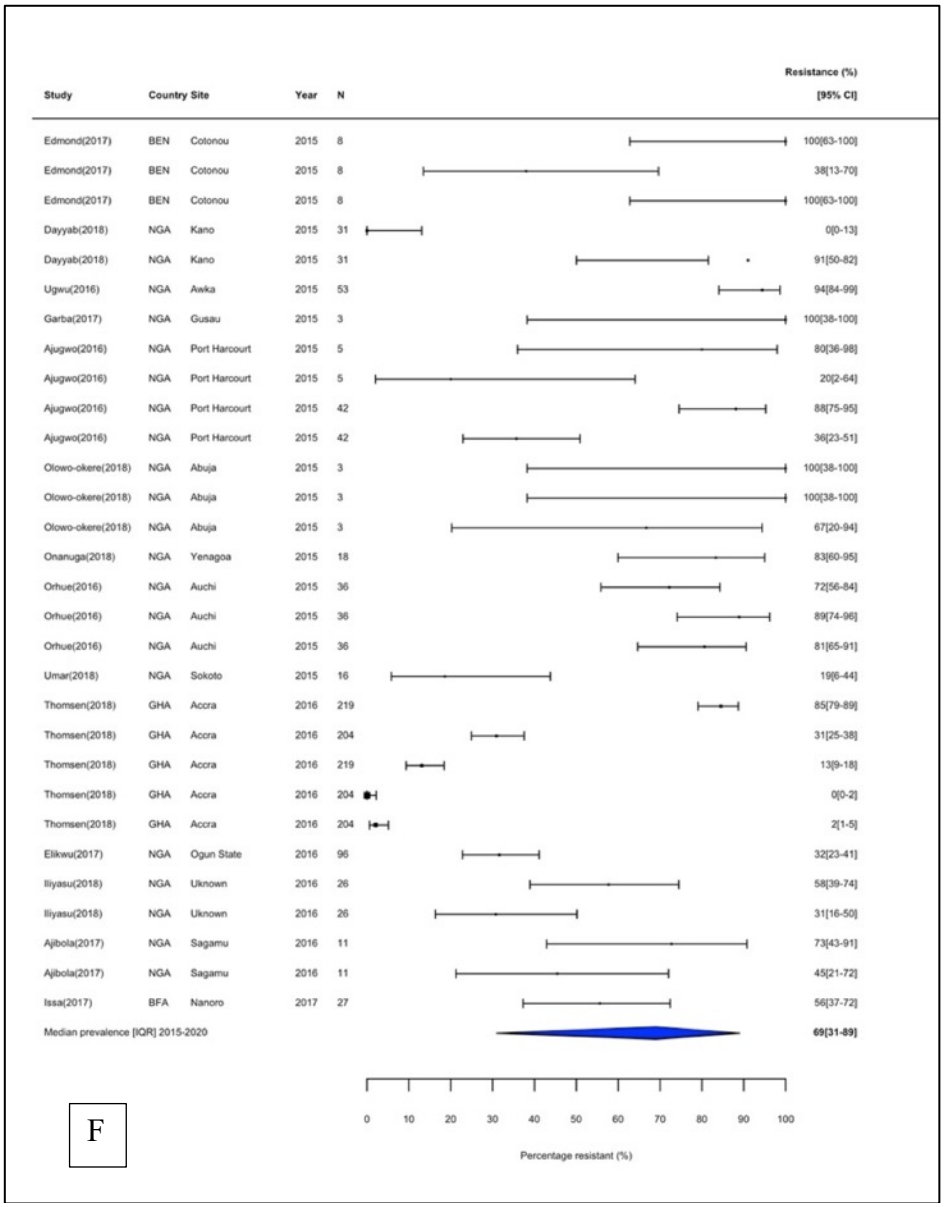
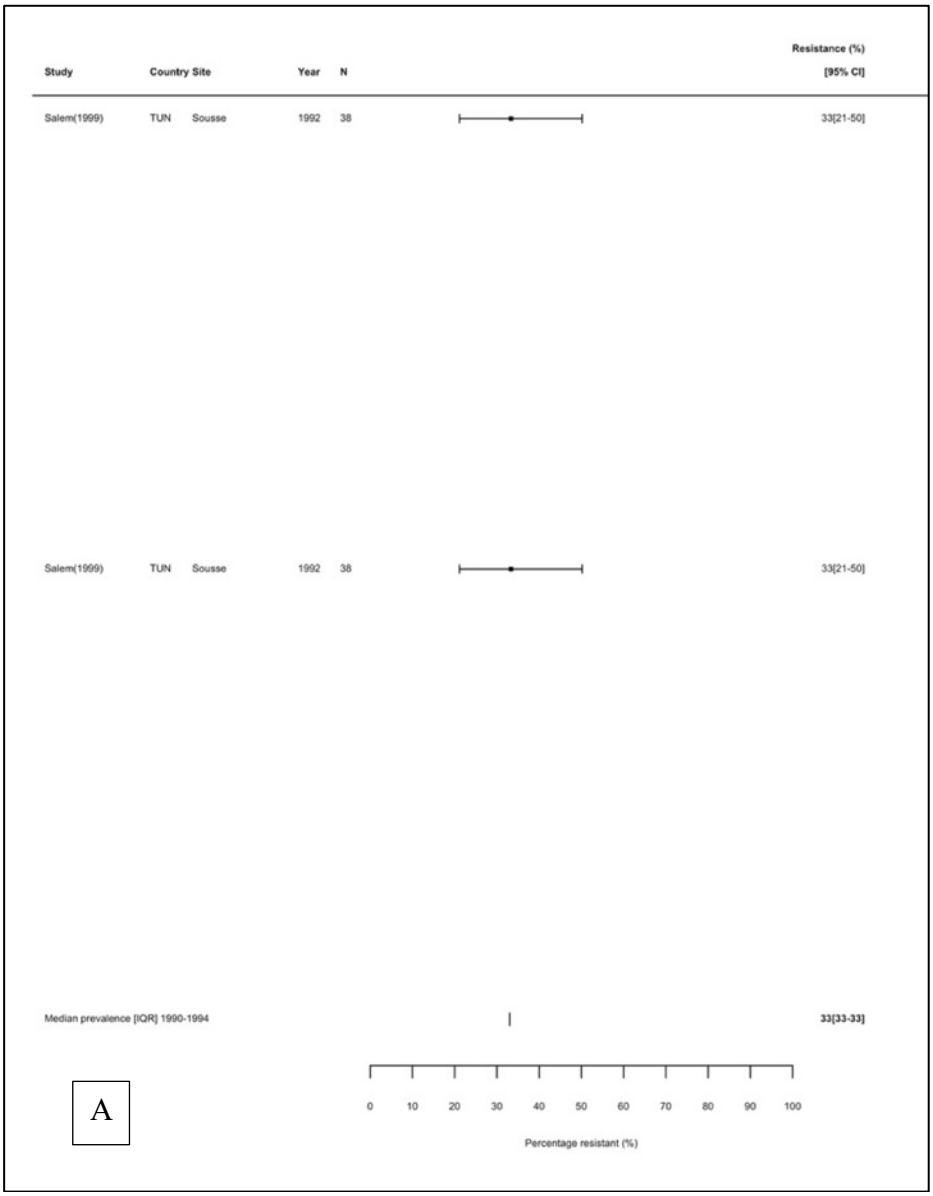
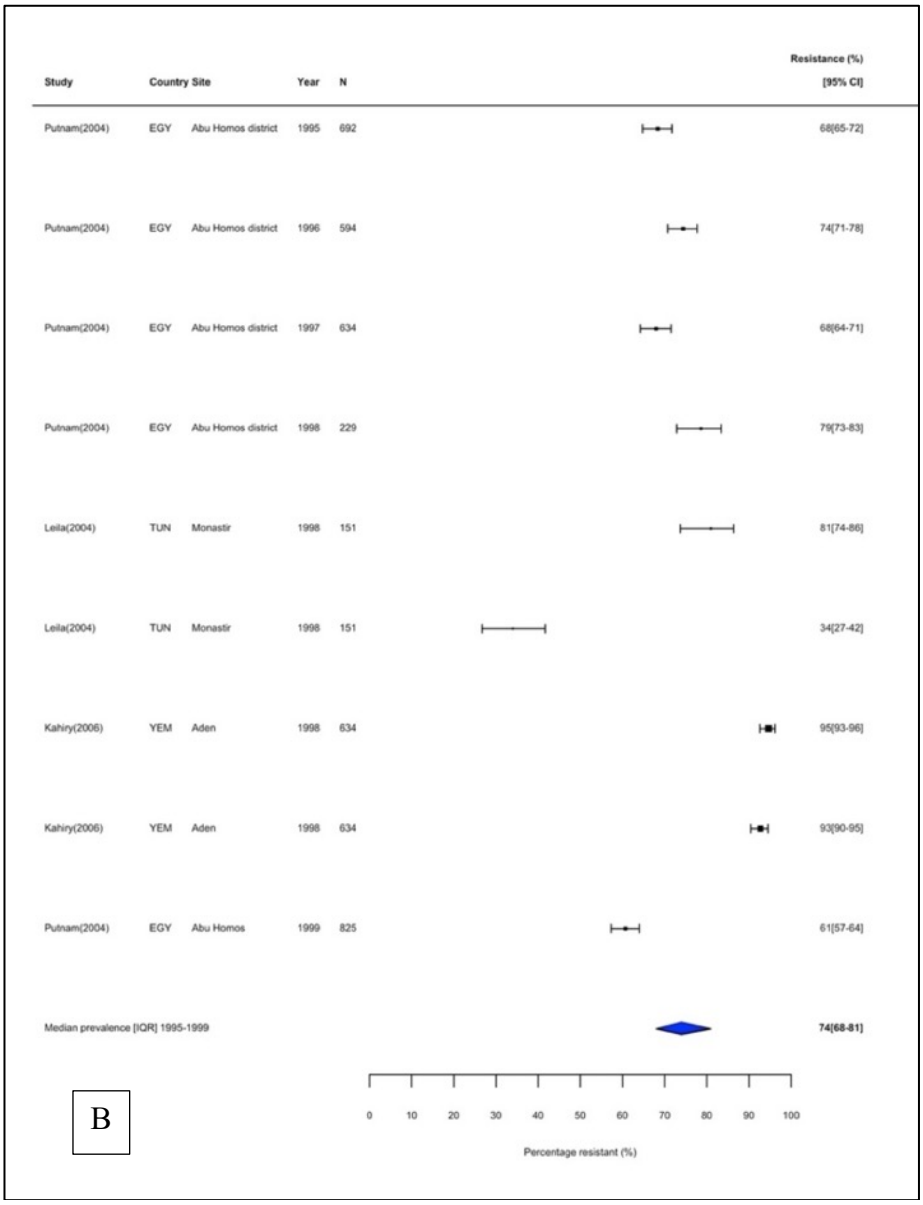
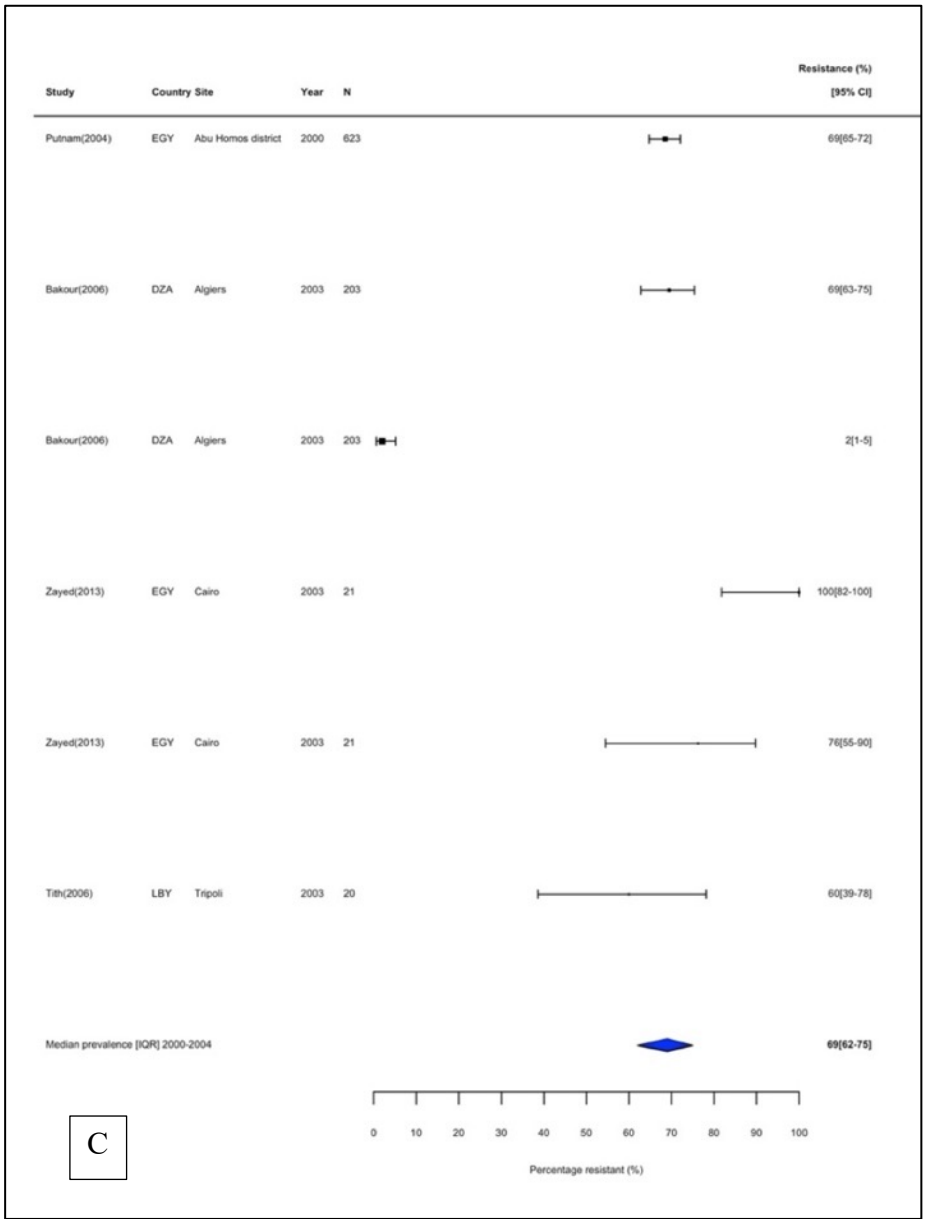


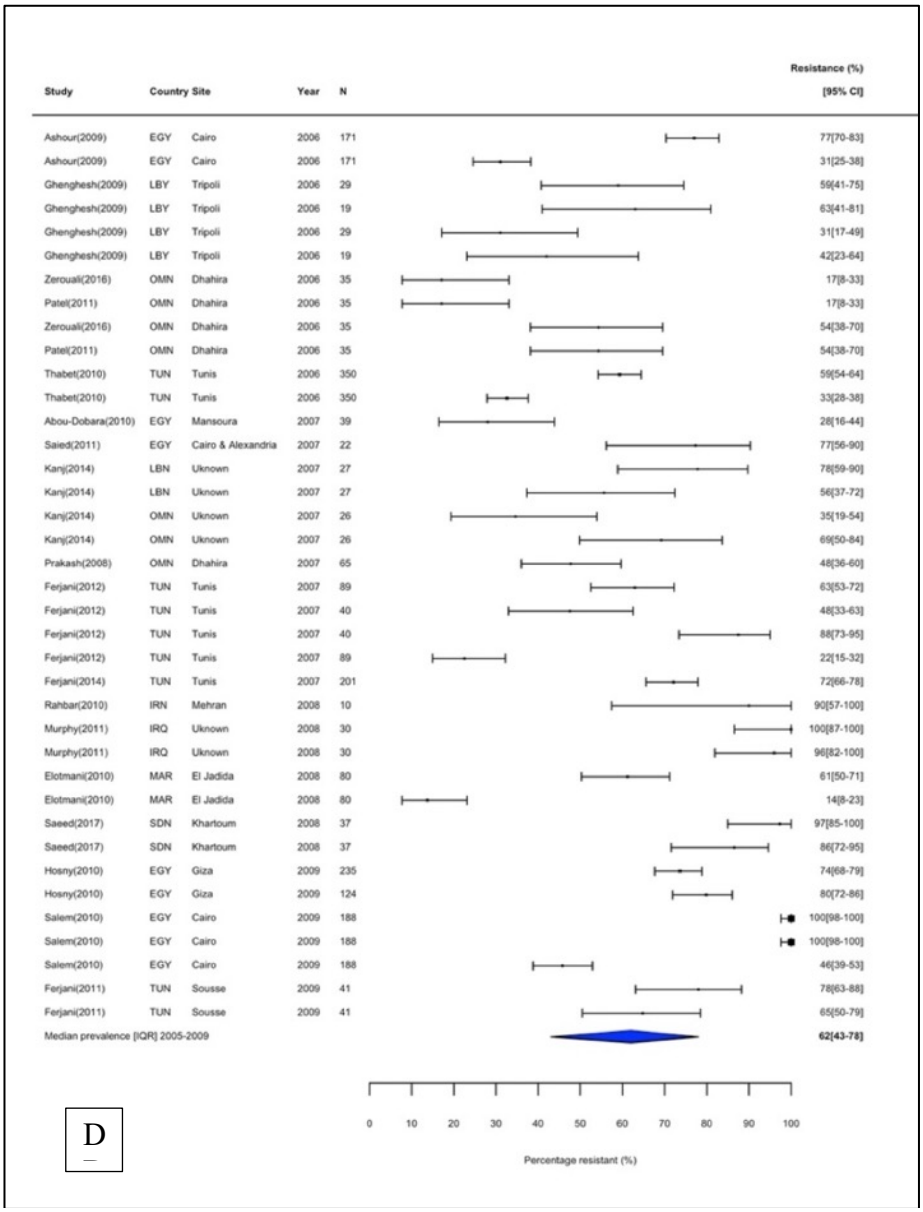
Figure C.21: Forest plot of penicillin resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B:2000-2004 C:2005-2009, D: 2010-2012, E: 2013-2014, F: 2015-2018.

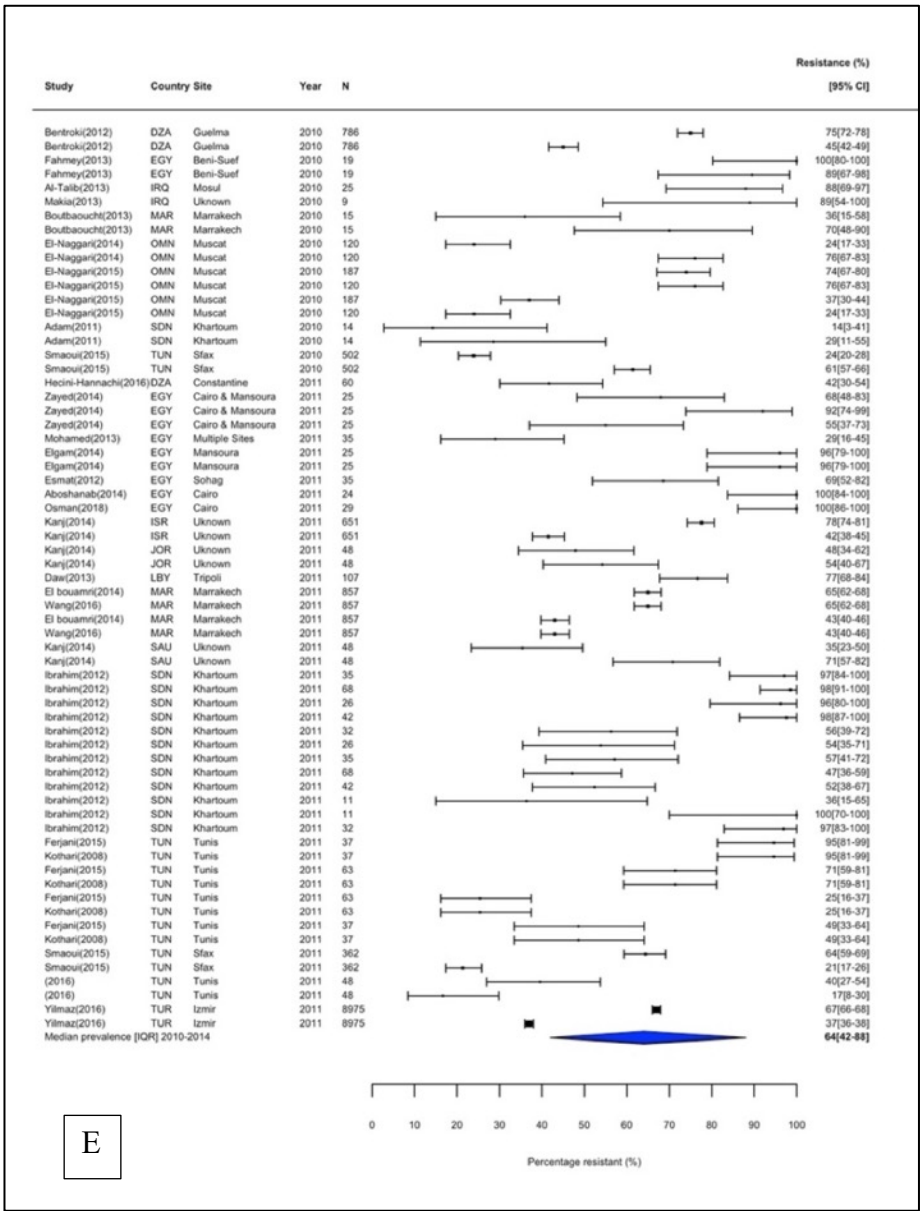

Study
Country Site
Year
N
Resistance (%)
[95% CI]
Salem(1999) TUN Sousse 1992 38 33[21-50]
Salem(1999) TUN Sousse 1992 38 33[21-50]
Median prevalence [IQR] 1990-1994 33[33-33]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Putnam(2004) EGY Abu Homos district 1995 692 68[65-72]
Putnam(2004) EGY Abu Homos district 1996 594 74[71-78]
Putnam(2004) EGY Abu Homos district 1997 634 68[64-71]
Putnam(2004) EGY Abu Homos district 1998 229 79[73-83]
Leila(2004) TUN Monastir 1998 151 81[74-86]
Leila(2004) TUN Monastir 1998 151 34[27-42]
Kahiry(2006) YEM Aden 1998 634 95[93-96]
Kahiry(2006) YEM Aden 1998 634 93[90-95]
Putnam(2004) EGY Abu Homos 1999 825 61[57-64]
Median prevalence [IQR] 1995-1999 74(68-81)
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
B

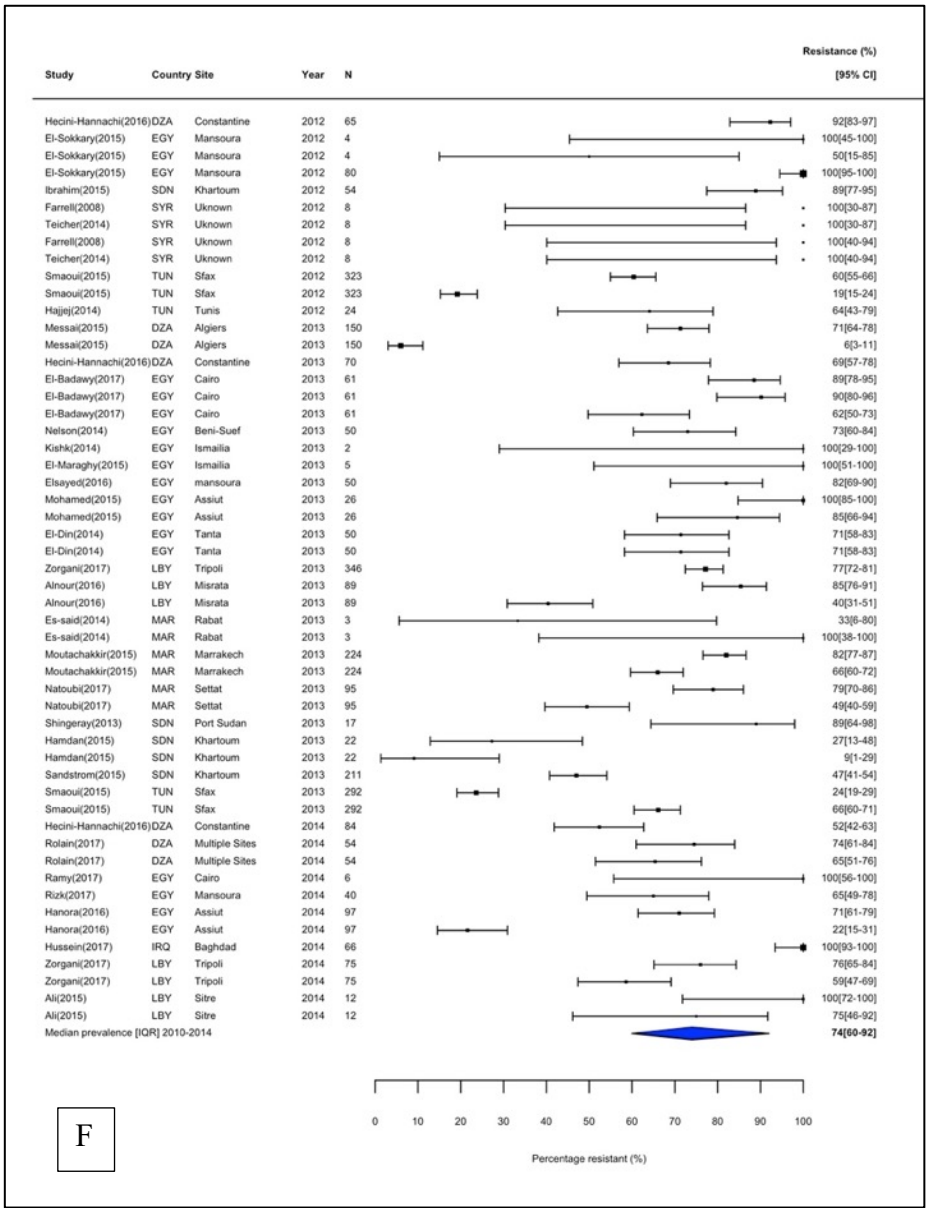

Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Putnam(2004) EGY Abu Homos district 2000 623 69[65-72]
Bakour(2006) DZA Algiers 2003 203 69[63-75]
Bakour(2006) DZA Algiers 2003 203 2[1-5]
Zayed(2013) EGY Cairo 2003 21 100[82-100]
Zayed(2013) EGY Cairo 2003 21 76[55-90]
Tith(2006) LBY Tripoli 2003 20 60[39-78]
Median prevalence [IQR] 2000-2004 69[62-75]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

C


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Ashour(2009) EGY Cairo 2006 171 77[70-83]
Ashour(2009) EGY Cairo 2006 171 31[25-38]
Ghenghesh(2009) LBY Tripoli 2006 29 59[41-75]
Ghenghesh(2009) LBY Tripoli 2006 19 63[41-81]
Ghenghesh(2009) LBY Tripoli 2006 29 31[17-49]
Ghenghesh(2009) LBY Tripoli 2006 19 42[23-64]
Zerouali(2016) OMN Dhahira 2006 35 17[8-33]
Patel(2011) OMN Dhahira 2006 35 17[8-33]
Zerouali(2016) OMN Dhahira 2006 35 54[38-70]
Patel(2011) OMN Dhahira 2006 35 54[38-70]
Thabet(2010) TUN Tunis 2006 350 59[54-64]
Thabet(2010) TUN Tunis 2006 350 33[28-38]
Abou-Dobara(2010) EGY Mansoura 2007 39 28[16-44]
Saied(2011) EGY Cairo & Alexandria 2007 22 77[56-90]
Kanj(2014) LBN Uknown 2007 27 78[59-90]
Kanj(2014) LBN Uknown 2007 27 56[37-72]
Kanj(2014) OMN Uknown 2007 26 35[19-54]
Kanj(2014) OMN Uknown 2007 26 69[50-84]
Prakash(2008) OMN Dhahira 2007 65 48[36-60]
Ferjani(2012) TUN Tunis 2007 89 63[53-72]
Ferjani(2012) TUN Tunis 2007 40 48[33-63]
Ferjani(2012) TUN Tunis 2007 40 88[73-95]
Ferjani(2012) TUN Tunis 2007 89 22[15-32]
Ferjani(2014) TUN Tunis 2007 201 72[66-78]
Rahbar(2010) IRN Mehran 2008 10 90[57-100]
Murphy(2011) IRQ Uknown 2008 30 100[87-100]
Murphy(2011) IRQ Uknown 2008 30 96[82-100]
Elotmani(2010) MAR El Jadida 2008 80 61[50-71]
Elotmani(2010) MAR El Jadida 2008 80 14[8-23]
Saeed(2017) SDN Khartoum 2008 37 97[85-100]
Saeed(2017) SDN Khartoum 2008 37 86[72-95]
Hosny(2010) EGY Giza 2009 235 74[68-79]
Hosny(2010) EGY Giza 2009 124 80[72-86]
Salem(2010) EGY Cairo 2009 188 100[98-100]
Salem(2010) EGY Cairo 2009 188 100[98-100]
Salem(2010) EGY Cairo 2009 188 46[39-53]
Ferjani(2011) TUN Sousse 2009 41 78[63-88]
Ferjani(2011) TUN Sousse 2009 41 65[50-79]
Median prevalence [IQR] 2005-2009 62[43-78]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
D


Resistance (%)
Study Country Site Year N [95% CI]
Bentroki(2012) DZA Guelma 2010 786 75[72-78]
Bentroki(2012) DZA Guelma 2010 786 45[42-49]
Fahmey(2013) EGY Beni-Suef 2010 19 100[80-100]
Fahmey(2013) EGY Beni-Suef 2010 19 89[67-98]
Al-Talib(2013) IRQ Mosul 2010 25 88[69-97]
Makia(2013) IRQ Uknown 2010 9 89[54-100]
Boutbaoucht(2013) MAR Marrakech 2010 15 36[15-58]
Boutbaoucht(2013) MAR Marrakech 2010 15 70[48-90]
El-Naggari(2014) OMN Muscat 2010 120 24[17-33]
El-Naggari(2014) OMN Muscat 2010 120 76[67-83]
El-Naggari(2015) OMN Muscat 2010 187 74[67-80]
El-Naggari(2015) OMN Muscat 2010 120 76[67-83]
El-Naggari(2015) OMN Muscat 2010 187 37[30-44]
El-Naggari(2015) OMN Muscat 2010 120 24[17-33]
Adam(2011) SDN Khartoum 2010 14 14[3-41]
Adam(2011) SDN Khartoum 2010 14 29[11-55]
Smaoui(2015) TUN Sfax 2010 502 24[20-28]
Smaoui(2015) TUN Sfax 2010 502 61[57-66]
Hecini-Hannachi(2016) DZA Constantine 2011 60 42[30-54]
Zayed(2014) EGY Cairo & Mansoura 2011 25 68[48-83]
Zayed(2014) EGY Cairo & Mansoura 2011 25 92[74-99]
Zayed(2014) EGY Cairo & Mansoura 2011 25 55[37-73]
Mohamed(2013) EGY Multiple Sites 2011 35 29[16-45]
Elgam(2014) EGY Mansoura 2011 25 96[79-100]
Elgam(2014) EGY Mansoura 2011 25 96[79-100]
Esmat(2012) EGY Sohag 2011 35 69[52-82]
Aboshanab(2014) EGY Cairo 2011 24 100[84-100]
Osman(2018) EGY Cairo 2011 29 100[86-100]
Kanj(2014) ISR Uknown 2011 651 78[74-81]
Kanj(2014) ISR Uknown 2011 651 42[38-45]
Kanj(2014) JOR Uknown 2011 48 48[34-62]
Kanj(2014) JOR Uknown 2011 48 54[40-67]
Daw(2013) LBY Tripoli 2011 107 77[68-84]
El bouamri(2014) MAR Marrakech 2011 857 65[62-68]
Wang(2016) MAR Marrakech 2011 857 65[62-68]
El bouamri(2014) MAR Marrakech 2011 857 43[40-46]
Wang(2016) MAR Marrakech 2011 857 43[40-46]
Kanj(2014) SAU Uknown 2011 48 35[23-50]
Kanj(2014) SAU Uknown 2011 48 71[57-82]
Ibrahim(2012) SDN Khartoum 2011 35 97[84-100]
Ibrahim(2012) SDN Khartoum 2011 68 98[91-100]
Ibrahim(2012) SDN Khartoum 2011 26 96[80-100]
Ibrahim(2012) SDN Khartoum 2011 42 98[87-100]
Ibrahim(2012) SDN Khartoum 2011 32 56[39-72]
Ibrahim(2012) SDN Khartoum 2011 26 54[35-71]
Ibrahim(2012) SDN Khartoum 2011 35 57[41-72]
Ibrahim(2012) SDN Khartoum 2011 68 47[36-59]
Ibrahim(2012) SDN Khartoum 2011 42 52[38-67]
Ibrahim(2012) SDN Khartoum 2011 11 36[15-65]
Ibrahim(2012) SDN Khartoum 2011 11 100[70-100]
Ibrahim(2012) SDN Khartoum 2011 32 97[83-100]
Ferjani(2015) TUN Tunis 2011 37 95[81-99]
Kothari(2008) TUN Tunis 2011 37 95[81-99]
Ferjani(2015) TUN Tunis 2011 63 71[59-81]
Kothari(2008) TUN Tunis 2011 63 71[59-81]
Ferjani(2015) TUN Tunis 2011 63 25[16-37]
Kothari(2008) TUN Tunis 2011 63 25[16-37]
Ferjani(2015) TUN Tunis 2011 37 49[33-64]
Kothari(2008) TUN Tunis 2011 37 49[33-64]
Smaoui(2015) TUN Sfax 2011 362 64[59-69]
Smaoui(2015) TUN Sfax 2011 362 21[17-26]
(2016) TUN Tunis 2011 48 40[27-54]
(2016) TUN Tunis 2011 48 17[8-30]
Yilmaz(2016) TUR Izmir 2011 8975 67[66-68]
Yilmaz(2016) TUR Izmir 2011 8975 37[36-38]
Median prevalence [IQR] 2010-2014 64[42-88]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

E


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Hecini-Hannachi(2016) DZA Constantine 2012 65 92[83-97]
El-Sokkary(2015) EGY Mansoura 2012 4 100[45-100]
El-Sokkary(2015) EGY Mansoura 2012 4 50[15-85]
El-Sokkary(2015) EGY Mansoura 2012 80 100[95-100]
Ibrahim(2015) SDN Khartoum 2012 54 89[77-95]
Farrell(2008) SYR Uknown 2012 8 100[30-87]
Teicher(2014) SYR Uknown 2012 8 100[30-87]
Farrell(2008) SYR Uknown 2012 8 100[40-94]
Teicher(2014) SYR Uknown 2012 8 100[40-94]
Smaoui(2015) TUN Sfax 2012 323 60[55-66]
Smaoui(2015) TUN Sfax 2012 323 19[15-24]
Hajjej(2014) TUN Tunis 2012 24 64[43-79]
Messai(2015) DZA Algiers 2013 150 71[64-78]
Messai(2015) DZA Algiers 2013 150 6[3-11]
Hecini-Hannachi(2016) DZA Constantine 2013 70 69[57-78]
El-Badawy(2017) EGY Cairo 2013 61 89[78-95]
El-Badawy(2017) EGY Cairo 2013 61 90[80-96]
El-Badawy(2017) EGY Cairo 2013 61 62[50-73]
Nelson(2014) EGY Beni-Suef 2013 50 73[60-84]
Kishk(2014) EGY Ismailia 2013 2 100[29-100]
El-Maraghy(2015) EGY Ismailia 2013 5 100[51-100]
Elsayed(2016) EGY mansoura 2013 50 82[69-90]
Mohamed(2015) EGY Assiut 2013 26 100[85-100]
Mohamed(2015) EGY Assiut 2013 26 85[66-94]
El-Din(2014) EGY Tanta 2013 50 71[58-83]
El-Din(2014) EGY Tanta 2013 50 71[58-83]
Zorgani(2017) LBY Tripoli 2013 346 77[72-81]
Alnour(2016) LBY Misrata 2013 89 85[76-91]
Alnour(2016) LBY Misrata 2013 89 40[31-51]
Es-said(2014) MAR Rabat 2013 3 33[6-80]
Es-said(2014) MAR Rabat 2013 3 100[38-100]
Moutachakkir(2015) MAR Marrakech 2013 224 82[77-87]
Moutachakkir(2015) MAR Marrakech 2013 224 66[60-72]
Natoubi(2017) MAR Settat 2013 95 79[70-86]
Natoubi(2017) MAR Settat 2013 95 49[40-59]
Shingeray(2013) SDN Port Sudan 2013 17 89[64-98]
Hamdan(2015) SDN Khartoum 2013 22 27[13-48]
Hamdan(2015) SDN Khartoum 2013 22 9[1-29]
Sandstrom(2015) SDN Khartoum 2013 211 47[41-54]
Smaoui(2015) TUN Sfax 2013 292 24[19-29]
Smaoui(2015) TUN Sfax 2013 292 66[60-71]
Hecini-Hannachi(2016) DZA Constantine 2014 84 52[42-63]
Rolain(2017) DZA Multiple Sites 2014 54 74[61-84]
Rolain(2017) DZA Multiple Sites 2014 54 65[51-76]
Ramy(2017) EGY Cairo 2014 6 100[56-100]
Rizk(2017) EGY Mansoura 2014 40 65[49-78]
Hanora(2016) EGY Assiut 2014 97 71[61-79]
Hanora(2016) EGY Assiut 2014 97 22[15-31]
Hussein(2017) IRQ Baghdad 2014 66 100[93-100]
Zorgani(2017) LBY Tripoli 2014 75 76[65-84]
Zorgani(2017) LBY Tripoli 2014 75 59[47-69]
Ali(2015) LBY Sitre 2014 12 100[72-100]
Ali(2015) LBY Sitre 2014 12 75[46-92]
Median prevalence [IQR] 2010-2014 74[60-92]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

F

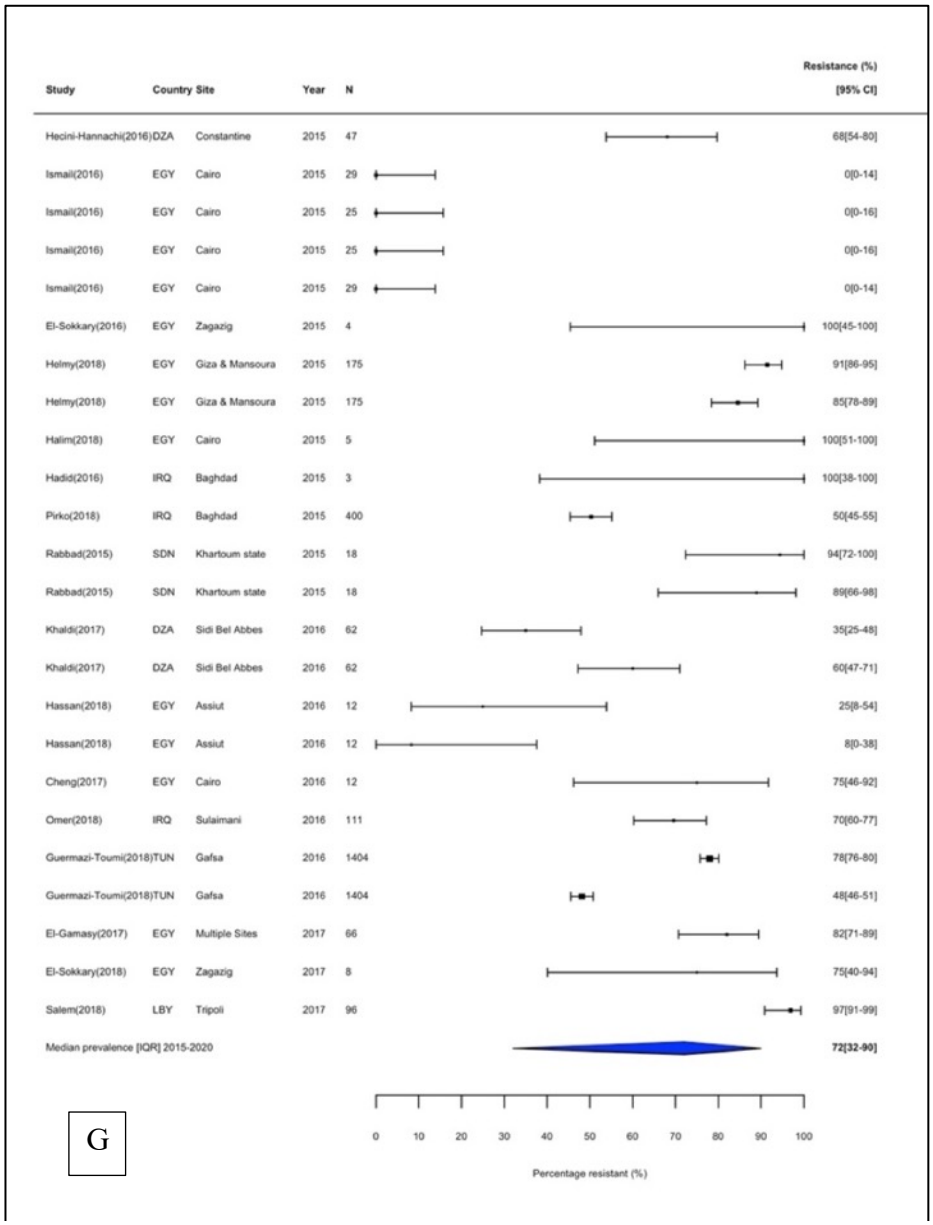


Figure C.22: Forest plot of penicillin resistance in North Africa and the Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1994, B:1995-1999, C: 2000-2004, D: 2005-2009, E: 2010-2012, F: 2013-2015, G:2016-2018.

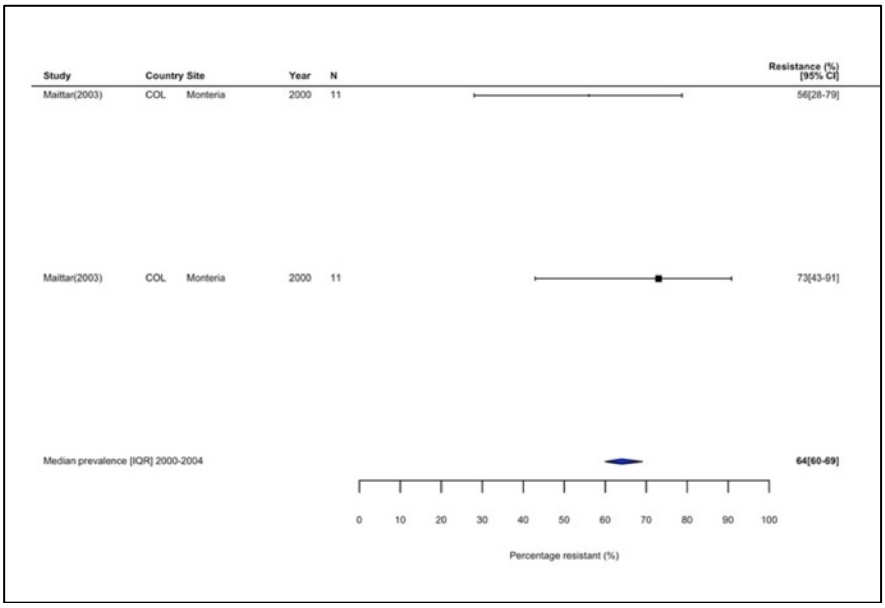


Figure C.23: Forest plot of penicillin resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

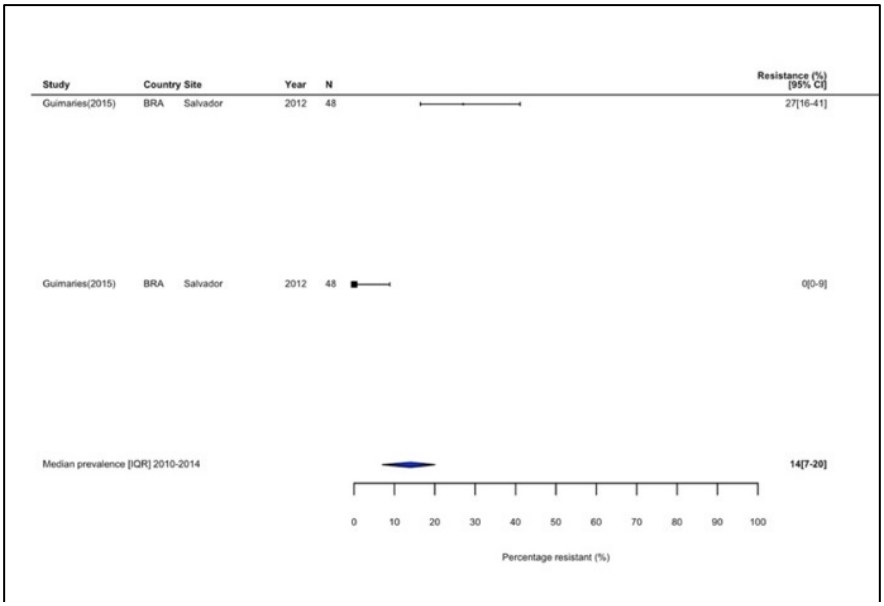


Figure C.24: Forest plot of penicillin resistance in Tropical Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

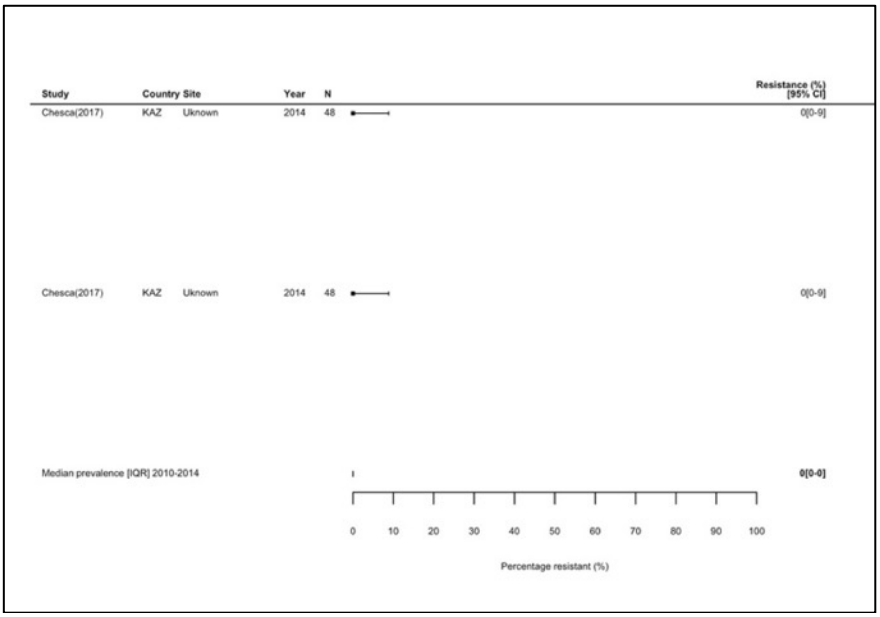
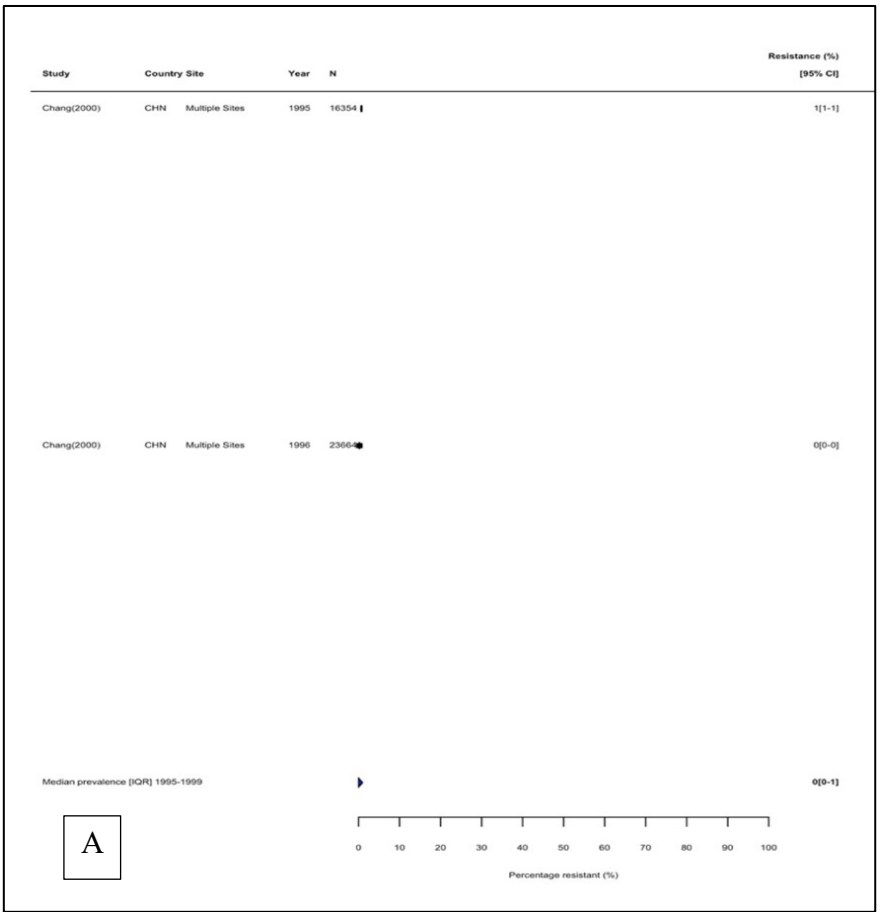
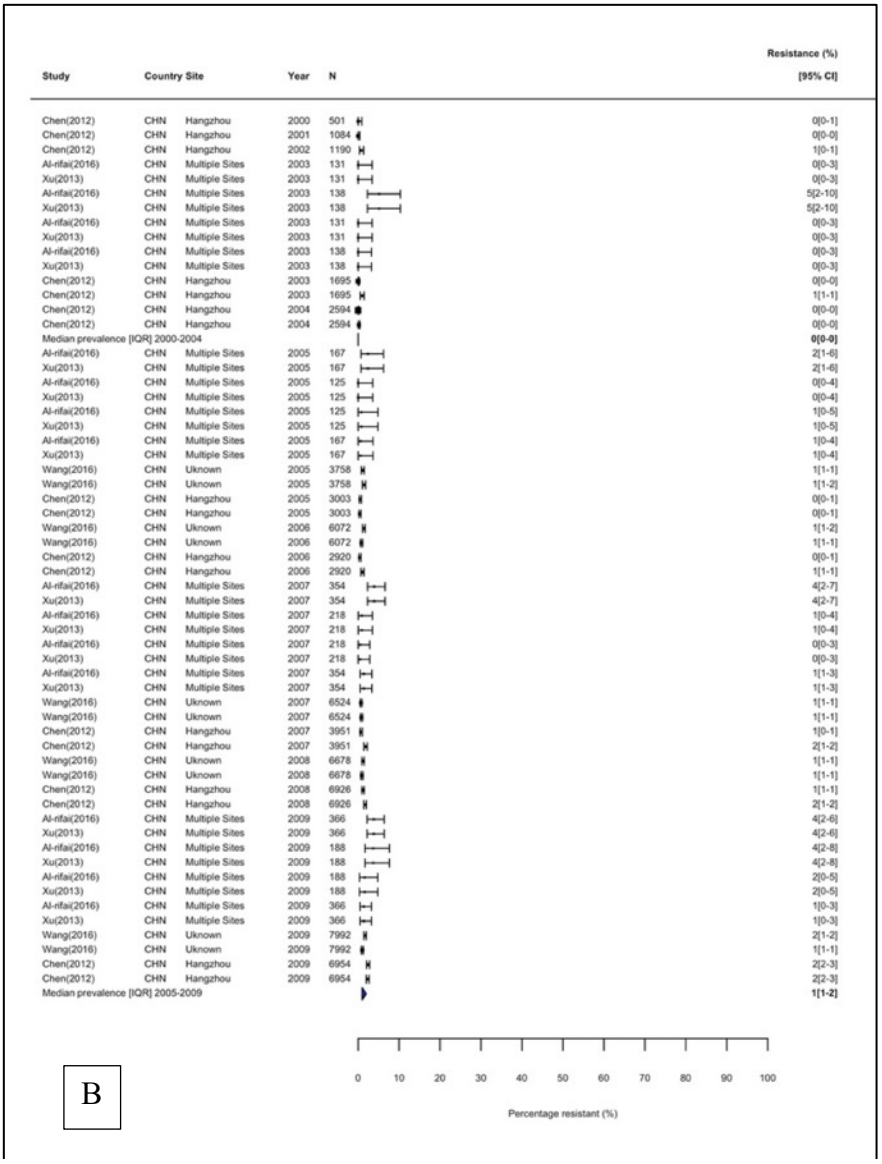


Figure C.25: Forest plot of carbapenems resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.




Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Chen(2012) CHN Hangzhou 2000 501 0[0-1]
Chen(2012) CHN Hangzhou 2001 1084 0[0-0]
Chen(2012) CHN Hangzhou 2002 1190 1[0-1]
Al-rifai(2016) CHN Multiple Sites 2003 131 0[0-3]
Xu(2013) CHN Multiple Sites 2003 131 0[0-3]
Al-rifai(2016) CHN Multiple Sites 2003 138 5[2-10]
Xu(2013) CHN Multiple Sites 2003 138 5[2-10]
Al-rifai(2016) CHN Multiple Sites 2003 131 0[0-3]
Xu(2013) CHN Multiple Sites 2003 131 0[0-3]
Al-rifai(2016) CHN Multiple Sites 2003 138 0[0-3]
Xu(2013) CHN Multiple Sites 2003 138 0[0-3]
Chen(2012) CHN Hangzhou 2003 1695 0[0-0]
Chen(2012) CHN Hangzhou 2003 1695 1[1-1]
Chen(2012) CHN Hangzhou 2004 2594 0[0-0]
Chen(2012) CHN Hangzhou 2004 2594 0[0-0]
Median prevalence [IQR] 2000-2004 0[0-0]
Al-rifai(2016) CHN Multiple Sites 2005 167 2[1-6]
Xu(2013) CHN Multiple Sites 2005 167 2[1-6]
Al-rifai(2016) CHN Multiple Sites 2005 125 0[0-4]
Xu(2013) CHN Multiple Sites 2005 125 0[0-4]
Al-rifai(2016) CHN Multiple Sites 2005 125 1[0-5]
Xu(2013) CHN Multiple Sites 2005 125 1[0-5]
Al-rifai(2016) CHN Multiple Sites 2005 167 1[0-4]
Xu(2013) CHN Multiple Sites 2005 167 1[0-4]
Wang(2016) CHN Uknown 2005 3758 1[1-1]
Wang(2016) CHN Uknown 2005 3758 1[1-2]
Chen(2012) CHN Hangzhou 2005 3003 0[0-1]
Chen(2012) CHN Hangzhou 2005 3003 0[0-1]
Wang(2016) CHN Uknown 2006 6072 1[1-2]
Wang(2016) CHN Uknown 2006 6072 1[1-1]
Chen(2012) CHN Hangzhou 2006 2920 0[0-1]
Chen(2012) CHN Hangzhou 2006 2920 1[1-1]
Al-rifai(2016) CHN Multiple Sites 2007 354 4[2-7]
Xu(2013) CHN Multiple Sites 2007 354 4[2-7]
Al-rifai(2016) CHN Multiple Sites 2007 218 1[0-4]
Xu(2013) CHN Multiple Sites 2007 218 1[0-4]
Al-rifai(2016) CHN Multiple Sites 2007 218 0[0-3]
Xu(2013) CHN Multiple Sites 2007 218 0[0-3]
Al-rifai(2016) CHN Multiple Sites 2007 354 1[1-3]
Xu(2013) CHN Multiple Sites 2007 354 1[1-3]
Wang(2016) CHN Uknown 2007 6524 1[1-1]
Wang(2016) CHN Uknown 2007 6524 1[1-1]
Chen(2012) CHN Hangzhou 2007 3951 1[0-1]
Chen(2012) CHN Hangzhou 2007 3951 2[1-2]
Wang(2016) CHN Uknown 2008 6678 1[1-1]
Wang(2016) CHN Uknown 2008 6678 1[1-1]
Chen(2012) CHN Hangzhou 2008 6926 1[1-1]
Chen(2012) CHN Hangzhou 2008 6926 2[1-2]
Al-rifai(2016) CHN Multiple Sites 2009 366 4[2-6]
Xu(2013) CHN Multiple Sites 2009 366 4[2-6]
Al-rifai(2016) CHN Multiple Sites 2009 188 4[2-8]
Xu(2013) CHN Multiple Sites 2009 188 4[2-8]
Al-rifai(2016) CHN Multiple Sites 2009 188 2[0-5]
Xu(2013) CHN Multiple Sites 2009 188 2[0-5]
Al-rifai(2016) CHN Multiple Sites 2009 366 1[0-3]
Xu(2013) CHN Multiple Sites 2009 366 1[0-3]
Wang(2016) CHN Uknown 2009 7992 2[1-2]
Wang(2016) CHN Uknown 2009 7992 1[1-1]
Chen(2012) CHN Hangzhou 2009 6954 2[2-3]
Chen(2012) CHN Hangzhou 2009 6954 2[2-3]
Median prevalence [IQR] 2005-2009 1[1-2]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B

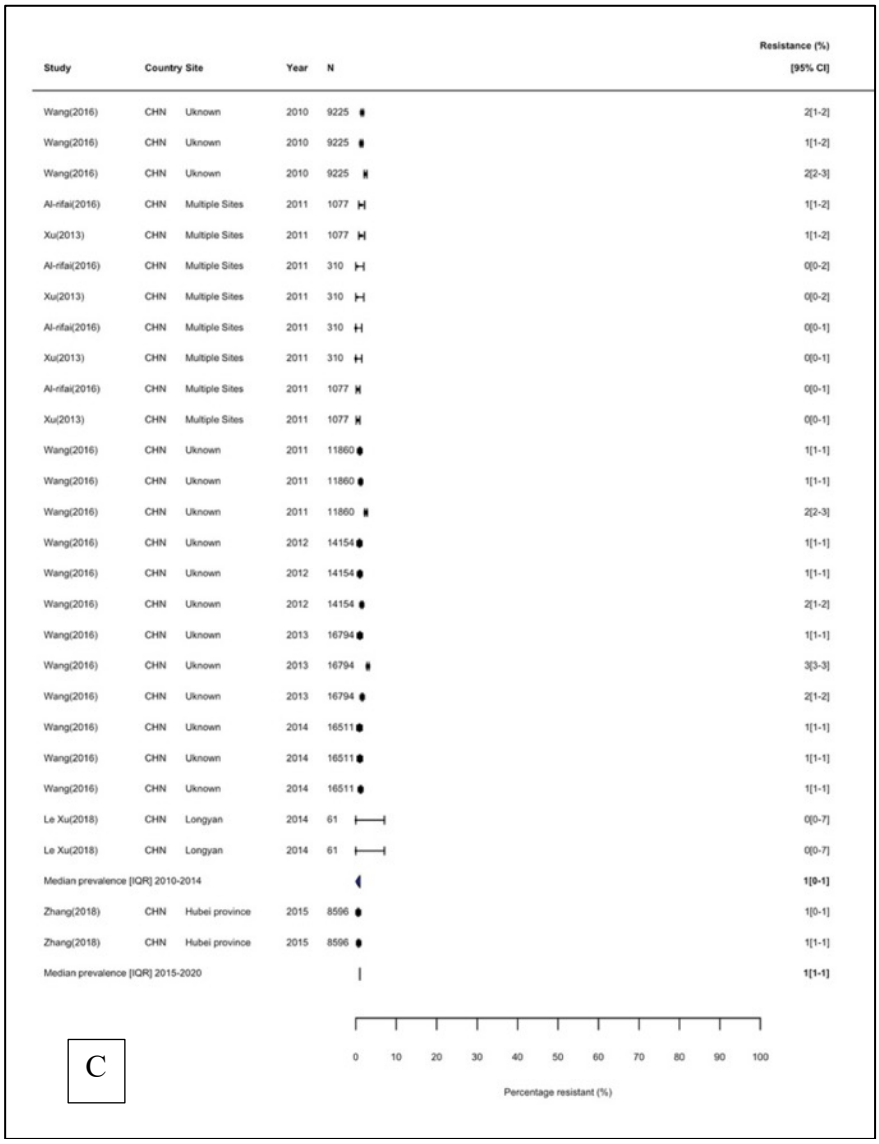


Figure C.26: Forest plot of carbapenems resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.

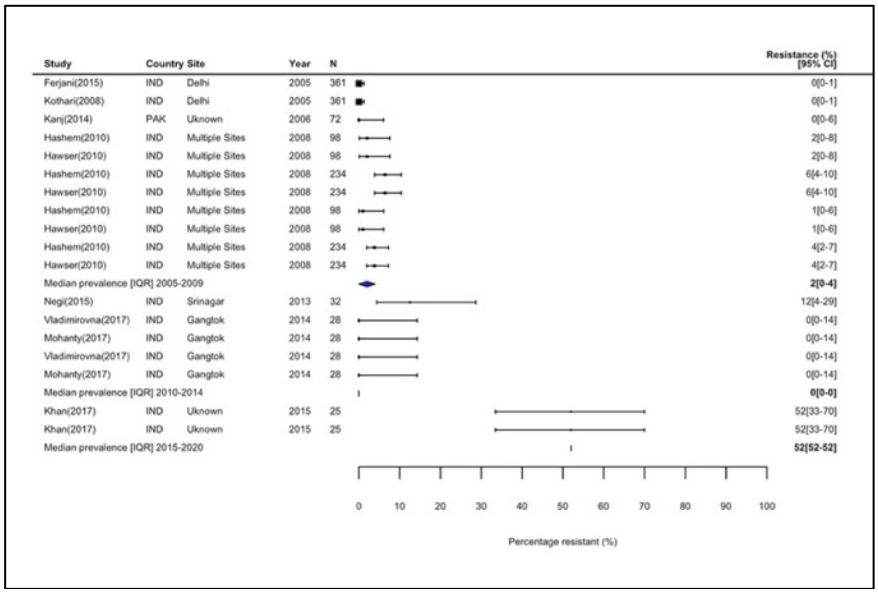


Figure C.27: Forest plot of carbapenems resistance in South Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

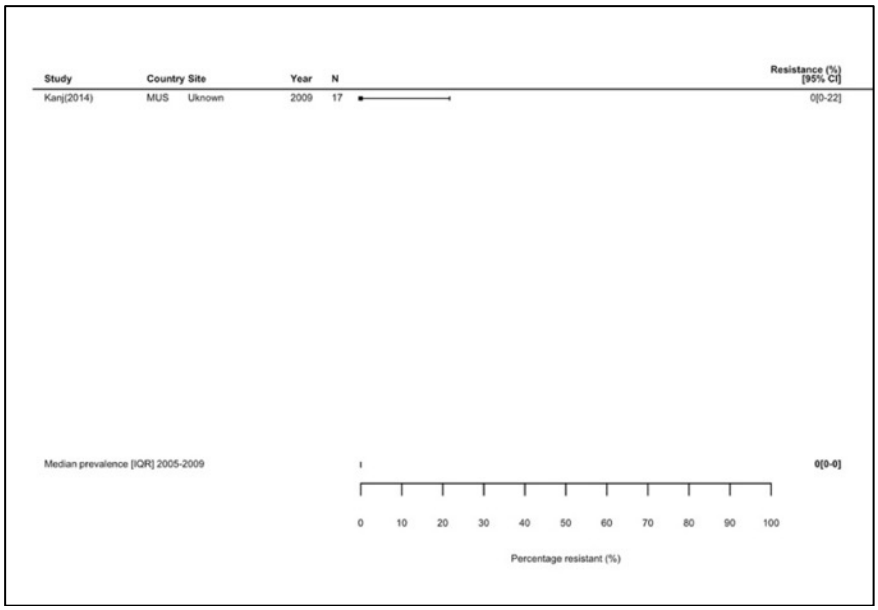


Figure C.28: Forest plot of carbapenems resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

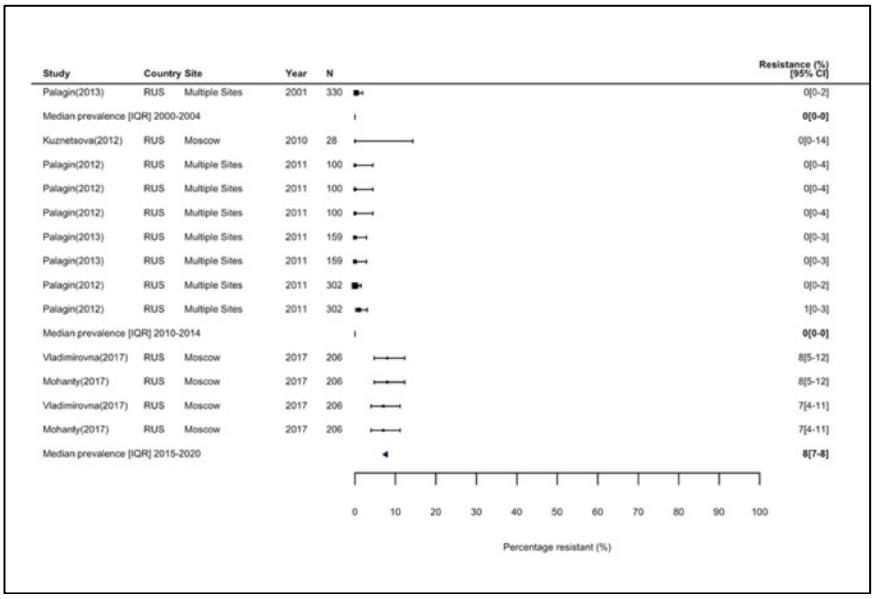


Figure C.29: Forest plot of carbapenems resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

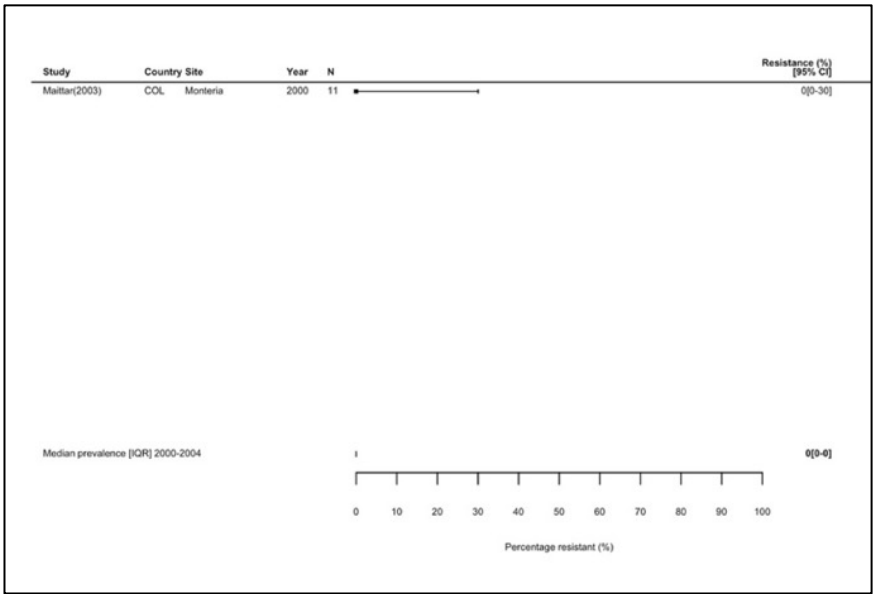


Figure C.30: Forest plot of carbapenems resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

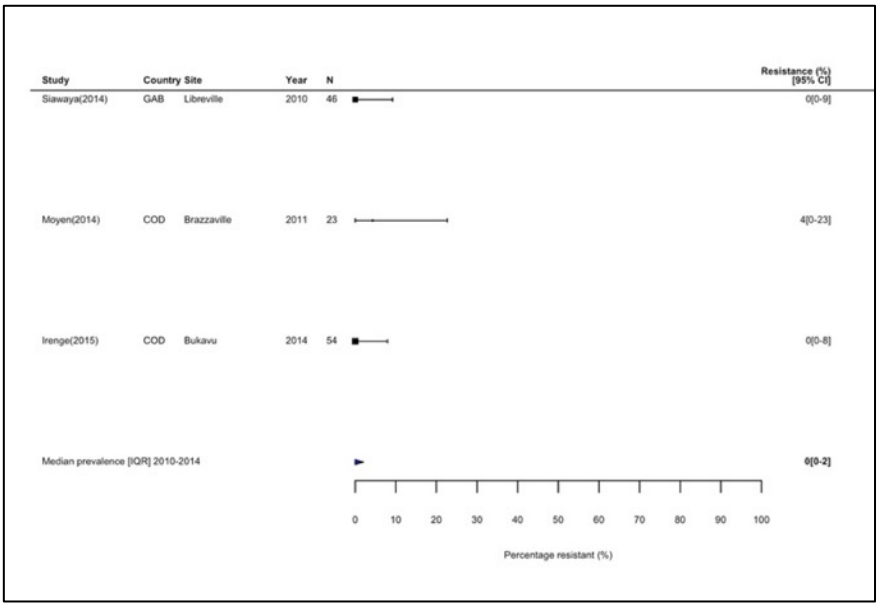


Figure C.31: Forest plot of carbapenems resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

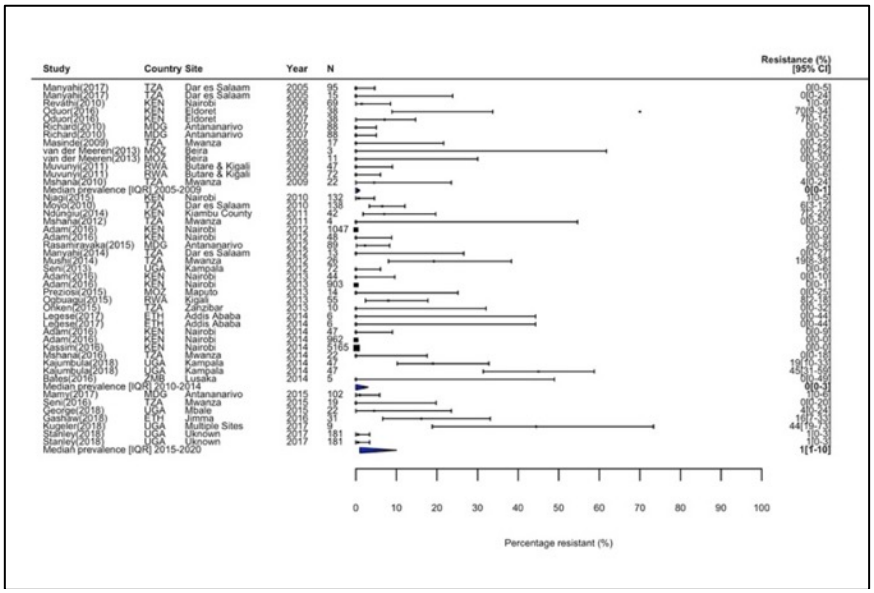


Figure C.32: Forest plot of carbapenems resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

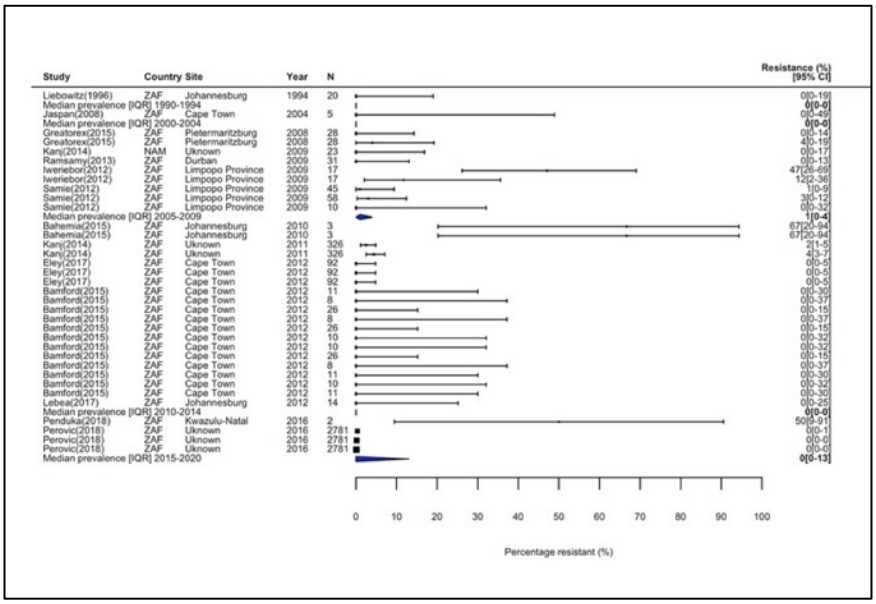
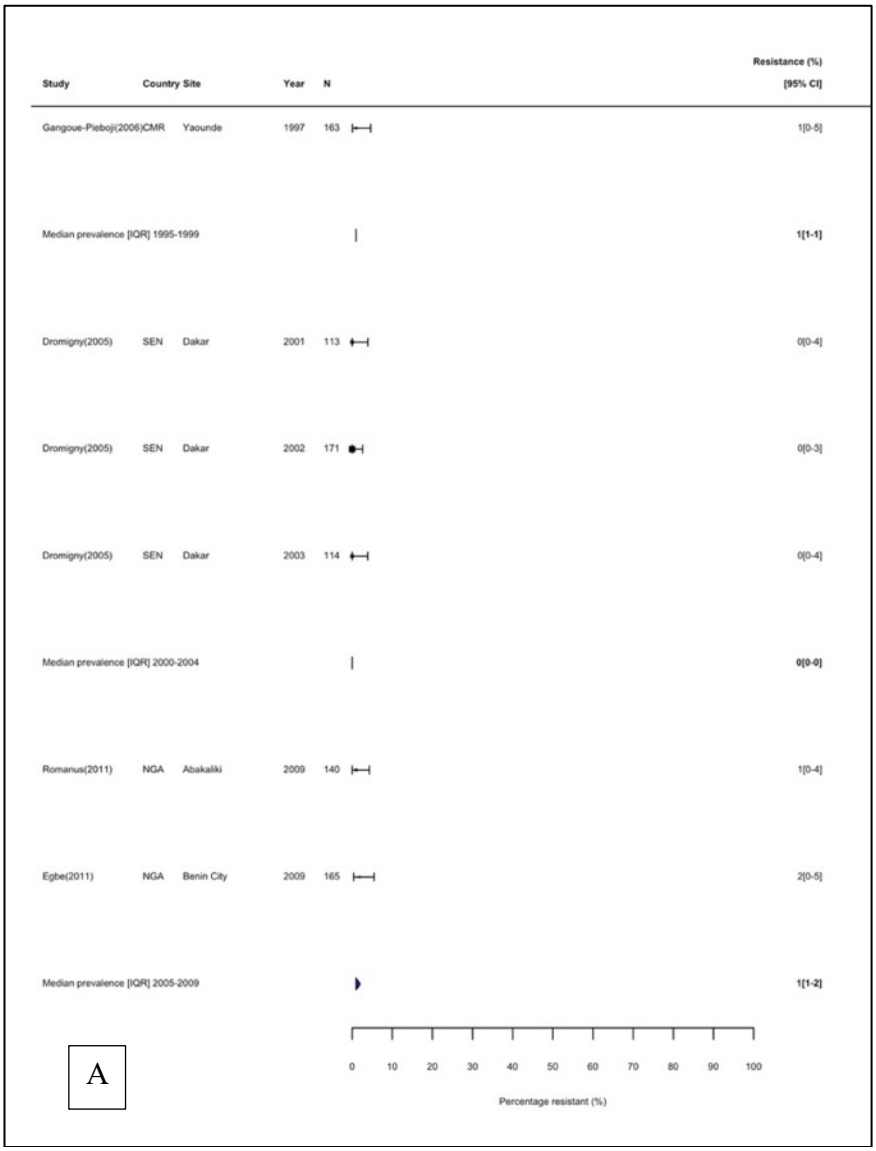


Figure C.33: Forest plot of carbapenems resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Gangoue-Pieboji(2006)
CMR
Yaounde
1997
163
1[0-5]
Median prevalence [IQR] 1995-1999
1[1-1]
Dromigny(2005)
SEN
Dakar
2001
113
0[0-4]
Dromigny(2005)
SEN
Dakar
2002
171
0[0-3]
Dromigny(2005)
SEN
Dakar
2003
114
0[0-4]
Median prevalence [IQR] 2000-2004
0[0-0]
Romanus(2011)
NGA
Abakaliki
2009
140
1[0-4]
Egbe(2011)
NGA
Benin City
2009
165
2[0-5]
Median prevalence [IQR] 2005-2009
1[1-2]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A

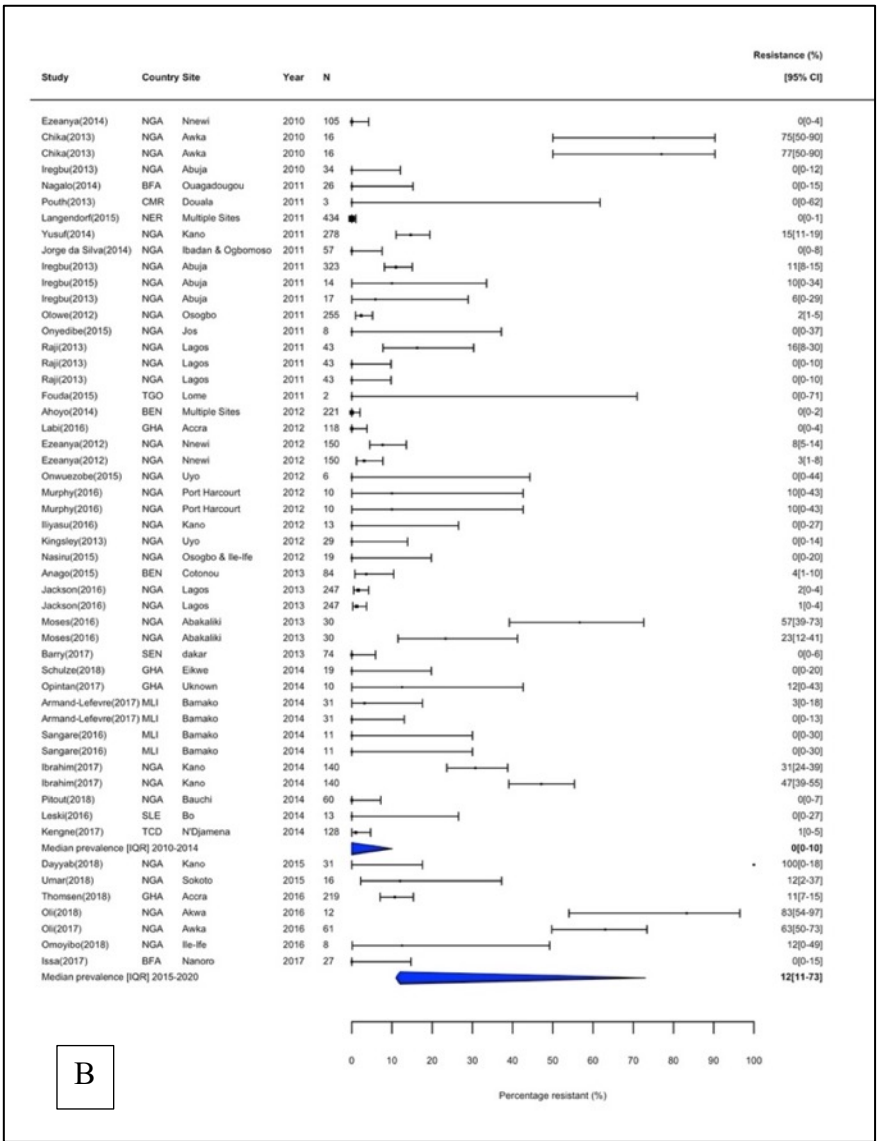
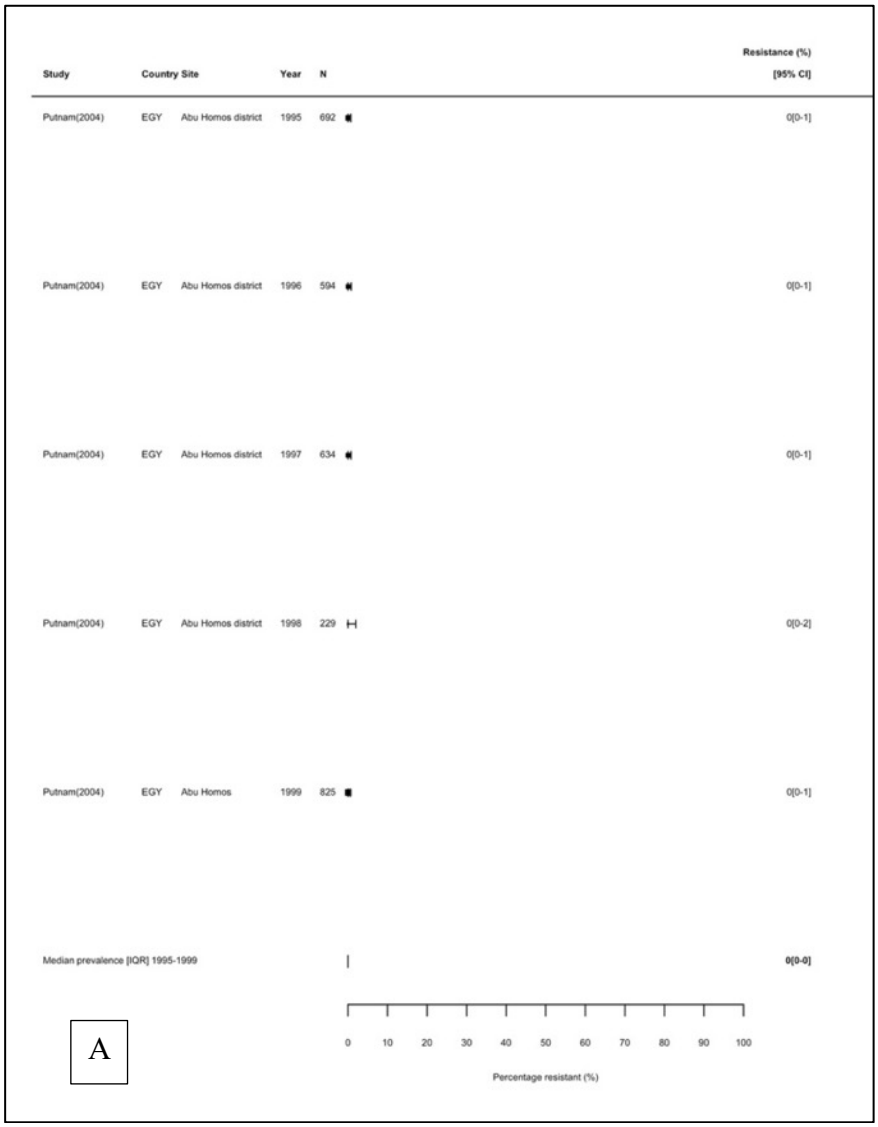
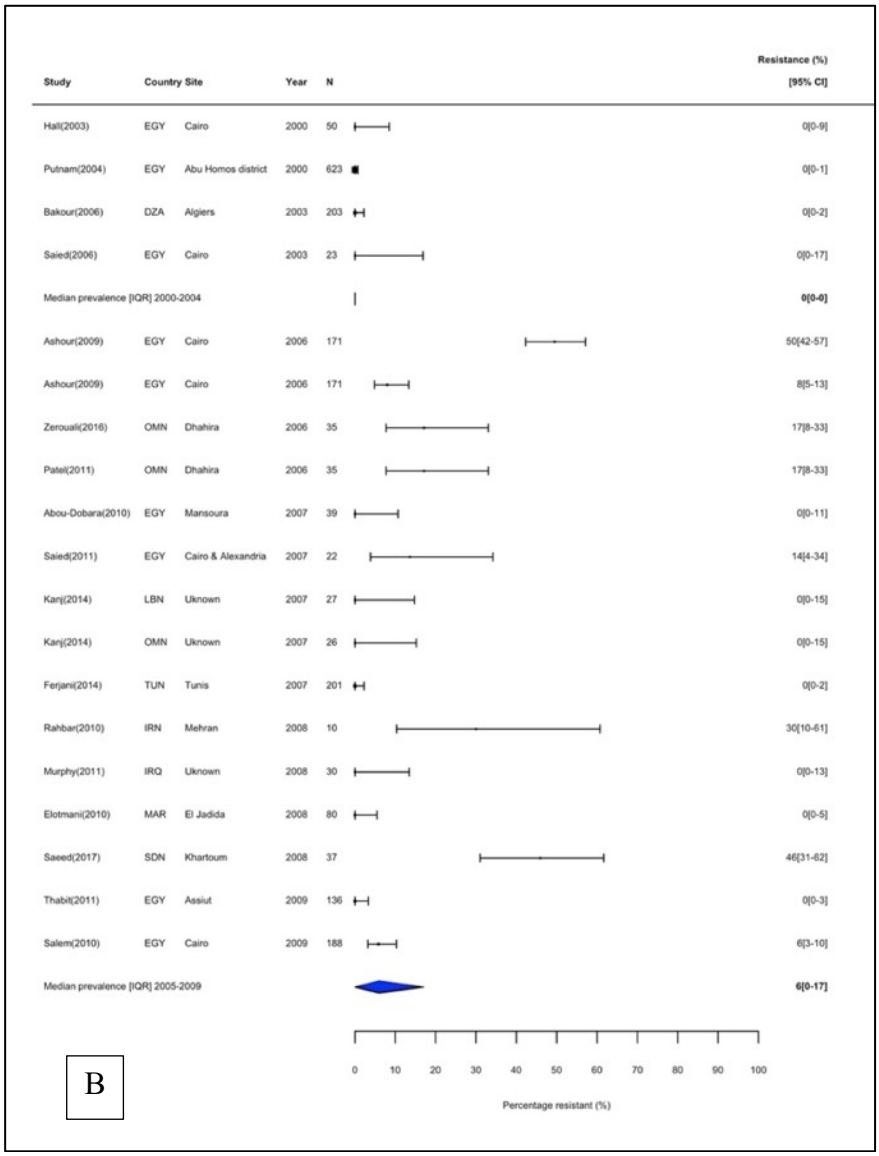


Figure C.34: Forest plot of carbapenems resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-2009, B: 2010-2018.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Putnam(2004) EGY Abu Homos district 1995 692 0[0-1]
Putnam(2004) EGY Abu Homos district 1996 594 0[0-1]
Putnam(2004) EGY Abu Homos district 1997 634 0[0-1]
Putnam(2004) EGY Abu Homos district 1998 229 0[0-2]
Putnam(2004) EGY Abu Homos 1999 825 0[0-1]
Median prevalence [IQR] 1995-1999 0[0-0]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Hall(2003) EGY Cairo 2000 50 0[0-9]
Putnam(2004) EGY Abu Homos district 2000 623 0[0-1]
Bakour(2006) DZA Algiers 2003 203 0[0-2]
Saied(2006) EGY Cairo 2003 23 0[0-17]
Median prevalence [IQR] 2000-2004 0[0-0]
Ashour(2009) EGY Cairo 2006 171 50[42-57]
Ashour(2009) EGY Cairo 2006 171 8[5-13]
Zerouali(2016) OMN Dhahira 2006 35 17[8-33]
Patel(2011) OMN Dhahira 2006 35 17[8-33]
Abou-Dobara(2010) EGY Mansoura 2007 39 0[0-11]
Saied(2011) EGY Cairo & Alexandria 2007 22 14[4-34]
Kanj(2014) LBN Uknown 2007 27 0[0-15]
Kanj(2014) OMN Uknown 2007 26 0[0-15]
Ferjani(2014) TUN Tunis 2007 201 0[0-2]
Rahbar(2010) IRN Mehran 2008 10 30[10-61]
Murphy(2011) IRQ Uknown 2008 30 0[0-13]
Elotmani(2010) MAR El Jadida 2008 80 0[0-5]
Saeed(2017) SDN Khartoum 2008 37 46[31-62]
Thabit(2011) EGY Assiut 2009 136 0[0-3]
Salem(2010) EGY Cairo 2009 188 6[3-10]
Median prevalence [IQR] 2005-2009 6[0-17]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
B

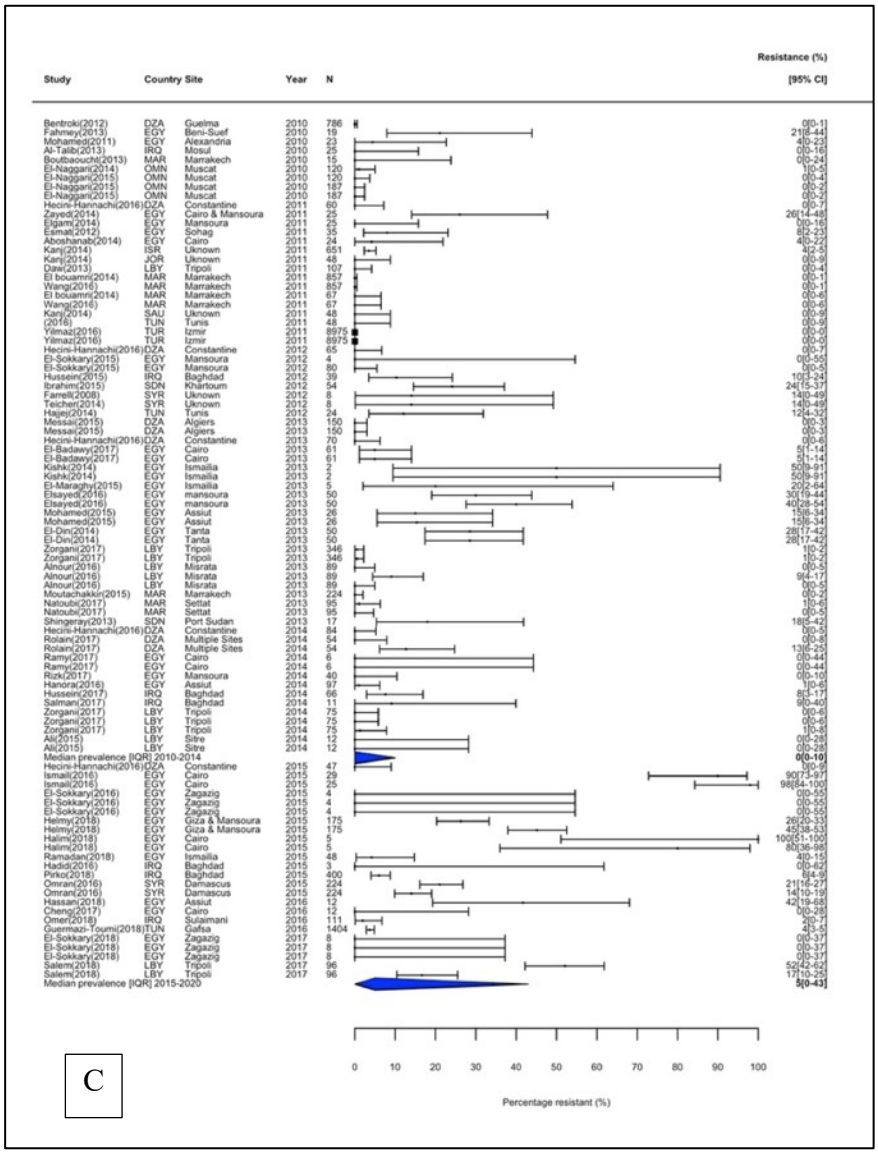


Figure C.35: Forest plot of carbapenems resistance in North Africa and the Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.

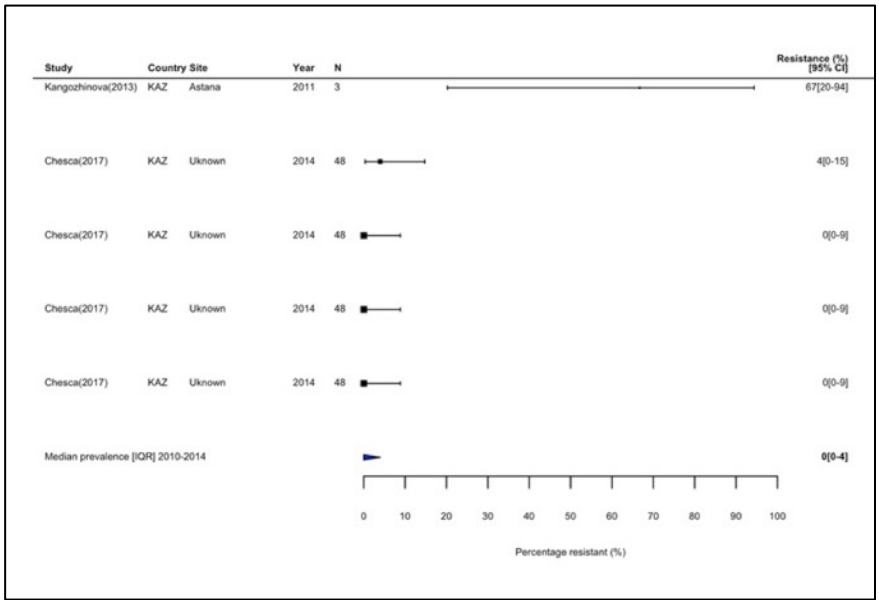
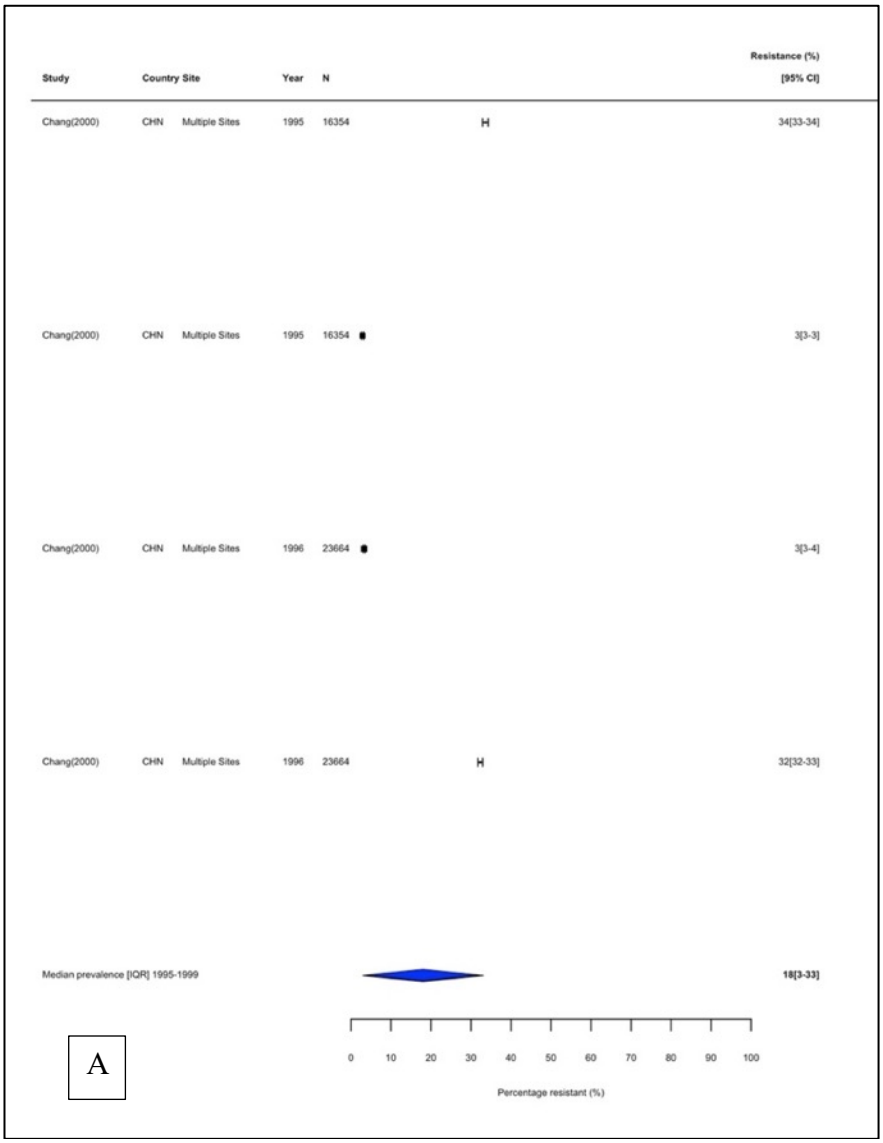
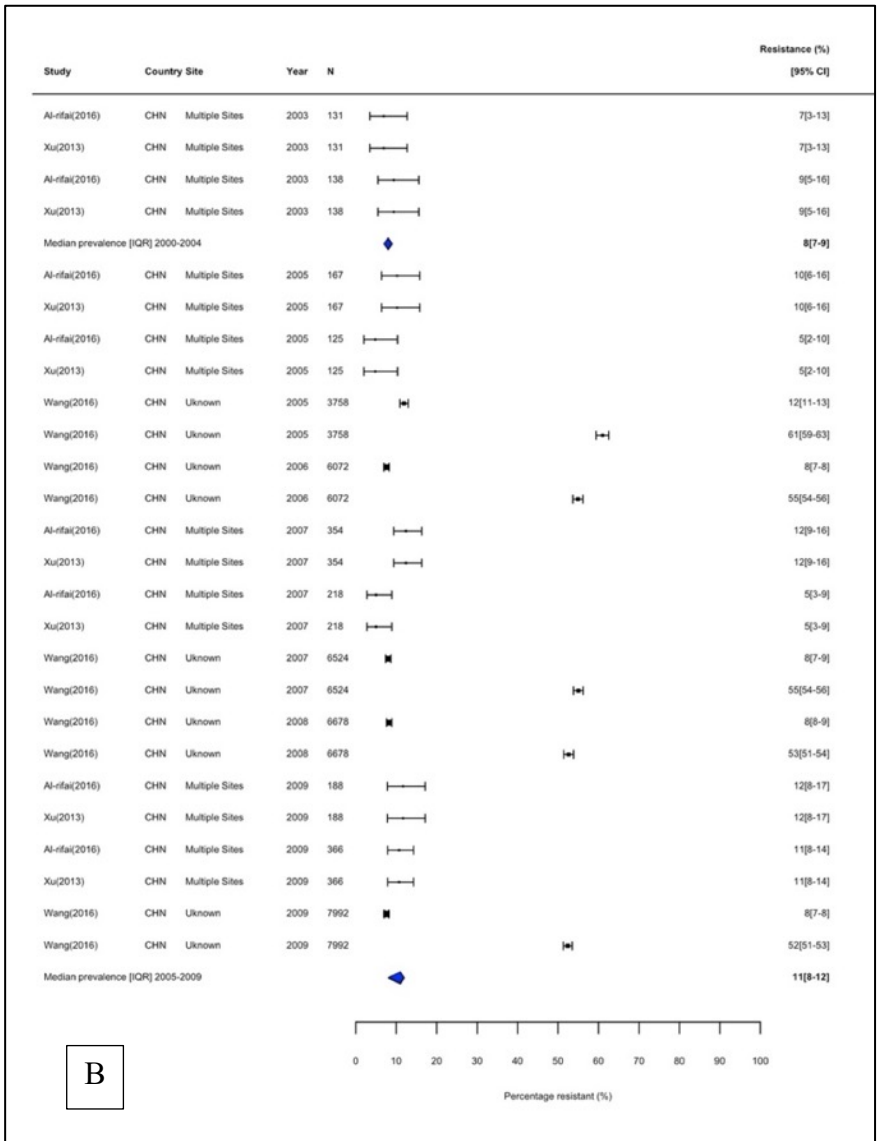


Figure C.36: Forest plot of aminoglycosides resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Chang(2000) CHN Multiple Sites 1995 16354 34[33-34]
Chang(2000) CHN Multiple Sites 1995 16354 3[3-3]
Chang(2000) CHN Multiple Sites 1996 23664 3[3-4]
Chang(2000) CHN Multiple Sites 1996 23664 32[32-33]
Median prevalence [IQR] 1995-1999 18[3-33]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Al-rifai(2016) CHN Multiple Sites 2003 131 7[3-13]
Xu(2013) CHN Multiple Sites 2003 131 7[3-13]
Al-rifai(2016) CHN Multiple Sites 2003 138 9[5-16]
Xu(2013) CHN Multiple Sites 2003 138 9[5-16]
Median prevalence [IQR] 2000-2004 8[7-9]
Al-rifai(2016) CHN Multiple Sites 2005 167 10[6-16]
Xu(2013) CHN Multiple Sites 2005 167 10[6-16]
Al-rifai(2016) CHN Multiple Sites 2005 125 5[2-10]
Xu(2013) CHN Multiple Sites 2005 125 5[2-10]
Wang(2016) CHN Uknown 2005 3758 12[11-13]
Wang(2016) CHN Uknown 2005 3758 61[59-63]
Wang(2016) CHN Uknown 2006 6072 8[7-8]
Wang(2016) CHN Uknown 2006 6072 55[54-56]
Al-rifai(2016) CHN Multiple Sites 2007 354 12[9-16]
Xu(2013) CHN Multiple Sites 2007 354 12[9-16]
Al-rifai(2016) CHN Multiple Sites 2007 218 5[3-9]
Xu(2013) CHN Multiple Sites 2007 218 5[3-9]
Wang(2016) CHN Uknown 2007 6524 8[7-9]
Wang(2016) CHN Uknown 2007 6524 55[54-56]
Wang(2016) CHN Uknown 2008 6678 8[8-9]
Wang(2016) CHN Uknown 2008 6678 53[51-54]
Al-rifai(2016) CHN Multiple Sites 2009 188 12[8-17]
Xu(2013) CHN Multiple Sites 2009 188 12[8-17]
Al-rifai(2016) CHN Multiple Sites 2009 366 11[8-14]
Xu(2013) CHN Multiple Sites 2009 366 11[8-14]
Wang(2016) CHN Uknown 2009 7992 8[7-8]
Wang(2016) CHN Uknown 2009 7992 52[51-53]
Median prevalence [IQR] 2005-2009 11[8-12]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
B

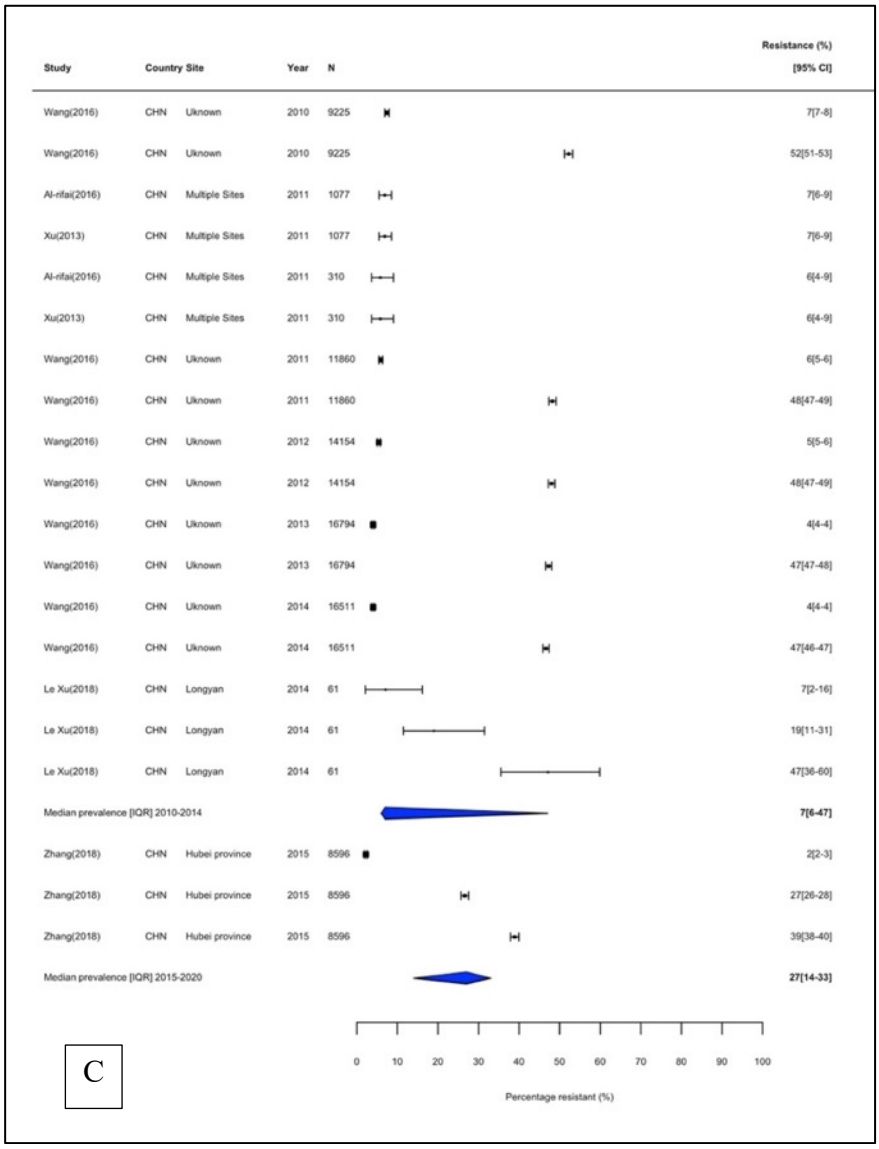


Figure C.37: Forest plot of aminoglycosides resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.

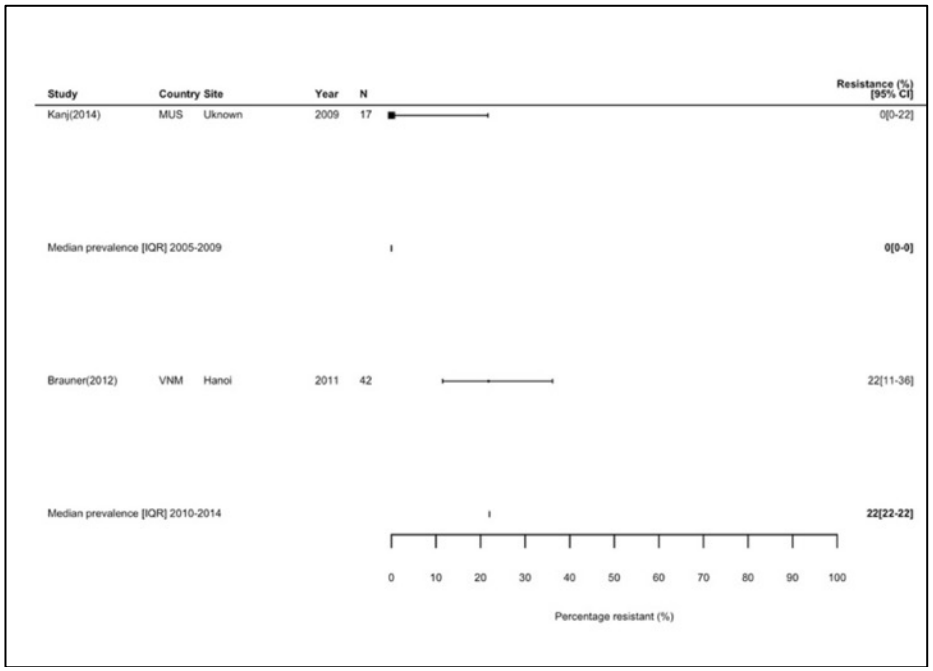


Figure C.38: Forest plot of aminoglycosides resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

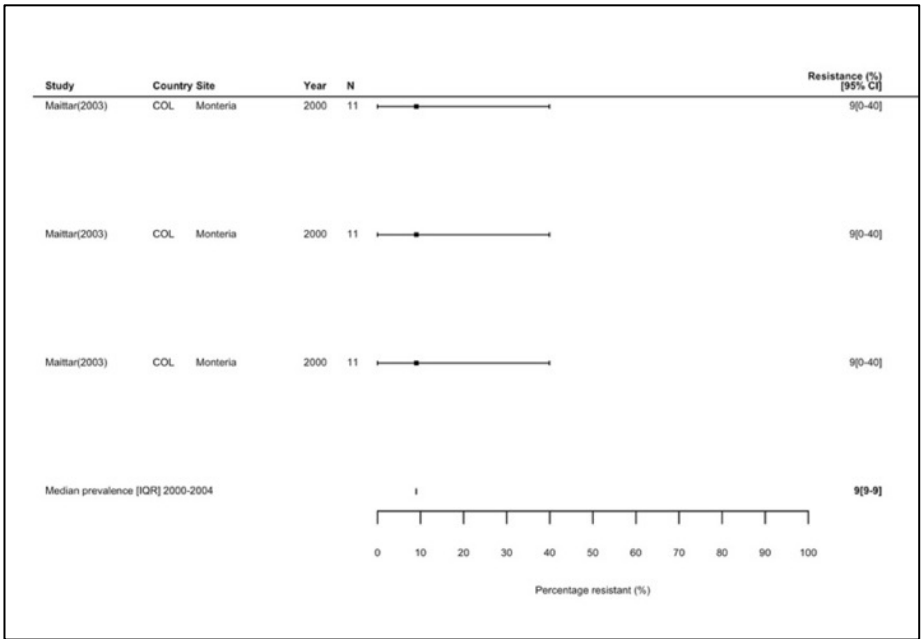


Figure C.39: Forest plot of aminoglycosides resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

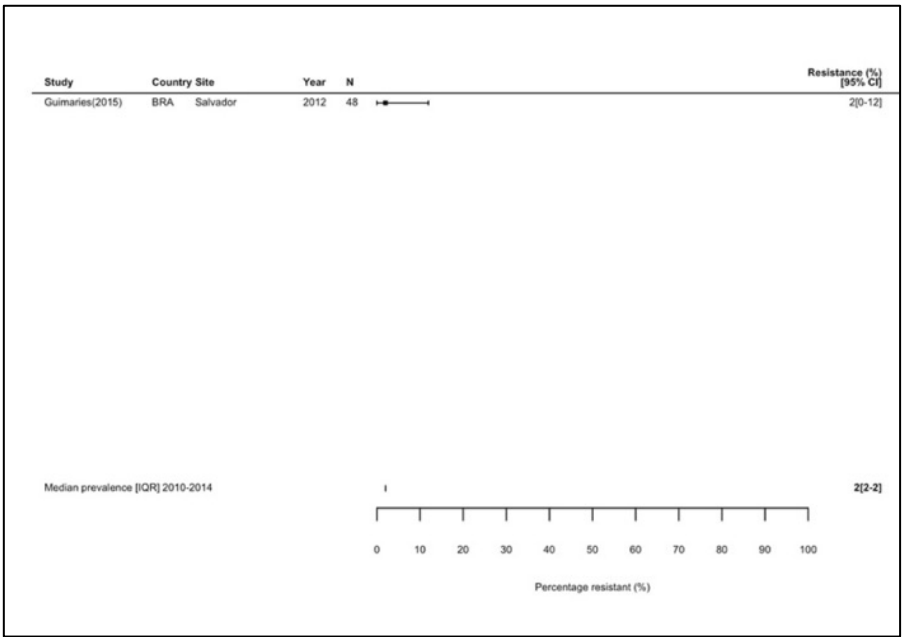


Figure C.40: Forest plot of aminoglycosides resistance in Tropical Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

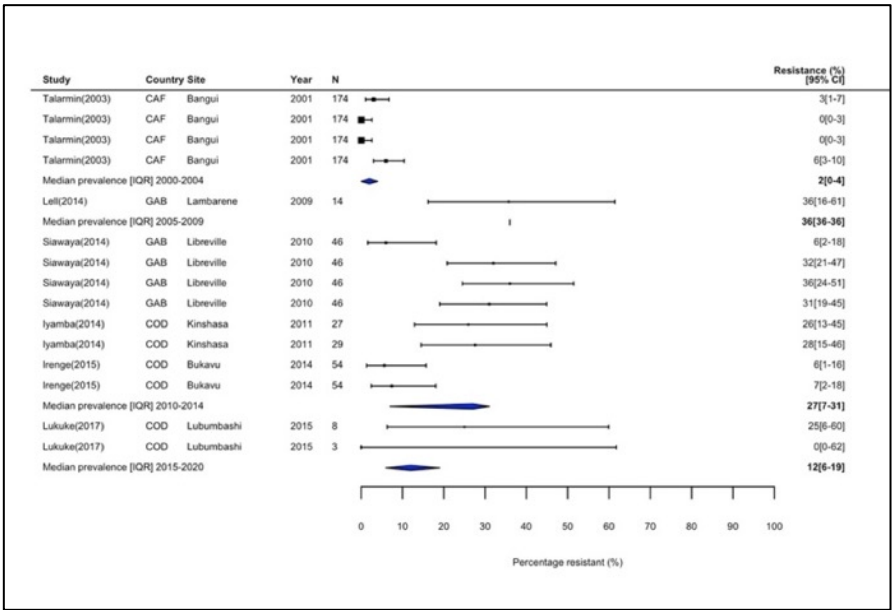
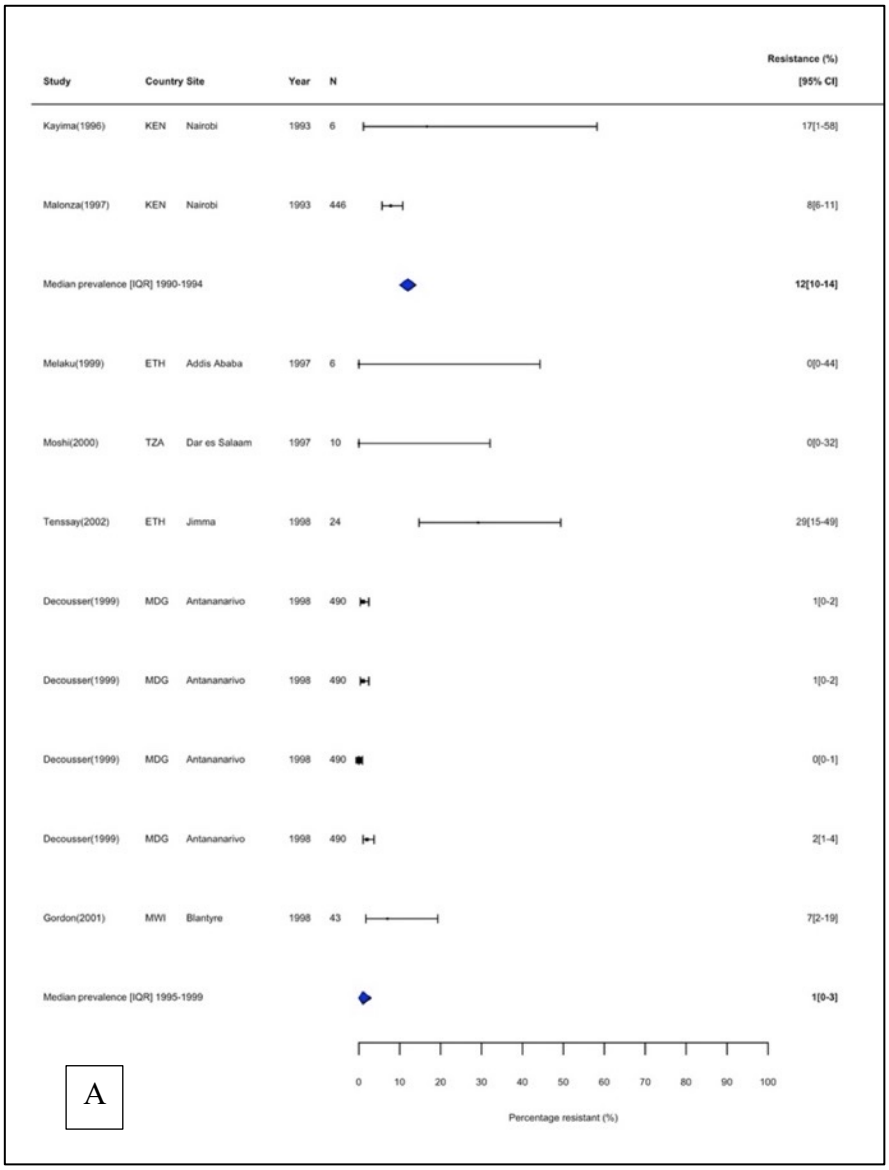
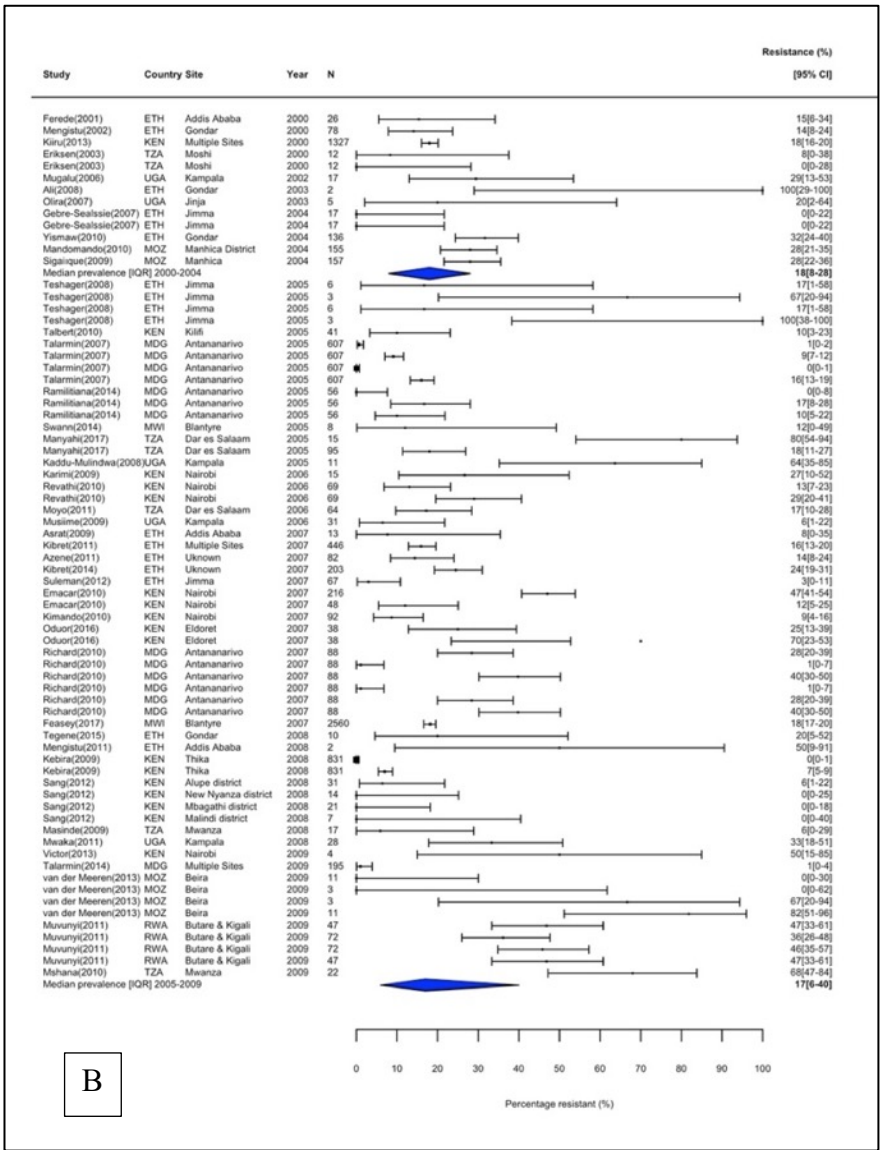
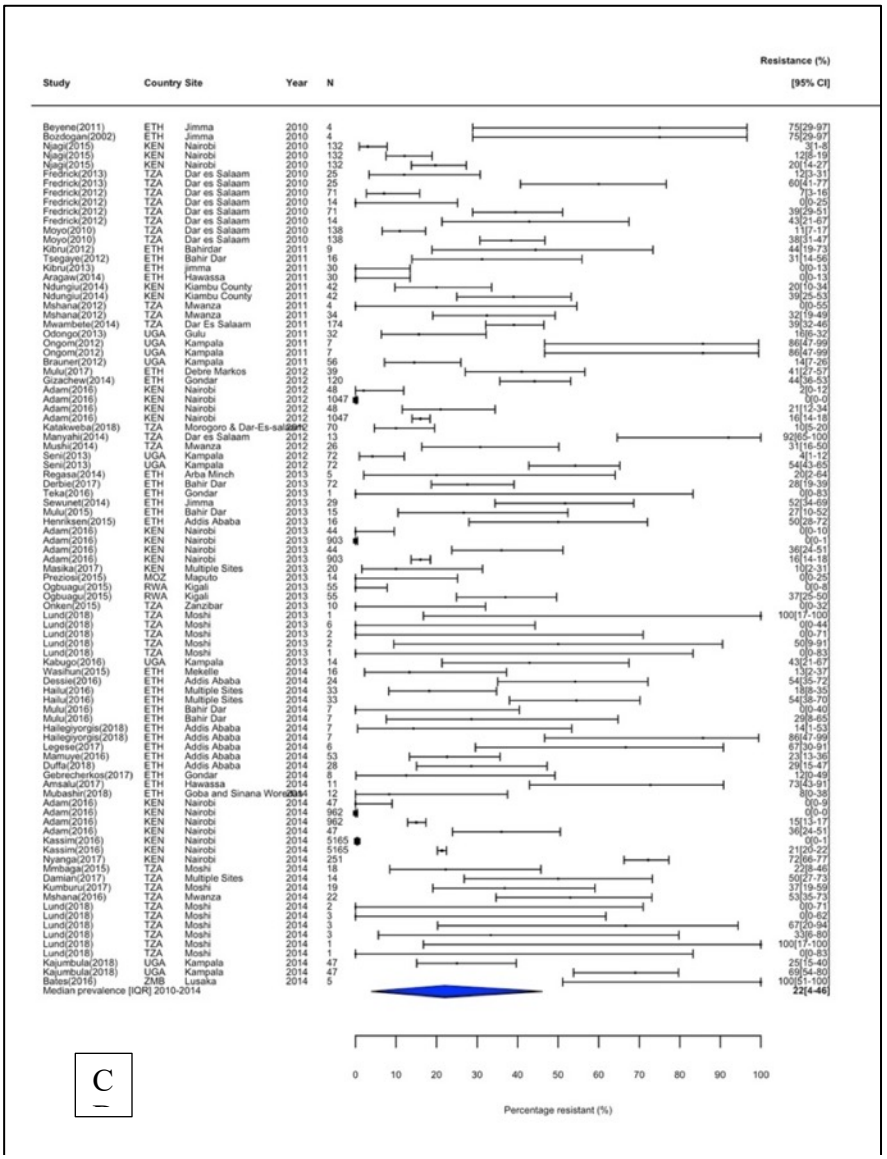


Figure C.41: Forest plot of aminoglycosides resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Kayima(1996) KEN Nairobi 1993 6 17[1-58]
Malonza(1997) KEN Nairobi 1993 446 8[6-11]
Median prevalence [IQR] 1990-1994 12[10-14]
Melaku(1999) ETH Addis Ababa 1997 6 0[0-44]
Moshi(2000) TZA Dar es Salaam 1997 10 0[0-32]
Tenssay(2002) ETH Jimma 1998 24 29[15-49]
Decousser(1999) MDG Antananarivo 1998 490 1[0-2]
Decousser(1999) MDG Antananarivo 1998 490 1[0-2]
Decousser(1999) MDG Antananarivo 1998 490 0[0-1]
Decousser(1999) MDG Antananarivo 1998 490 2[1-4]
Gordon(2001) MWI Blantyre 1998 43 7[2-19]
Median prevalence [IQR] 1995-1999 1[0-3]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Ferede(2001) ETH Addis Ababa 2000 26 15[8-34]
Mengistu(2002) ETH Gondar 2000 78 14[8-24]
Kiiru(2013) KEN Multiple Sites 2000 1327 18[16-20]
Eriksen(2003) TZA Moshi 2000 12 8[0-38]
Eriksen(2003) TZA Moshi 2000 12 0[0-28]
Mugalu(2006) UGA Kampala 2002 17 29[13-53]
Ali(2008) ETH Gondar 2003 2 100[29-100]
Olira(2007) UGA Jinja 2003 5 20[2-64]
Gebre-Sealssie(2007) ETH Jimma 2004 17 0[0-22]
Gebre-Sealssie(2007) ETH Jimma 2004 17 0[0-22]
Yismaw(2010) ETH Gondar 2004 136 32[24-40]
Mandomando(2010) MOZ Manhica District 2004 155 28[21-35]
Sigaúque(2009) MOZ Manhica 2004 157 28[22-36]
Median prevalence [IQR] 2000-2004 18[8-28]
Teshager(2008) ETH Jimma 2005 6 17[1-58]
Teshager(2008) ETH Jimma 2005 3 67[20-94]
Teshager(2008) ETH Jimma 2005 6 17[1-58]
Teshager(2008) ETH Jimma 2005 3 100[38-100]
Talbert(2010) KEN Kilifi 2005 41 10[3-23]
Talarmin(2007) MDG Antananarivo 2005 607 1[0-2]
Talarmin(2007) MDG Antananarivo 2005 607 9[7-12]
Talarmin(2007) MDG Antananarivo 2005 607 0[0-1]
Talarmin(2007) MDG Antananarivo 2005 607 16[13-19]
Ramilitiana(2014) MDG Antananarivo 2005 56 0[0-8]
Ramilitiana(2014) MDG Antananarivo 2005 56 17[8-28]
Ramilitiana(2014) MDG Antananarivo 2005 56 10[5-22]
Swann(2014) MWI Blantyre 2005 8 12[0-49]
Manyahi(2017) TZA Dar es Salaam 2005 15 80[54-94]
Manyahi(2017) TZA Dar es Salaam 2005 95 18[11-27]
Kaddu-Mulindwa(2008) UGA Kampala 2005 11 64[35-85]
Karimi(2009) KEN Nairobi 2006 15 27[10-52]
Revathi(2010) KEN Nairobi 2006 69 13[7-23]
Revathi(2010) KEN Nairobi 2006 69 29[20-41]
Moyo(2011) TZA Dar es Salaam 2006 64 17[10-28]
Musiime(2009) UGA Kampala 2006 31 6[1-22]
Asrat(2009) ETH Addis Ababa 2007 13 8[0-35]
Kibret(2011) ETH Multiple Sites 2007 446 16[13-20]
Azene(2011) ETH Uknown 2007 82 14[8-24]
Kibret(2014) ETH Uknown 2007 203 24[19-31]
Suleman(2012) ETH Jimma 2007 67 3[0-11]
Emacar(2010) KEN Nairobi 2007 216 47[41-54]
Emacar(2010) KEN Nairobi 2007 48 12[5-25]
Kimando(2010) KEN Nairobi 2007 92 9[4-16]
Oduor(2016) KEN Eldoret 2007 38 25[13-39]
Oduor(2016) KEN Eldoret 2007 38 70[23-53]
Richard(2010) MDG Antananarivo 2007 88 28[20-39]
Richard(2010) MDG Antananarivo 2007 88 1[0-7]
Richard(2010) MDG Antananarivo 2007 88 40[30-50]
Richard(2010) MDG Antananarivo 2007 88 1[0-7]
Richard(2010) MDG Antananarivo 2007 88 28[20-39]
Richard(2010) MDG Antananarivo 2007 88 40[30-50]
Feasey(2017) MWI Blantyre 2007 2560 18[17-20]
Tegene(2015) ETH Gondar 2008 10 20[5-52]
Mengistu(2011) ETH Addis Ababa 2008 2 50[9-91]
Kebira(2009) KEN Thika 2008 831 0[0-1]
Kebira(2009) KEN Thika 2008 831 7[5-9]
Sang(2012) KEN Alupe district 2008 31 6[1-22]
Sang(2012) KEN New Nyanza district 2008 14 0[0-25]
Sang(2012) KEN Mbagathi district 2008 21 0[0-18]
Sang(2012) KEN Malindi district 2008 7 0[0-40]
Masinde(2009) TZA Mwanza 2008 17 6[0-29]
Mwaka(2011) UGA Kampala 2008 28 33[18-51]
Victor(2013) KEN Nairobi 2009 4 50[15-85]
Talarmin(2014) MDG Multiple Sites 2009 195 1[0-4]
van der Meeren(2013) MOZ Beira 2009 11 0[0-30]
van der Meeren(2013) MOZ Beira 2009 3 0[0-62]
van der Meeren(2013) MOZ Beira 2009 3 67[20-94]
van der Meeren(2013) MOZ Beira 2009 11 82[51-96]
Muvunyi(2011) RWA Butare & Kigali 2009 47 47[33-61]
Muvunyi(2011) RWA Butare & Kigali 2009 72 36[26-48]
Muvunyi(2011) RWA Butare & Kigali 2009 72 46[35-57]
Muvunyi(2011) RWA Butare & Kigali 2009 47 47[33-61]
Mshana(2010) TZA Mwanza 2009 22 68[47-84]
Median prevalence [IQR] 2005-2009 17[6-40]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2010-2014
22[4-46]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

C

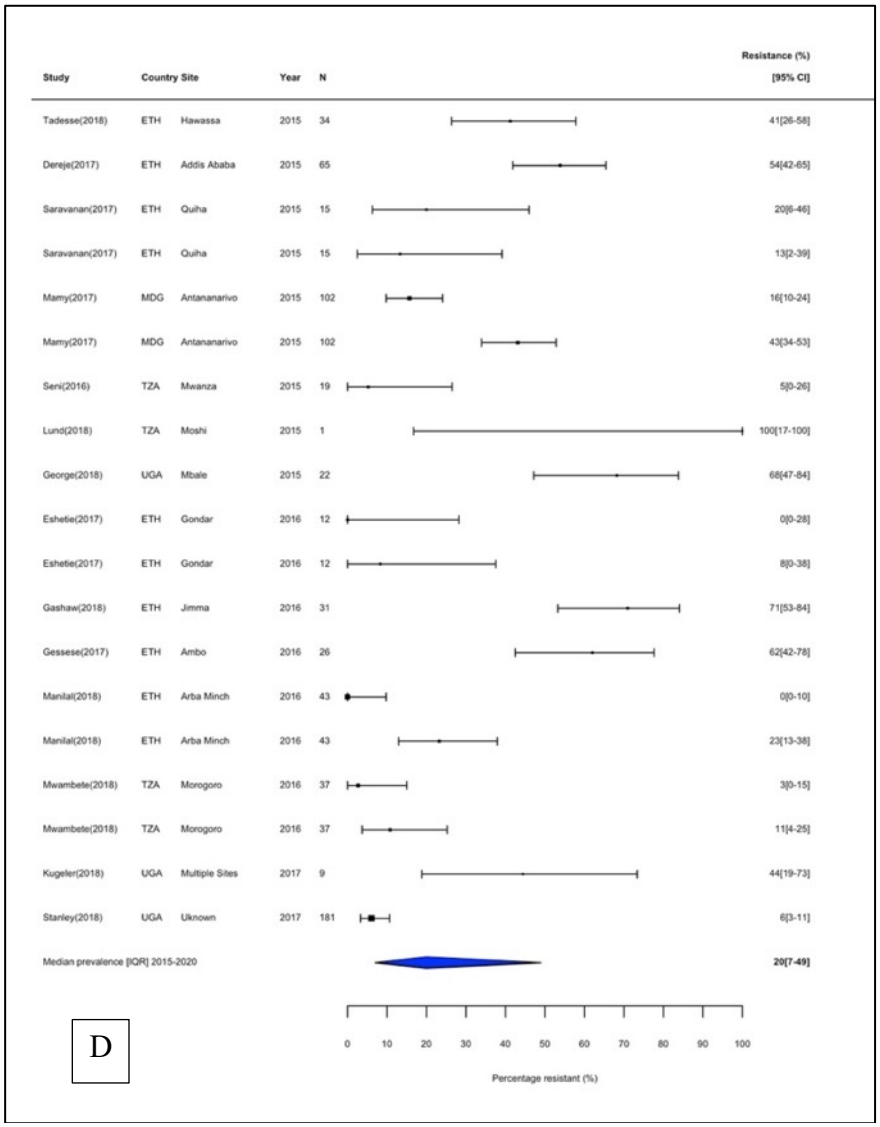
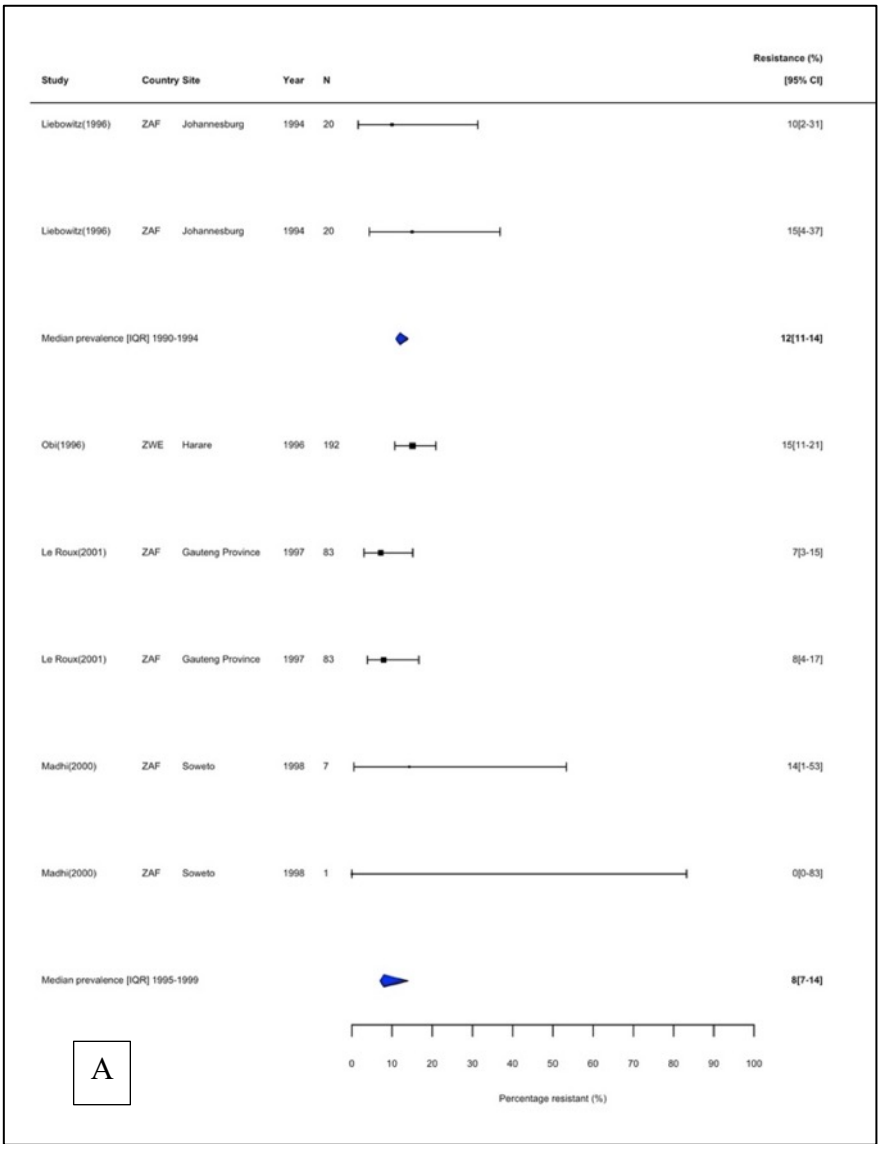
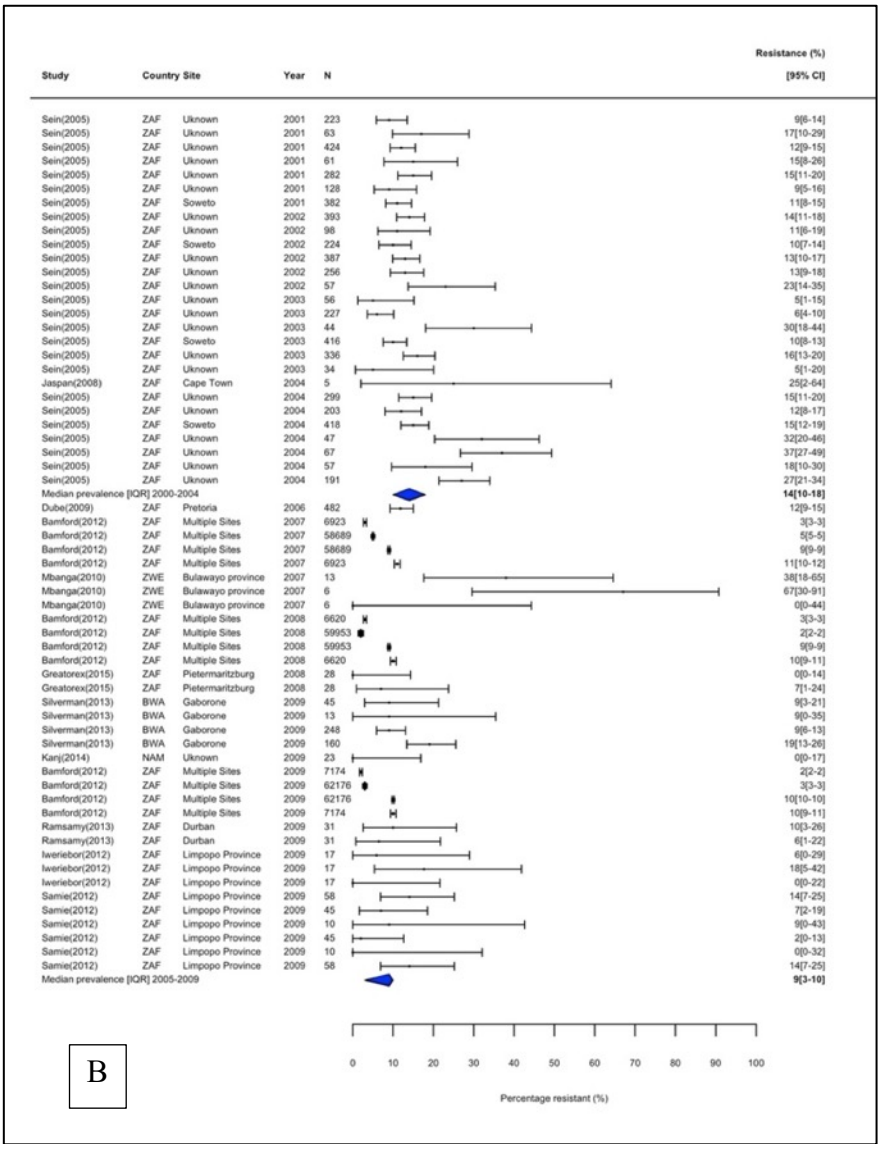


Figure C.42: Forest plot of aminoglycosides resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2004, B: 2005-2009, C: 2010-2018.


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Liebowitz(1996) ZAF Johannesburg 1994 20 10[2-31]
Liebowitz(1996) ZAF Johannesburg 1994 20 15[4-37]
Median prevalence [IQR] 1990-1994 12[11-14]
Obi(1996) ZWE Harare 1996 192 15[11-21]
Le Roux(2001) ZAF Gauteng Province 1997 83 7[3-15]
Le Roux(2001) ZAF Gauteng Province 1997 83 8[4-17]
Madhi(2000) ZAF Soweto 1998 7 14[1-53]
Madhi(2000) ZAF Soweto 1998 1 0[0-83]
Median prevalence [IQR] 1995-1999 8[7-14]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Sein(2005) ZAF Uknown 2001 223 9[6-14]
Sein(2005) ZAF Uknown 2001 63 17[10-29]
Sein(2005) ZAF Uknown 2001 424 12[9-15]
Sein(2005) ZAF Uknown 2001 61 15[8-26]
Sein(2005) ZAF Uknown 2001 282 15[11-20]
Sein(2005) ZAF Uknown 2001 128 9[5-16]
Sein(2005) ZAF Soweto 2001 382 11[8-15]
Sein(2005) ZAF Uknown 2002 393 14[11-18]
Sein(2005) ZAF Uknown 2002 98 11[6-19]
Sein(2005) ZAF Soweto 2002 224 10[7-14]
Sein(2005) ZAF Uknown 2002 387 13[10-17]
Sein(2005) ZAF Uknown 2002 256 13[9-18]
Sein(2005) ZAF Uknown 2002 57 23[14-35]
Sein(2005) ZAF Uknown 2003 56 5[1-15]
Sein(2005) ZAF Uknown 2003 227 6[4-10]
Sein(2005) ZAF Uknown 2003 44 30[18-44]
Sein(2005) ZAF Soweto 2003 416 10[8-13]
Sein(2005) ZAF Uknown 2003 336 16[13-20]
Sein(2005) ZAF Uknown 2003 34 5[1-20]
Jaspan(2008) ZAF Cape Town 2004 5 25[2-64]
Sein(2005) ZAF Uknown 2004 299 15[11-20]
Sein(2005) ZAF Uknown 2004 203 12[8-17]
Sein(2005) ZAF Soweto 2004 418 15[12-19]
Sein(2005) ZAF Uknown 2004 47 32[20-46]
Sein(2005) ZAF Uknown 2004 67 37[27-49]
Sein(2005) ZAF Uknown 2004 57 18[10-30]
Sein(2005) ZAF Uknown 2004 191 27[21-34]
Median prevalence [IQR] 2000-2004 14[10-18]
Dube(2009) ZAF Pretoria 2006 482 12[9-15]
Bamford(2012) ZAF Multiple Sites 2007 6923 3[3-3]
Bamford(2012) ZAF Multiple Sites 2007 58689 5[5-5]
Bamford(2012) ZAF Multiple Sites 2007 58689 9[9-9]
Bamford(2012) ZAF Multiple Sites 2007 6923 11[10-12]
Mbanga(2010) ZWE Bulawayo province 2007 13 38[18-65]
Mbanga(2010) ZWE Bulawayo province 2007 6 67[30-91]
Mbanga(2010) ZWE Bulawayo province 2007 6 0[0-44]
Bamford(2012) ZAF Multiple Sites 2008 6620 3[3-3]
Bamford(2012) ZAF Multiple Sites 2008 59953 2[2-2]
Bamford(2012) ZAF Multiple Sites 2008 59953 9[9-9]
Bamford(2012) ZAF Multiple Sites 2008 6620 10[9-11]
Greatorex(2015) ZAF Pietermaritzburg 2008 28 0[0-14]
Greatorex(2015) ZAF Pietermaritzburg 2008 28 7[1-24]
Silverman(2013) BWA Gaborone 2009 45 9[3-21]
Silverman(2013) BWA Gaborone 2009 13 9[0-35]
Silverman(2013) BWA Gaborone 2009 248 9[6-13]
Silverman(2013) BWA Gaborone 2009 160 19[13-26]
Kanj(2014) NAM Uknown 2009 23 0[0-17]
Bamford(2012) ZAF Multiple Sites 2009 7174 2[2-2]
Bamford(2012) ZAF Multiple Sites 2009 62176 3[3-3]
Bamford(2012) ZAF Multiple Sites 2009 62176 10[10-10]
Bamford(2012) ZAF Multiple Sites 2009 7174 10[9-11]
Ramsamy(2013) ZAF Durban 2009 31 10[3-26]
Ramsamy(2013) ZAF Durban 2009 31 6[1-22]
Iweriebor(2012) ZAF Limpopo Province 2009 17 6[0-29]
Iweriebor(2012) ZAF Limpopo Province 2009 17 18[5-42]
Iweriebor(2012) ZAF Limpopo Province 2009 17 0[0-22]
Samie(2012) ZAF Limpopo Province 2009 58 14[7-25]
Samie(2012) ZAF Limpopo Province 2009 45 7[2-19]
Samie(2012) ZAF Limpopo Province 2009 10 9[0-43]
Samie(2012) ZAF Limpopo Province 2009 45 2[0-13]
Samie(2012) ZAF Limpopo Province 2009 10 0[0-32]
Samie(2012) ZAF Limpopo Province 2009 58 14[7-25]
Median prevalence [IQR] 2005-2009 9[3-10]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B

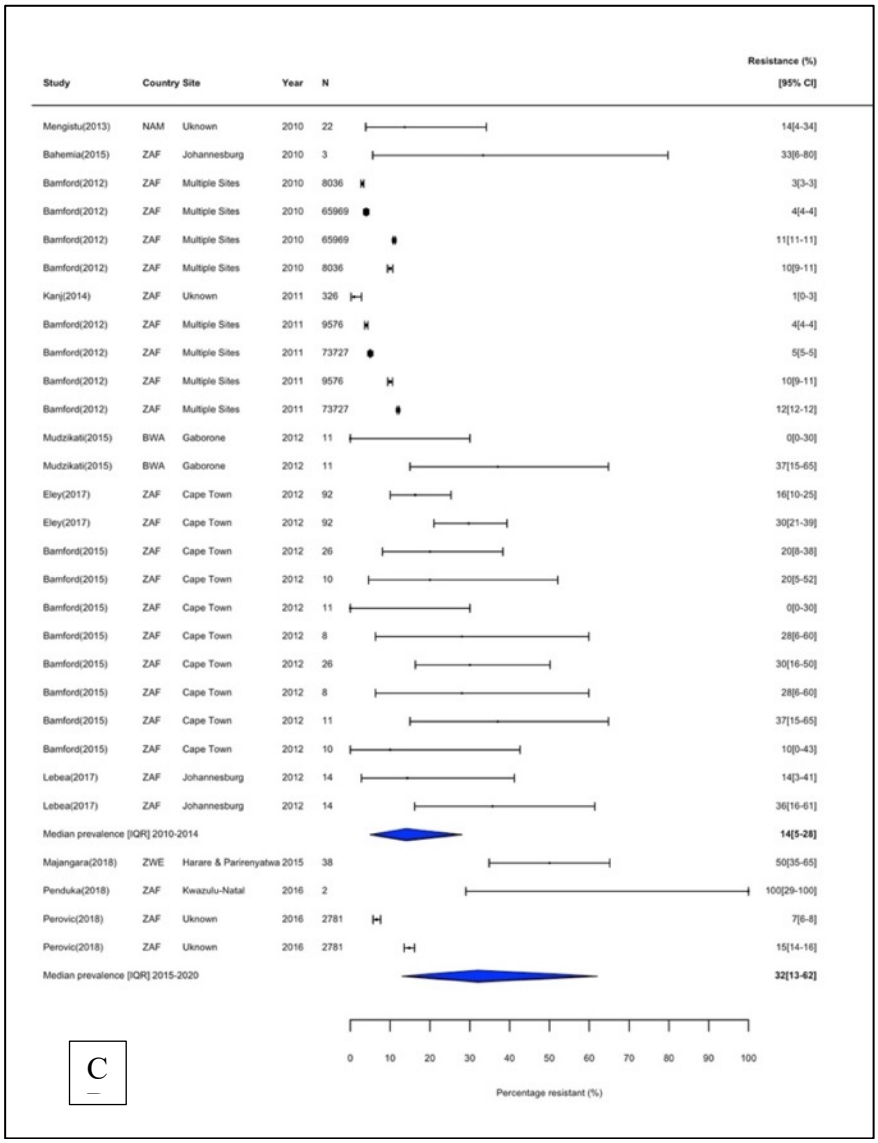
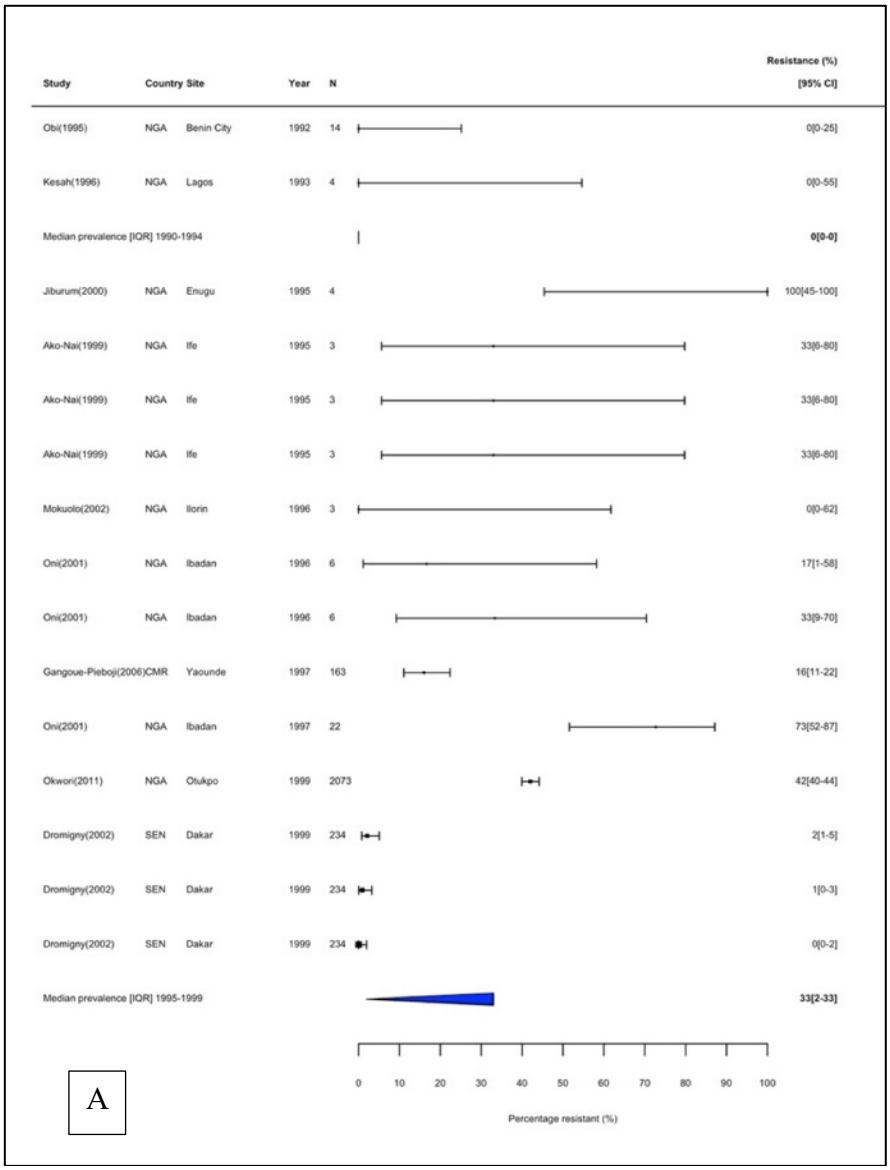
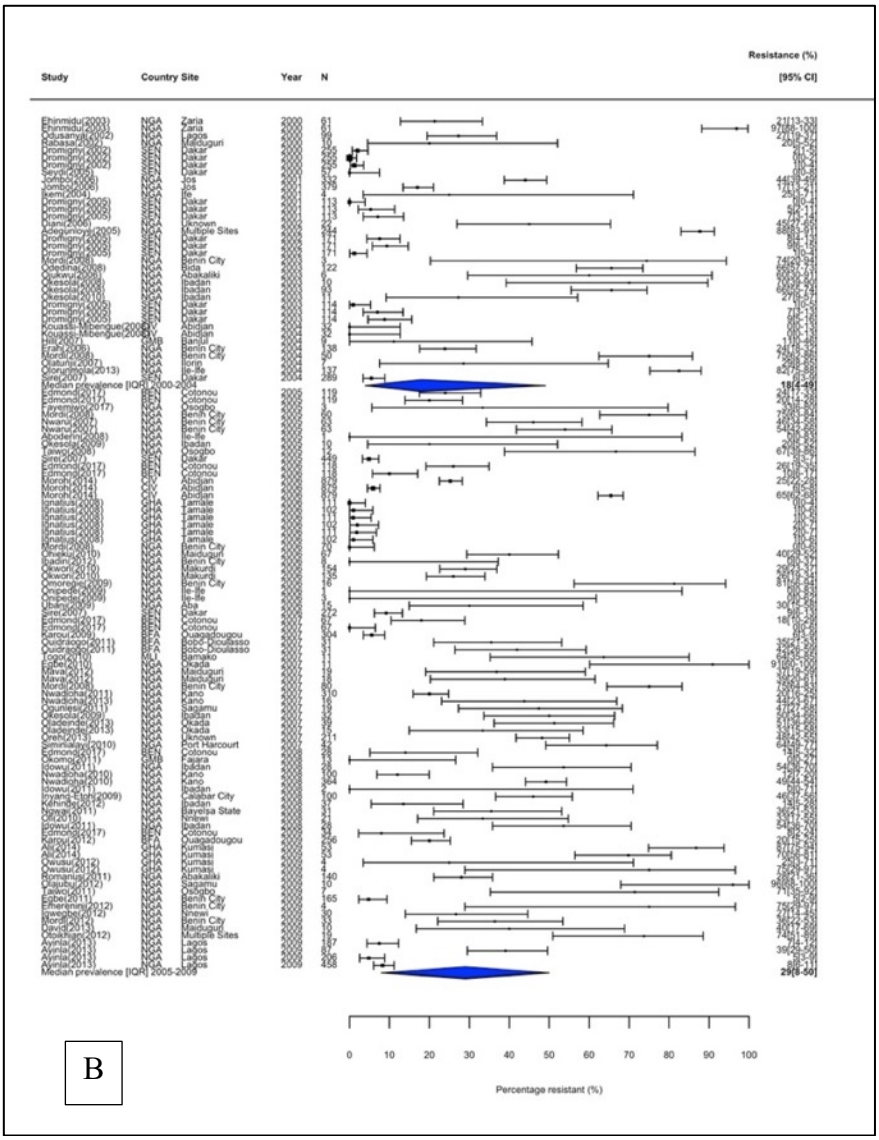
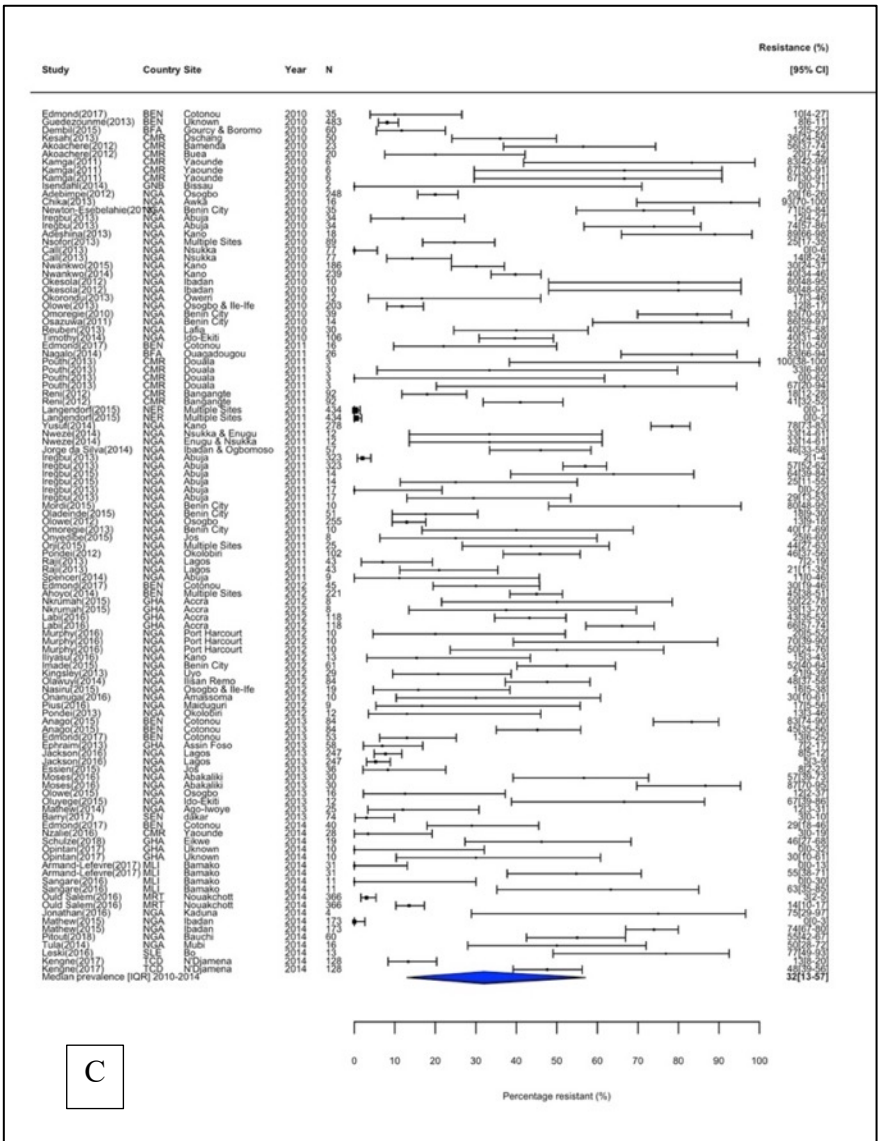


Figure C.43: Forest plot of aminoglycosides resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018.


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Obi(1995) NGA Benin City 1992 14 0[0-25]
Kesah(1996) NGA Lagos 1993 4 0[0-55]
Median prevalence [IQR] 1990-1994 0[0-0]
Jiburum(2000) NGA Enugu 1995 4 100[45-100]
Ako-Nai(1999) NGA Ife 1995 3 33[6-80]
Ako-Nai(1999) NGA Ife 1995 3 33[6-80]
Ako-Nai(1999) NGA Ife 1995 3 33[6-80]
Mokuolo(2002) NGA Ilorin 1996 3 0[0-62]
Oni(2001) NGA Ibadan 1996 6 17[1-58]
Oni(2001) NGA Ibadan 1996 6 33[9-70]
Gangoue-Pieboji(2006)CMR Yaounde 1997 163 16[11-22]
Oni(2001) NGA Ibadan 1997 22 73[52-87]
Okwori(2011) NGA Otukpo 1999 2073 42[40-44]
Dromigny(2002) SEN Dakar 1999 234 2[1-5]
Dromigny(2002) SEN Dakar 1999 234 1[0-3]
Dromigny(2002) SEN Dakar 1999 234 0[0-2]
Median prevalence [IQR] 1995-1999 33[2-33]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2000-2004
18[4-49]
Median prevalence [IQR] 2005-2009
29[8-50]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2010-2014
32[13-57]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

C

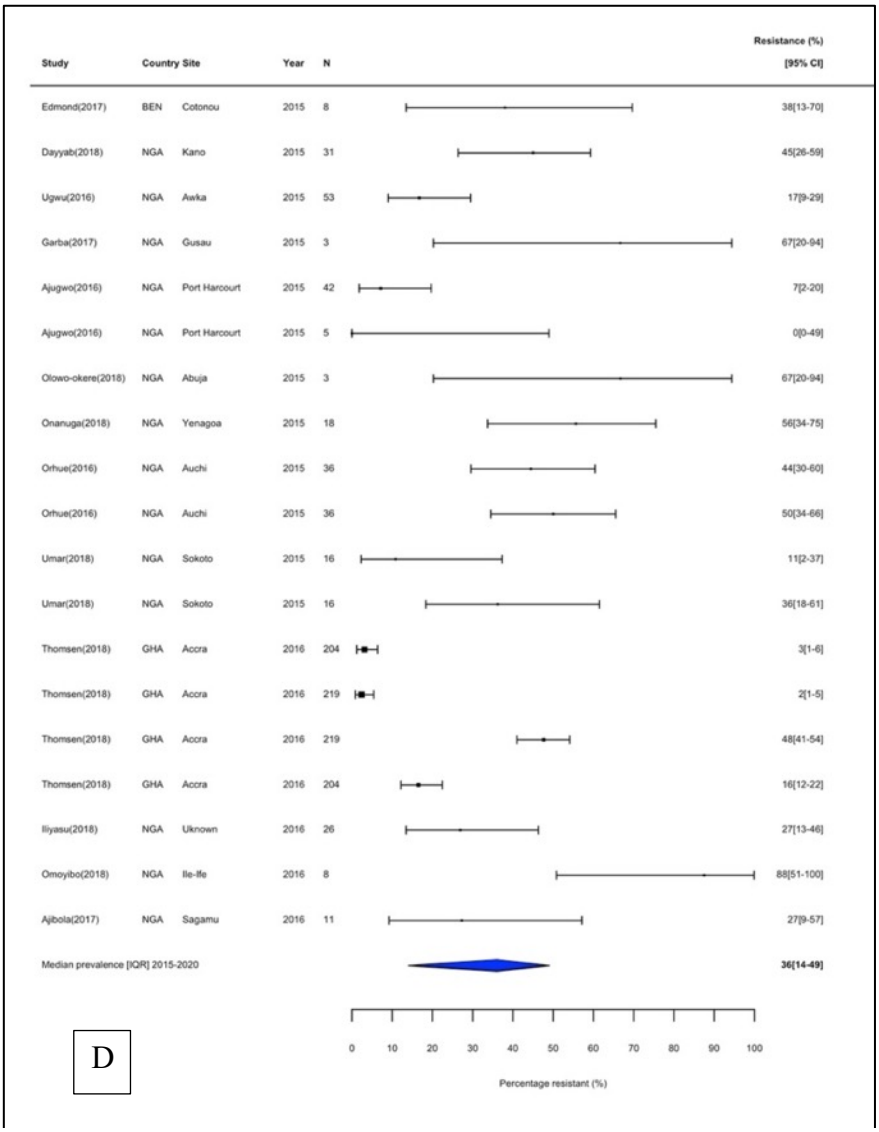
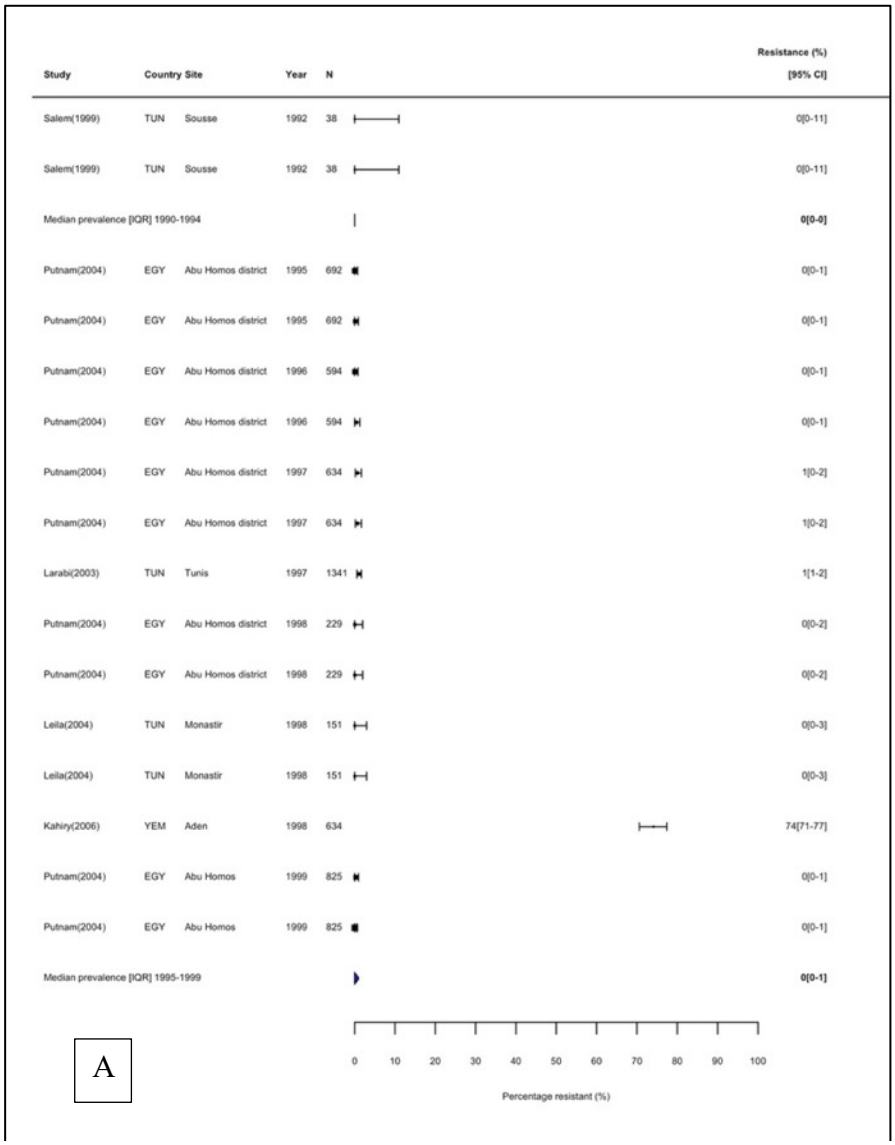
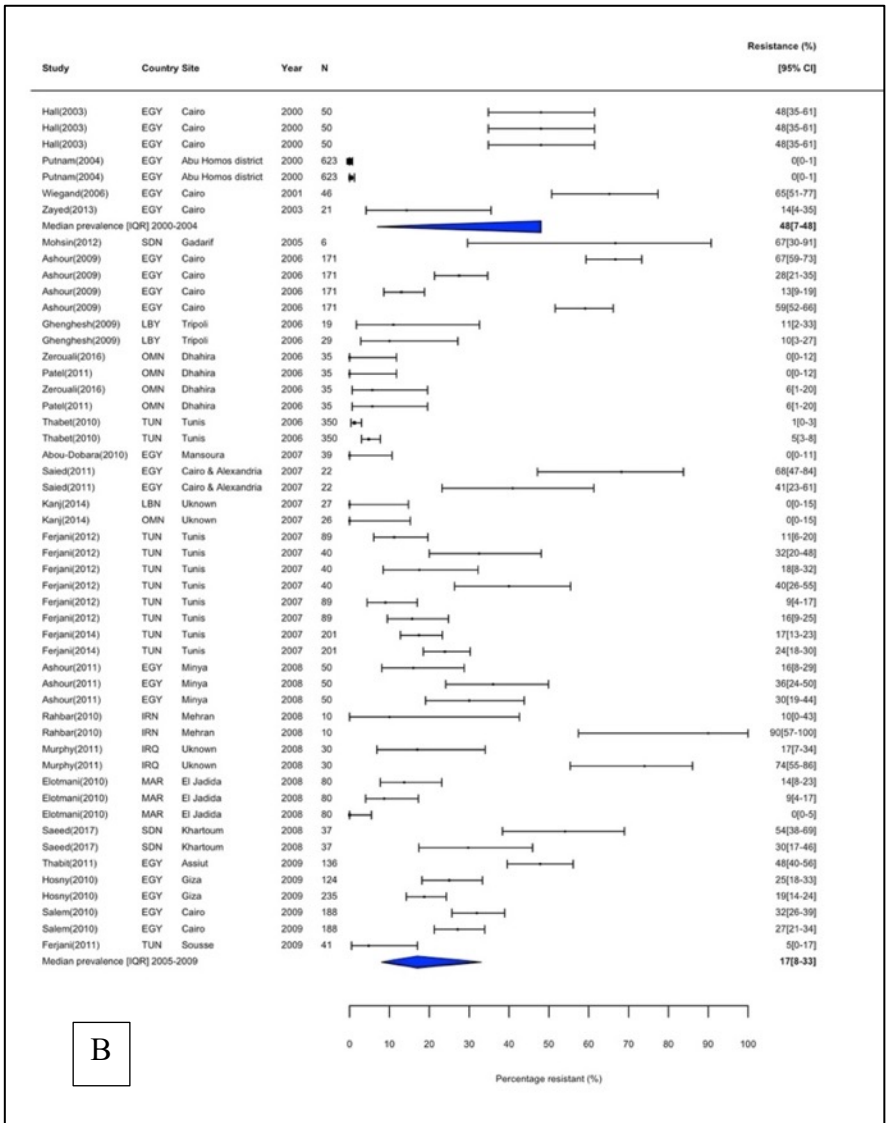
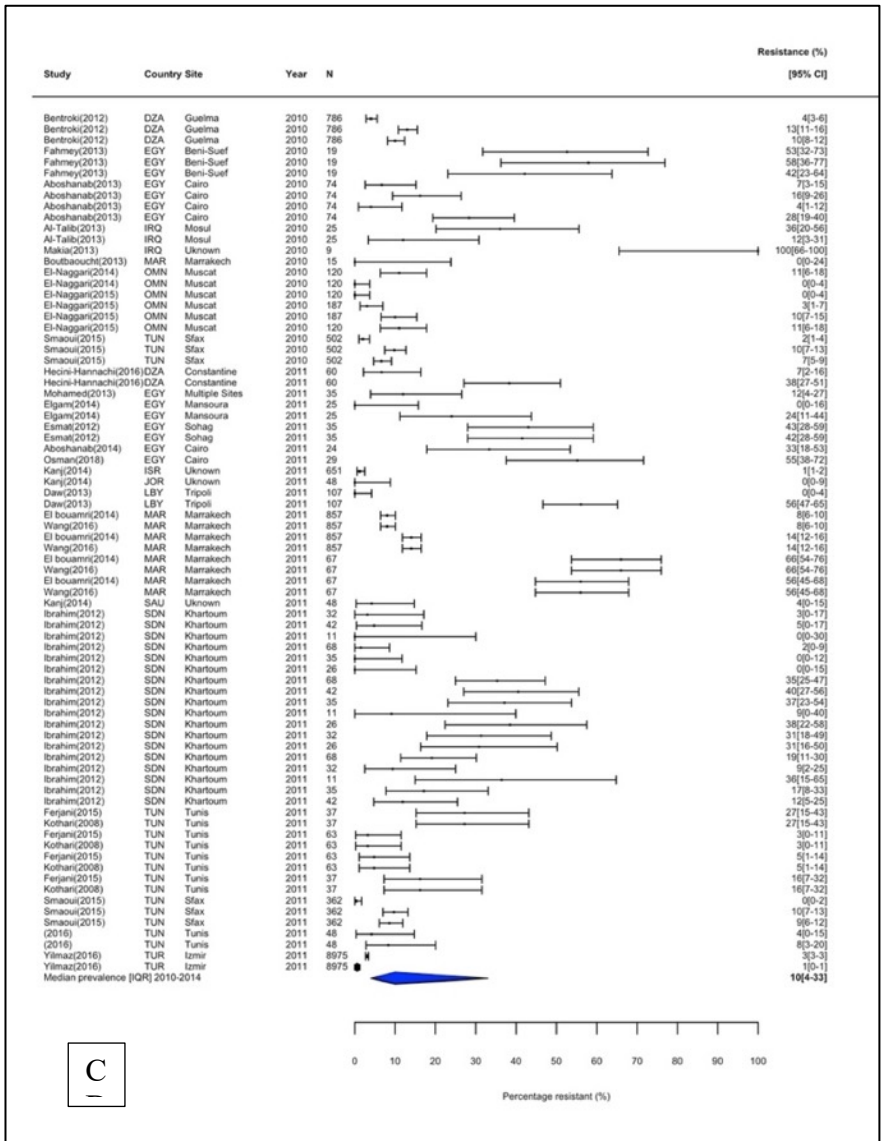


Figure C.44: Forest plot of Aminoglycosides resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2014, D: 2015-2018.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Salem(1999) TUN Sousse 1992 38 0[0-11]
Salem(1999) TUN Sousse 1992 38 0[0-11]
Median prevalence [IQR] 1990-1994 0[0-0]
Putnam(2004) EGY Abu Homos district 1995 692 0[0-1]
Putnam(2004) EGY Abu Homos district 1995 692 0[0-1]
Putnam(2004) EGY Abu Homos district 1996 594 0[0-1]
Putnam(2004) EGY Abu Homos district 1996 594 0[0-1]
Putnam(2004) EGY Abu Homos district 1997 634 1[0-2]
Putnam(2004) EGY Abu Homos district 1997 634 1[0-2]
Larabi(2003) TUN Tunis 1997 1341 1[1-2]
Putnam(2004) EGY Abu Homos district 1998 229 0[0-2]
Putnam(2004) EGY Abu Homos district 1998 229 0[0-2]
Leila(2004) TUN Monastir 1998 151 0[0-3]
Leila(2004) TUN Monastir 1998 151 0[0-3]
Kahiry(2006) YEM Aden 1998 634 74[71-77]
Putnam(2004) EGY Abu Homos 1999 825 0[0-1]
Putnam(2004) EGY Abu Homos 1999 825 0[0-1]
Median prevalence [IQR] 1995-1999 0[0-1]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Hall(2003) EGY Cairo 2000 50 48[35-61]
Hall(2003) EGY Cairo 2000 50 48[35-61]
Hall(2003) EGY Cairo 2000 50 48[35-61]
Putnam(2004) EGY Abu Homos district 2000 623 0[0-1]
Putnam(2004) EGY Abu Homos district 2000 623 0[0-1]
Wiegand(2006) EGY Cairo 2001 46 65[51-77]
Zayed(2013) EGY Cairo 2003 21 14[4-35]
Median prevalence [IQR] 2000-2004 48[7-48]
Mohsin(2012) SDN Gadarif 2005 6 67[30-91]
Ashour(2009) EGY Cairo 2006 171 67[59-73]
Ashour(2009) EGY Cairo 2006 171 28[21-35]
Ashour(2009) EGY Cairo 2006 171 13[9-19]
Ashour(2009) EGY Cairo 2006 171 59[52-66]
Ghenghesh(2009) LBY Tripoli 2006 19 11[2-33]
Ghenghesh(2009) LBY Tripoli 2006 29 10[3-27]
Zerouali(2016) OMN Dhahira 2006 35 0[0-12]
Patel(2011) OMN Dhahira 2006 35 0[0-12]
Zerouali(2016) OMN Dhahira 2006 35 6[1-20]
Patel(2011) OMN Dhahira 2006 35 6[1-20]
Thabet(2010) TUN Tunis 2006 350 1[0-3]
Thabet(2010) TUN Tunis 2006 350 5[3-8]
Abou-Dobara(2010) EGY Mansoura 2007 39 0[0-11]
Saied(2011) EGY Cairo & Alexandria 2007 22 68[47-84]
Saied(2011) EGY Cairo & Alexandria 2007 22 41[23-61]
Kanj(2014) LBN Uknown 2007 27 0[0-15]
Kanj(2014) OMN Uknown 2007 26 0[0-15]
Ferjani(2012) TUN Tunis 2007 89 11[6-20]
Ferjani(2012) TUN Tunis 2007 40 32[20-48]
Ferjani(2012) TUN Tunis 2007 40 18[8-32]
Ferjani(2012) TUN Tunis 2007 40 40[26-55]
Ferjani(2012) TUN Tunis 2007 89 9[4-17]
Ferjani(2012) TUN Tunis 2007 89 16[9-25]
Ferjani(2014) TUN Tunis 2007 201 17[13-23]
Ferjani(2014) TUN Tunis 2007 201 24[18-30]
Ashour(2011) EGY Minya 2008 50 16[8-29]
Ashour(2011) EGY Minya 2008 50 36[24-50]
Ashour(2011) EGY Minya 2008 50 30[19-44]
Rahbar(2010) IRN Mehran 2008 10 10[0-43]
Rahbar(2010) IRN Mehran 2008 10 90[57-100]
Murphy(2011) IRQ Uknown 2008 30 17[7-34]
Murphy(2011) IRQ Uknown 2008 30 74[55-86]
Elotmani(2010) MAR El Jadida 2008 80 14[8-23]
Elotmani(2010) MAR El Jadida 2008 80 9[4-17]
Elotmani(2010) MAR El Jadida 2008 80 0[0-5]
Saeed(2017) SDN Khartoum 2008 37 54[38-69]
Saeed(2017) SDN Khartoum 2008 37 30[17-46]
Thabit(2011) EGY Assiut 2009 136 48[40-56]
Hosny(2010) EGY Giza 2009 124 25[18-33]
Hosny(2010) EGY Giza 2009 235 19[14-24]
Salem(2010) EGY Cairo 2009 188 32[26-39]
Salem(2010) EGY Cairo 2009 188 27[21-34]
Ferjani(2011) TUN Sousse 2009 41 5[0-17]
Median prevalence [IQR] 2005-2009 17[8-33]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Bentroki(2012) DZA Guelma 2010 786 4[3-6]
Bentroki(2012) DZA Guelma 2010 786 13[11-16]
Bentroki(2012) DZA Guelma 2010 786 1[0-2]
Fahmey(2013) EGY Beni-Suef 2010 19 53[32-73]
Fahmey(2013) EGY Beni-Suef 2010 19 58[36-77]
Fahmey(2013) EGY Beni-Suef 2010 19 42[23-64]
Aboshanab(2013) EGY Cairo 2010 74 7[3-15]
Aboshanab(2013) EGY Cairo 2010 74 16[9-26]
Aboshanab(2013) EGY Cairo 2010 74 4[1-12]
Aboshanab(2013) EGY Cairo 2010 74 28[19-40]
Al-Talib(2013) IRQ Mosul 2010 25 36[20-56]
Al-Talib(2013) IRQ Mosul 2010 25 12[3-31]
Makia(2013) IRQ Uknown 2010 9 100[66-100]
Boutbaoucht(2013) MAR Marrakech 2010 15 0[0-24]
El-Naggari(2014) OMN Muscat 2010 120 11[6-18]
El-Naggari(2014) OMN Muscat 2010 120 0[0-4]
El-Naggari(2015) OMN Muscat 2010 120 0[0-4]
El-Naggari(2015) OMN Muscat 2010 187 3[1-7]
El-Naggari(2015) OMN Muscat 2010 187 10[7-15]
El-Naggari(2015) OMN Muscat 2010 120 11[6-18]
Smaoui(2015) TUN Sfax 2010 502 2[1-4]
Smaoui(2015) TUN Sfax 2010 502 10[7-13]
Smaoui(2015) TUN Sfax 2010 502 7[5-9]
Hecini-Hannachi(2016) DZA Constantine 2011 60 7[2-16]
Hecini-Hannachi(2016) DZA Constantine 2011 60 38[27-51]
Mohamed(2013) EGY Multiple Sites 2011 35 12[4-27]
Elgam(2014) EGY Mansoura 2011 25 0[0-16]
Elgam(2014) EGY Mansoura 2011 25 24[11-44]
Esmat(2012) EGY Sohag 2011 35 43[28-59]
Esmat(2012) EGY Sohag 2011 35 42[28-59]
Aboshanab(2014) EGY Cairo 2011 24 33[18-53]
Osman(2018) EGY Cairo 2011 29 55[38-72]
Kanj(2014) ISR Uknown 2011 651 1[1-2]
Kanj(2014) JOR Uknown 2011 48 0[0-9]
Daw(2013) LBY Tripoli 2011 107 0[0-4]
Daw(2013) LBY Tripoli 2011 107 56[47-65]
El bouamri(2014) MAR Marrakech 2011 857 8[6-10]
Wang(2016) MAR Marrakech 2011 857 8[6-10]
El bouamri(2014) MAR Marrakech 2011 857 14[12-16]
Wang(2016) MAR Marrakech 2011 857 14[12-16]
El bouamri(2014) MAR Marrakech 2011 67 66[54-76]
Wang(2016) MAR Marrakech 2011 67 66[54-76]
El bouamri(2014) MAR Marrakech 2011 67 56[45-68]
Wang(2016) MAR Marrakech 2011 67 56[45-68]
Kanj(2014) SAU Uknown 2011 48 4[0-15]
Ibrahim(2012) SDN Khartoum 2011 32 3[0-17]
Ibrahim(2012) SDN Khartoum 2011 42 5[0-17]
Ibrahim(2012) SDN Khartoum 2011 11 0[0-30]
Ibrahim(2012) SDN Khartoum 2011 68 2[0-9]
Ibrahim(2012) SDN Khartoum 2011 35 0[0-12]
Ibrahim(2012) SDN Khartoum 2011 26 0[0-15]
Ibrahim(2012) SDN Khartoum 2011 68 35[25-47]
Ibrahim(2012) SDN Khartoum 2011 42 40[27-56]
Ibrahim(2012) SDN Khartoum 2011 35 37[23-54]
Ibrahim(2012) SDN Khartoum 2011 11 9[0-40]
Ibrahim(2012) SDN Khartoum 2011 26 38[22-58]
Ibrahim(2012) SDN Khartoum 2011 32 31[18-49]
Ibrahim(2012) SDN Khartoum 2011 26 31[16-50]
Ibrahim(2012) SDN Khartoum 2011 68 19[11-30]
Ibrahim(2012) SDN Khartoum 2011 32 9[2-25]
Ibrahim(2012) SDN Khartoum 2011 11 36[15-65]
Ibrahim(2012) SDN Khartoum 2011 35 17[8-33]
Ibrahim(2012) SDN Khartoum 2011 42 12[5-25]
Ferjani(2015) TUN Tunis 2011 37 27[15-43]
Kothari(2008) TUN Tunis 2011 37 27[15-43]
Ferjani(2015) TUN Tunis 2011 63 3[0-11]
Kothari(2008) TUN Tunis 2011 63 3[0-11]
Ferjani(2015) TUN Tunis 2011 63 5[1-14]
Kothari(2008) TUN Tunis 2011 63 5[1-14]
Ferjani(2015) TUN Tunis 2011 37 16[7-32]
Kothari(2008) TUN Tunis 2011 37 16[7-32]
Smaoui(2015) TUN Sfax 2011 362 0[0-2]
Smaoui(2015) TUN Sfax 2011 362 10[7-13]
Smaoui(2015) TUN Sfax 2011 362 9[6-12]
(2016) TUN Tunis 2011 48 4[0-15]
(2016) TUN Tunis 2011 48 8[3-20]
Yilmaz(2016) TUR Izmir 2011 8975 3[3-3]
Yilmaz(2016) TUR Izmir 2011 8975 1[0-1]
Median prevalence [IQR] 2010-2014 10[4-33]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

C

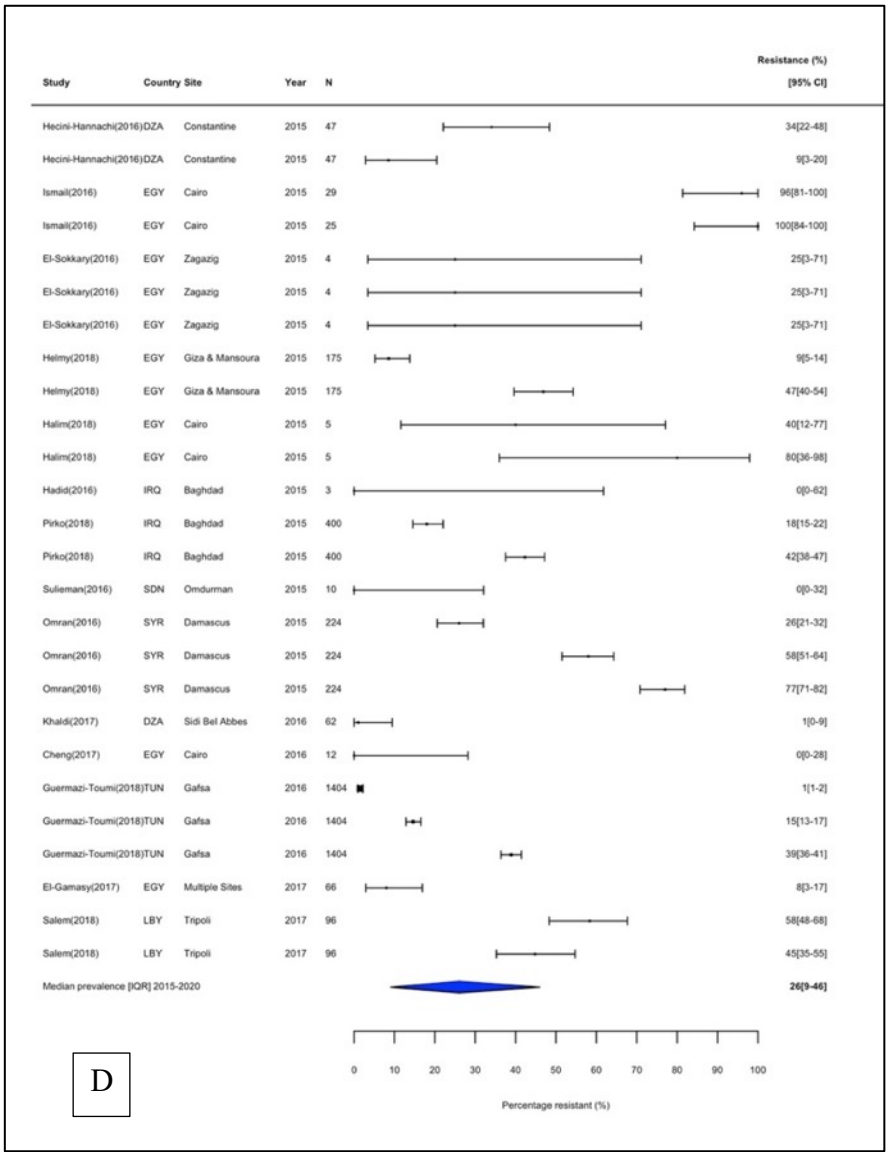


Figure C.45: Forest plot of aminoglycosides resistance in North Africa and the Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2014, D: 2015-2018.

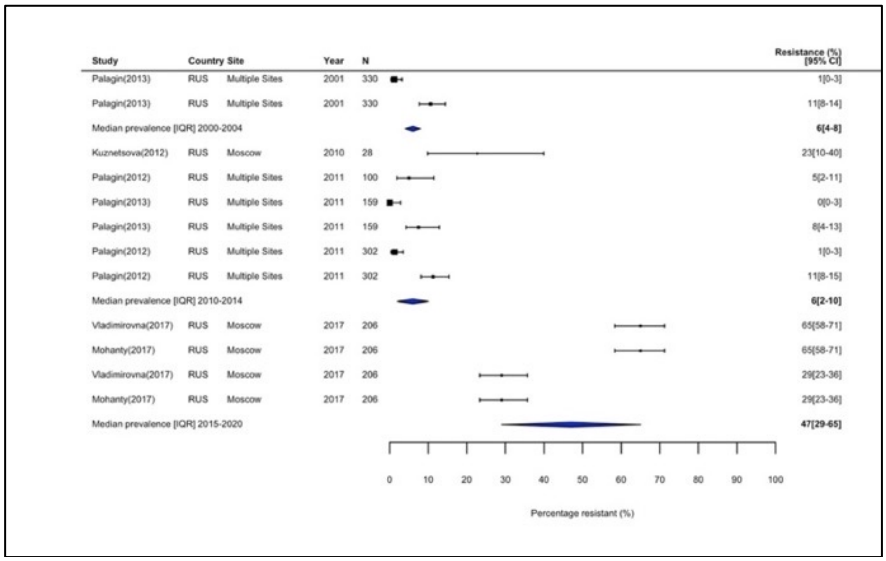
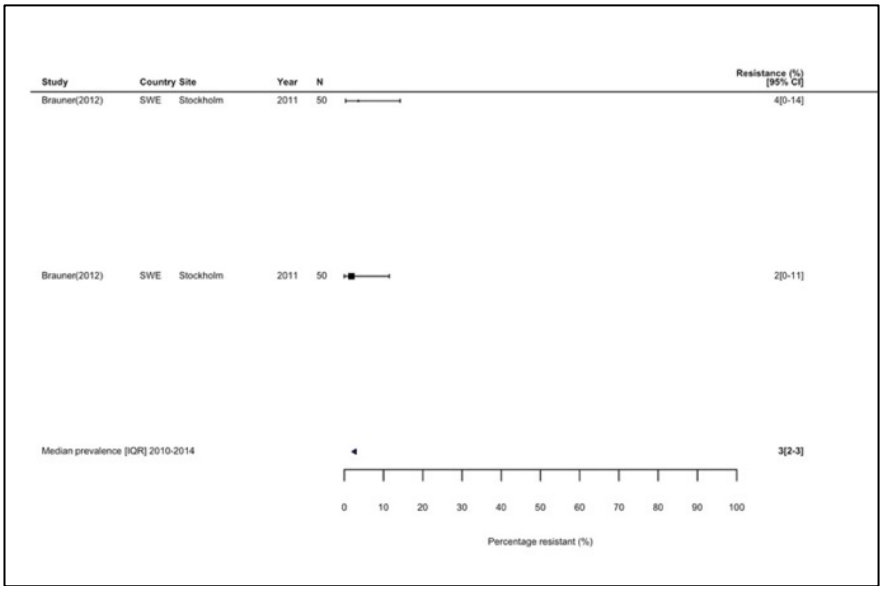


Figure C.46: Forest plot of aminoglycosides resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.



***Fi**gure C.47: Forest plot of aminoglycosides resistance in Western Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.*

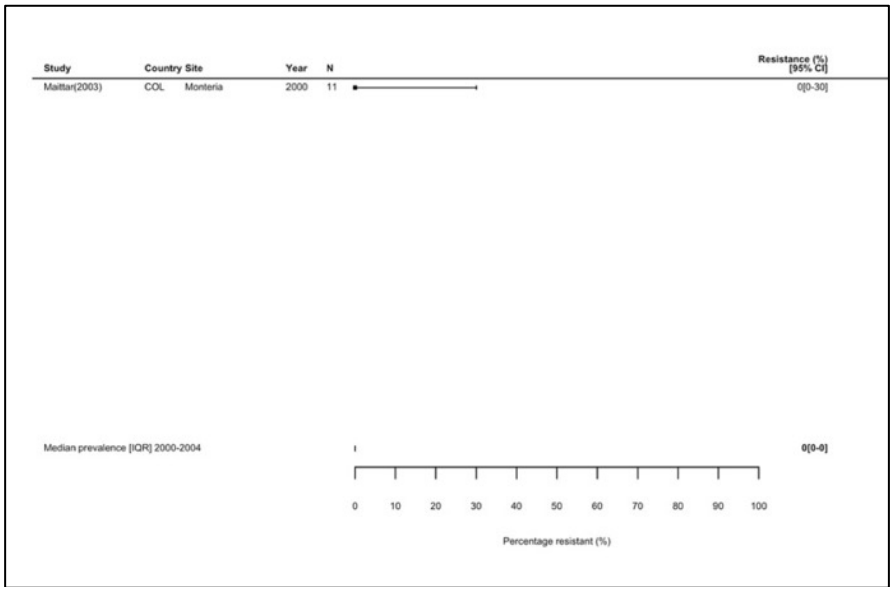


Figure C.48: Forest plot of piperacillin-tazobactam resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

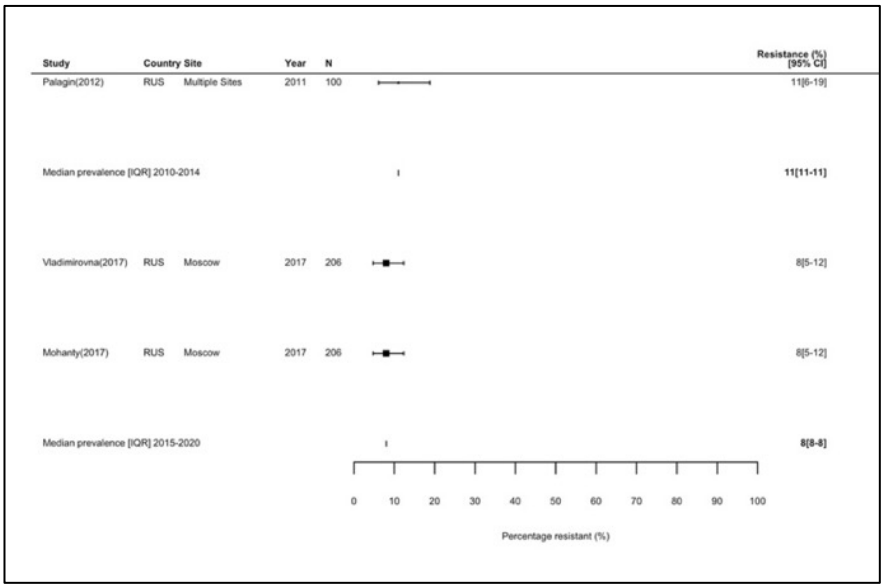


Figure C.49: Forest plot of piperacillin-tazobactam resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

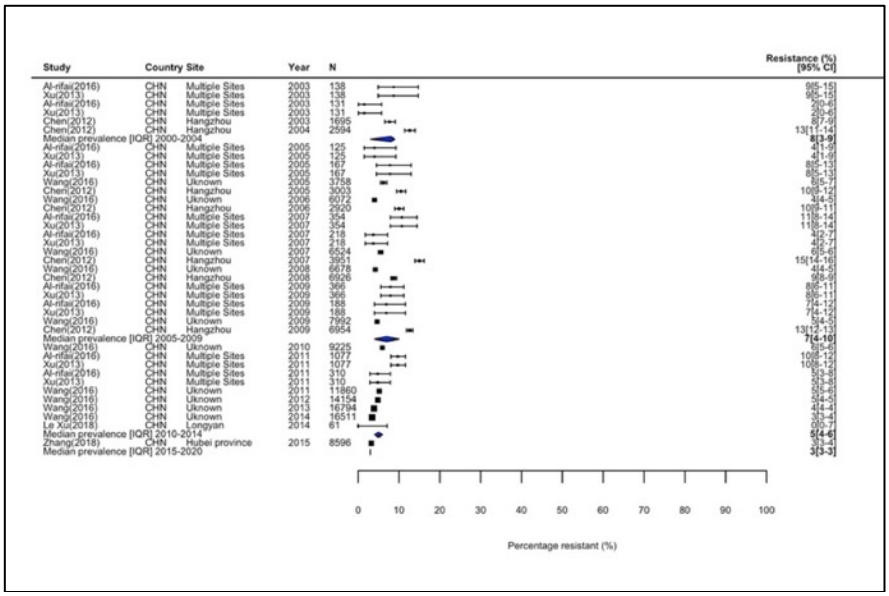


Figure C.50: Forest plot of piperacillin-tazobactam resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

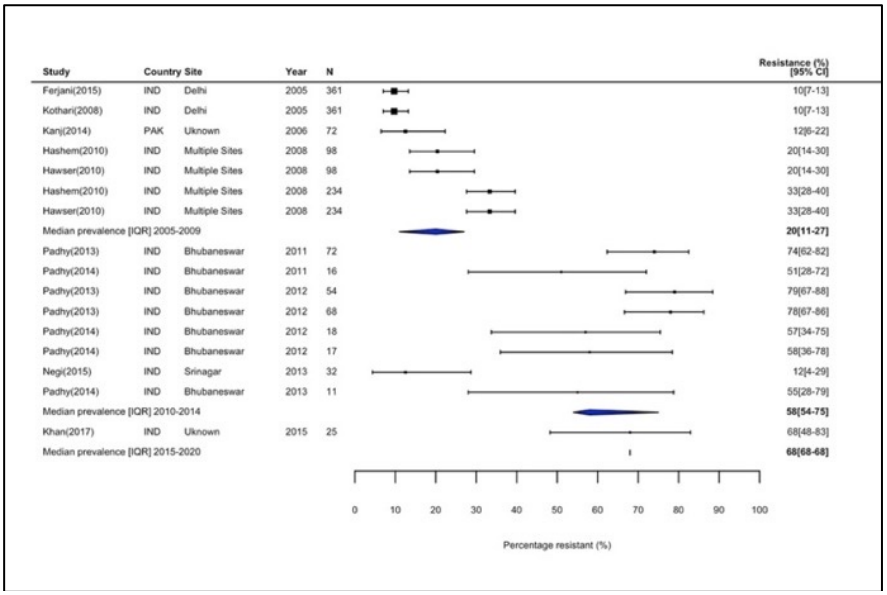


Figure C.51: Forest plot of piperacillin-tazobactam resistance in South Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

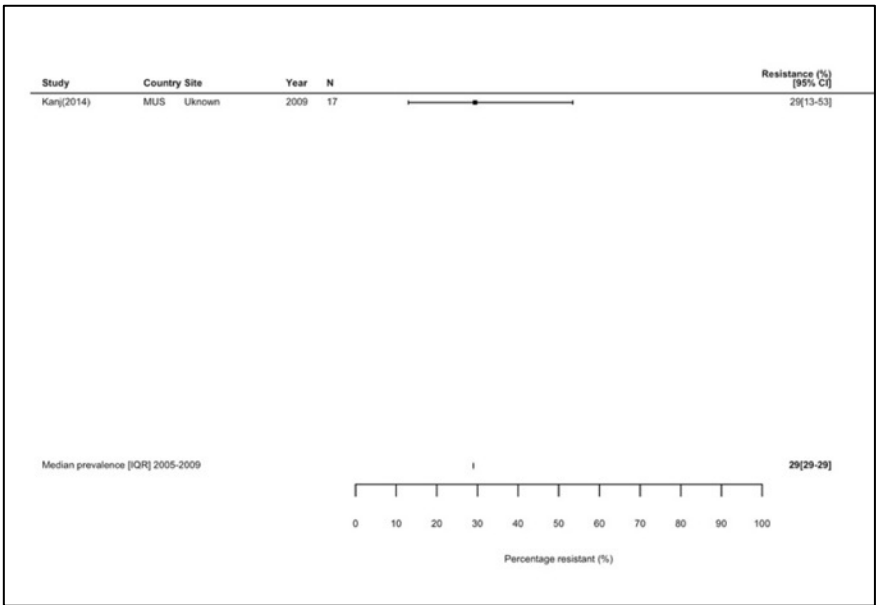


Figure C.52: Forest plot of piperacillin-tazobactam resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

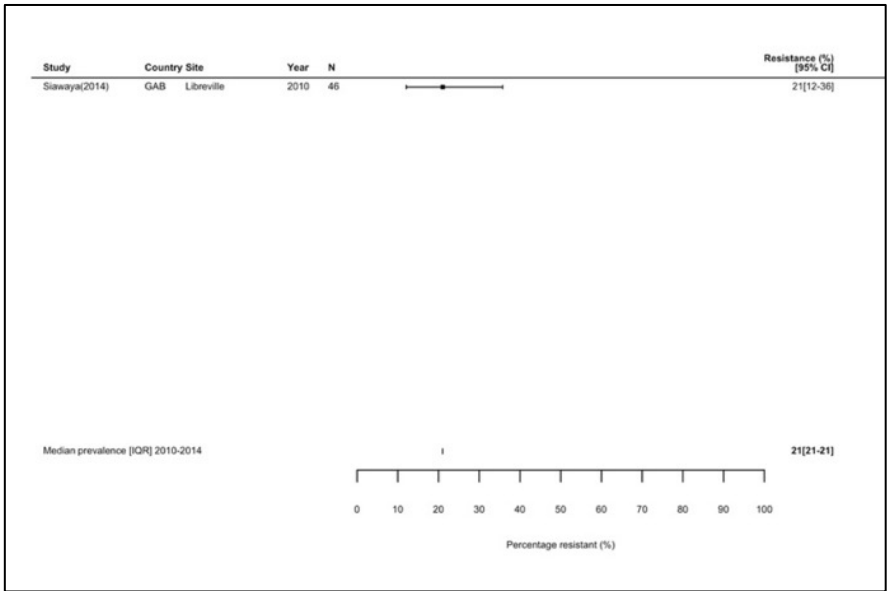


Figure C.53: Forest plot of piperacillin-tazobactam resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

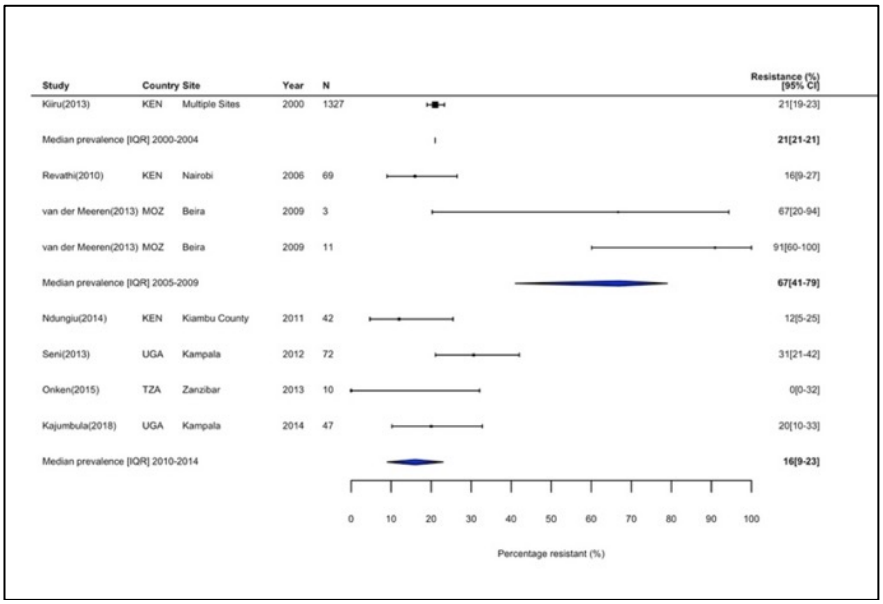


Figure C.54: Forest plot of piperacillin-tazobactam resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

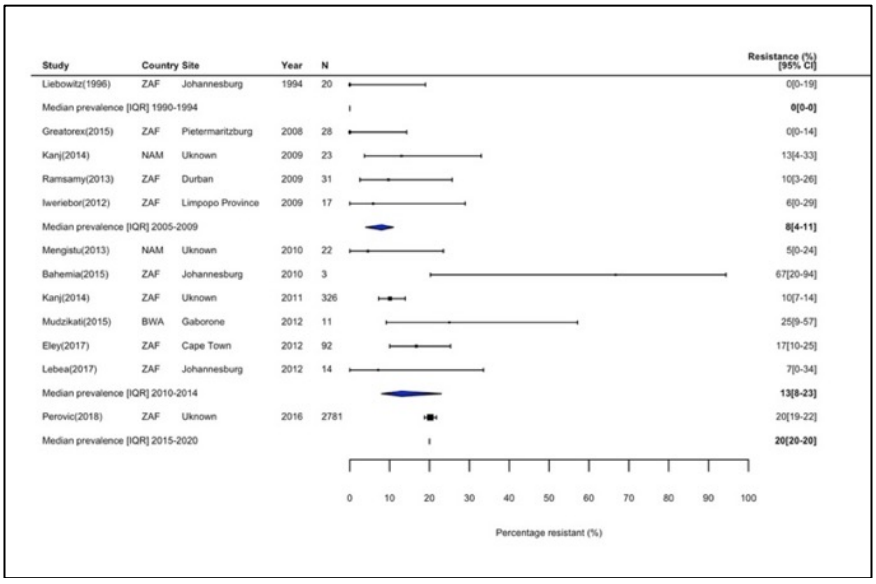


Figure C.55: Forest plot of piperacillin-tazobactam resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

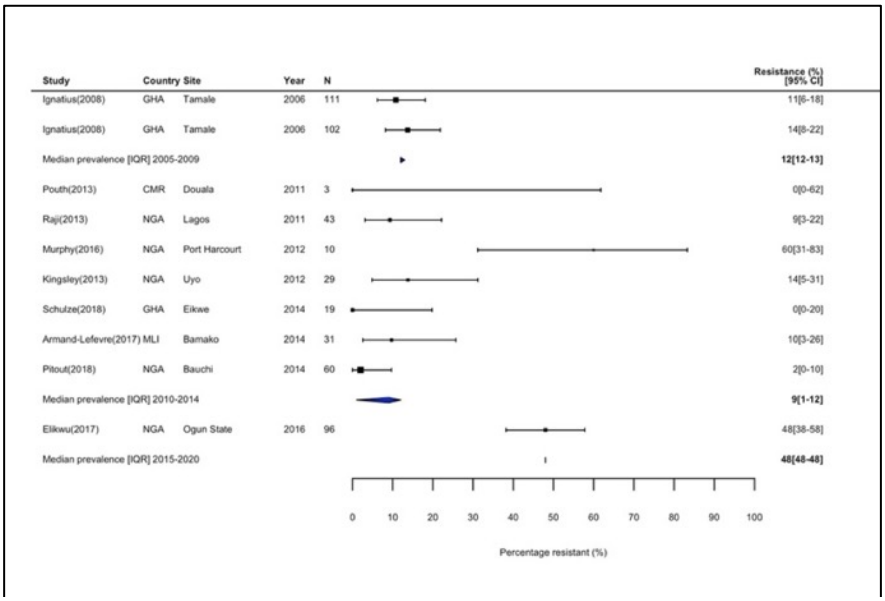


Figure C.56: Forest plot of piperacillin-tazobactam resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

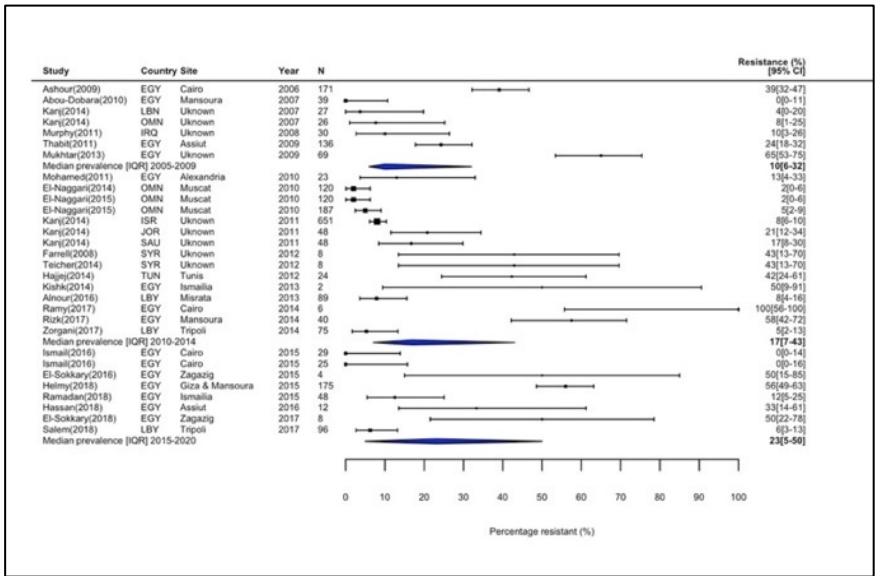


Figure C.57: Forest plot of piperacillin-tazobactam resistance in North Africa Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

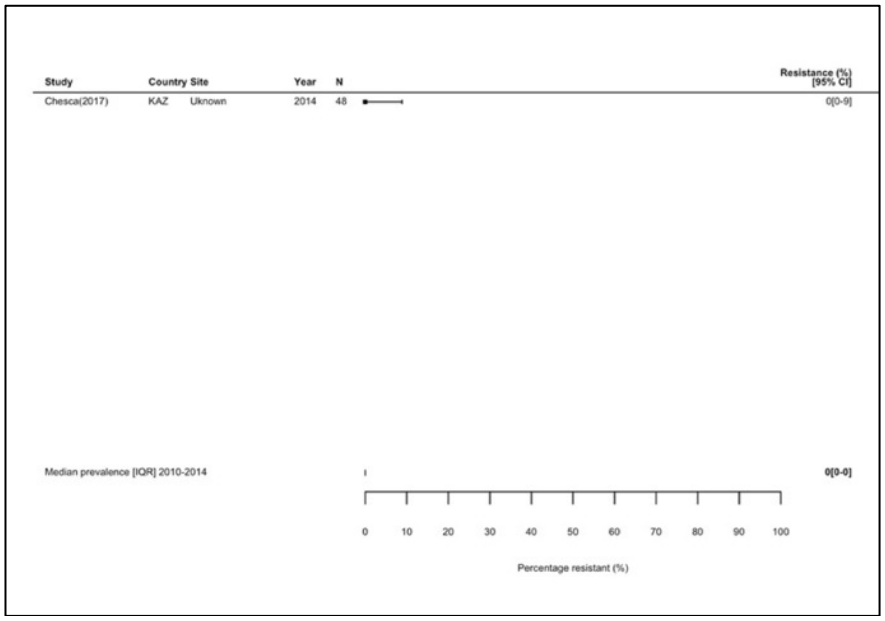


Figure C.58: Forest plot of fourth-generation cephalosporin resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

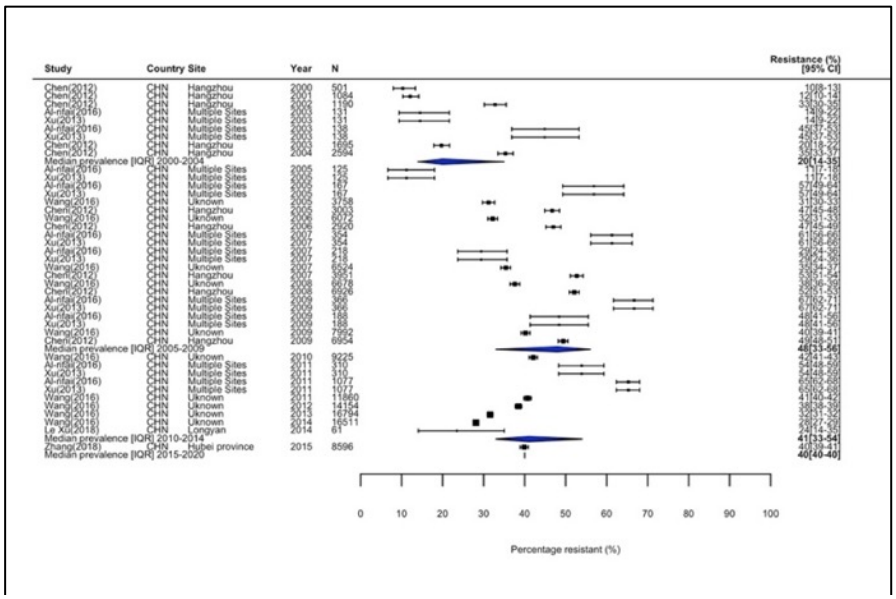


Figure C.59: Forest plot of fourth-generation cephalosporin resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

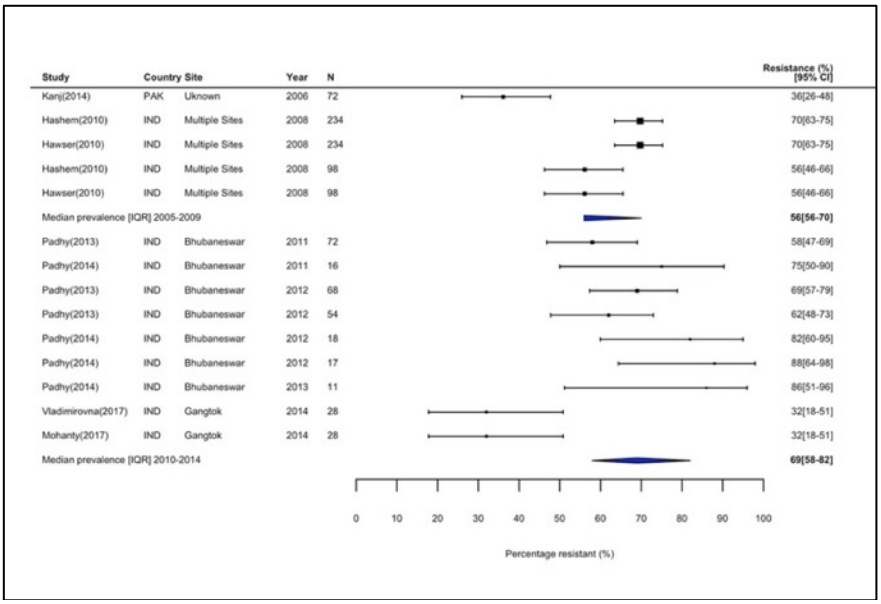


Figure C.60: Forest plot of fourth-generation cephalosporin resistance in South Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

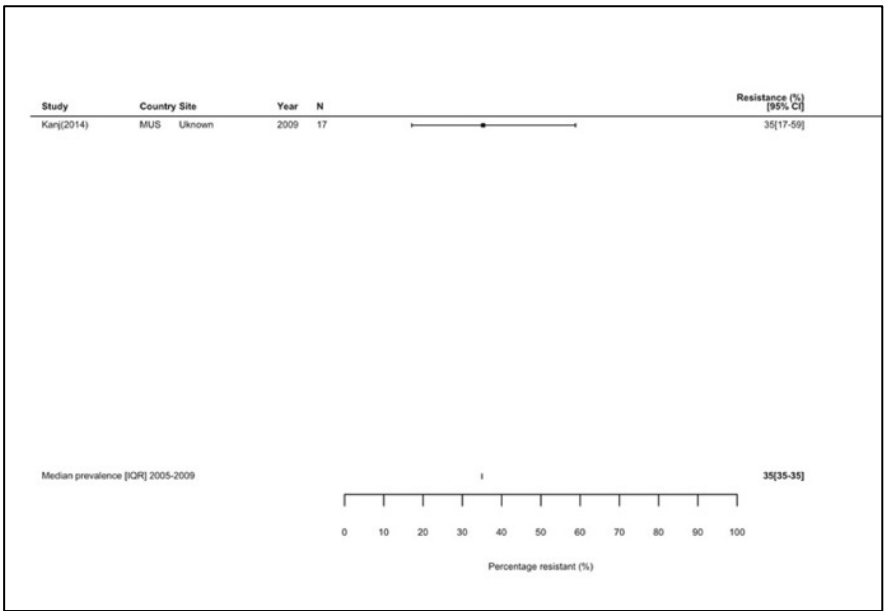


Figure C.61: Forest plot of fourth-generation cephalosporin resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

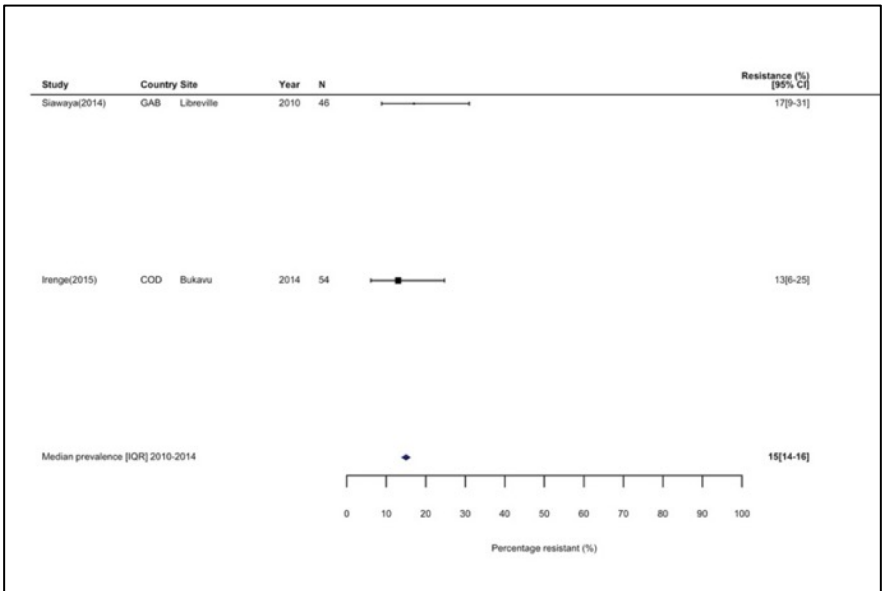


Figure C.62: Forest plot of fourth-generation cephalosporin resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

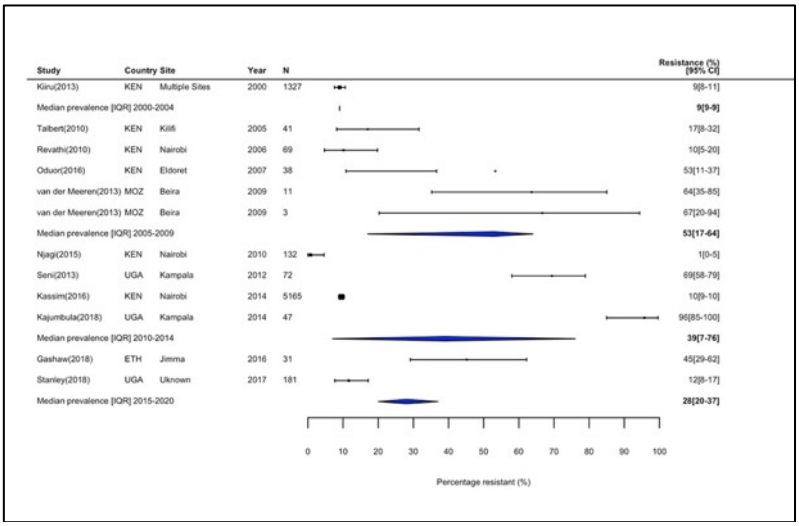


Figure C.63 Forest plot of fourth-generation cephalosporin resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

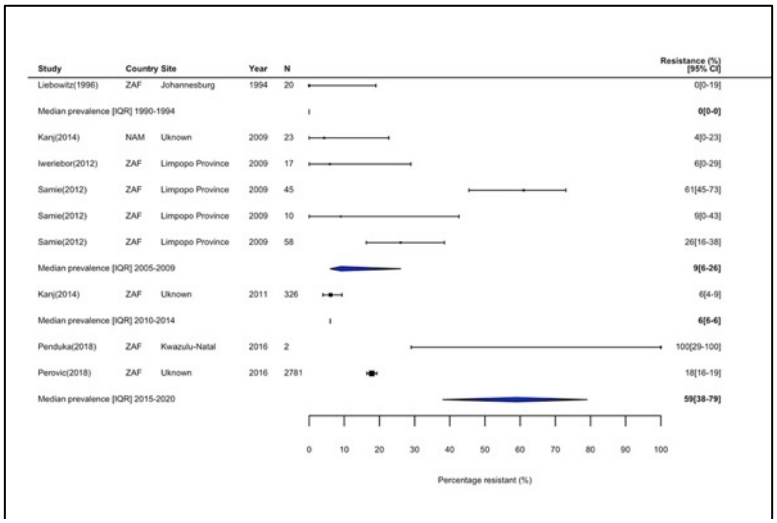


Figure C.64: Forest plot of fourth-generation cephalosporin resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

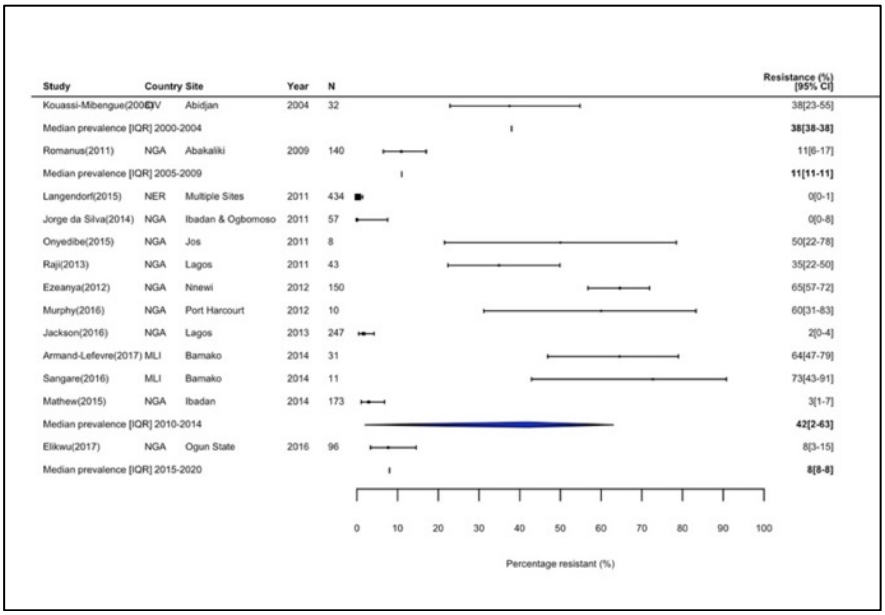


Figure C.65: Forest plot of fourth-generation cephalosporin resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

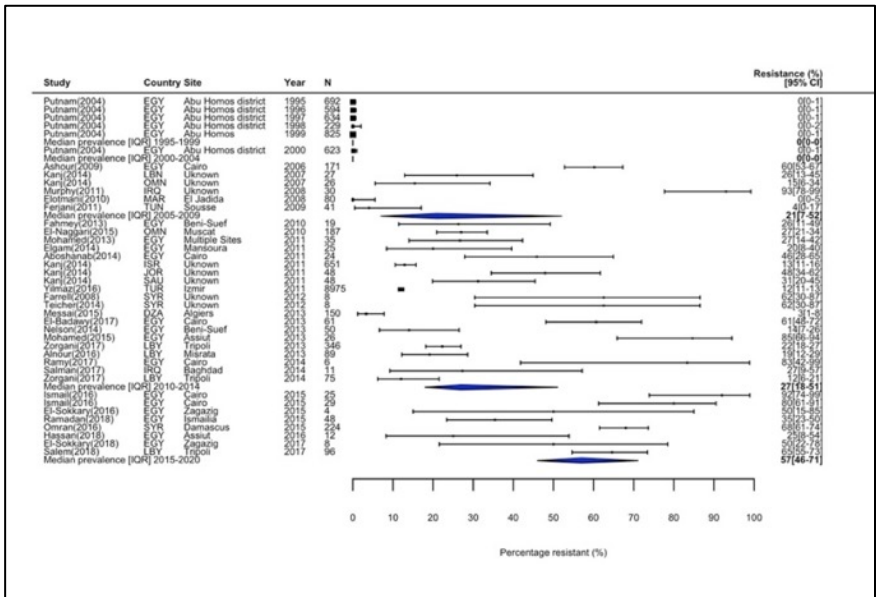


Figure C.66: Forest plot of fourth-generation cephalosporin resistance in North Africa and the Middle East. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

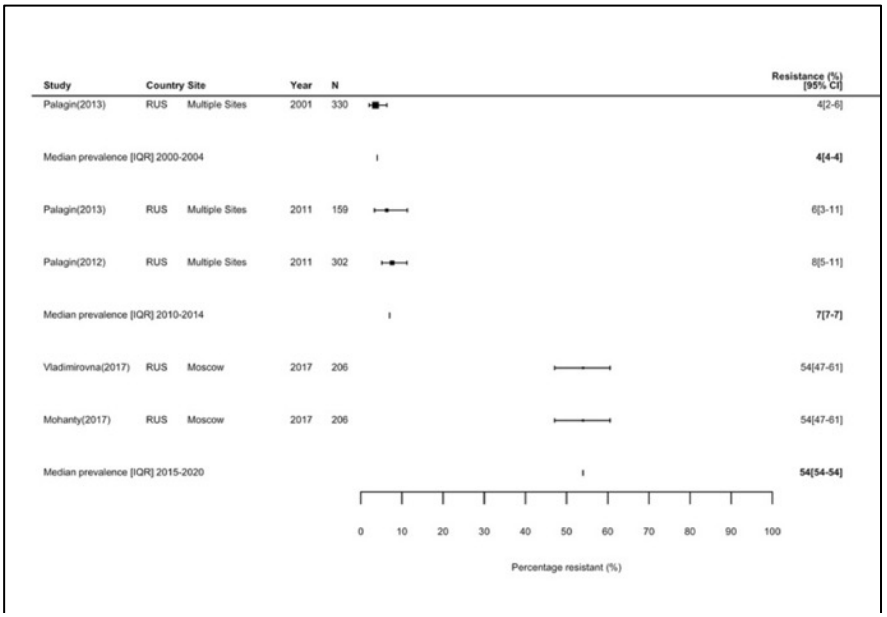


Figure C.67: Forest plot of fourth-generation cephalosporin resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

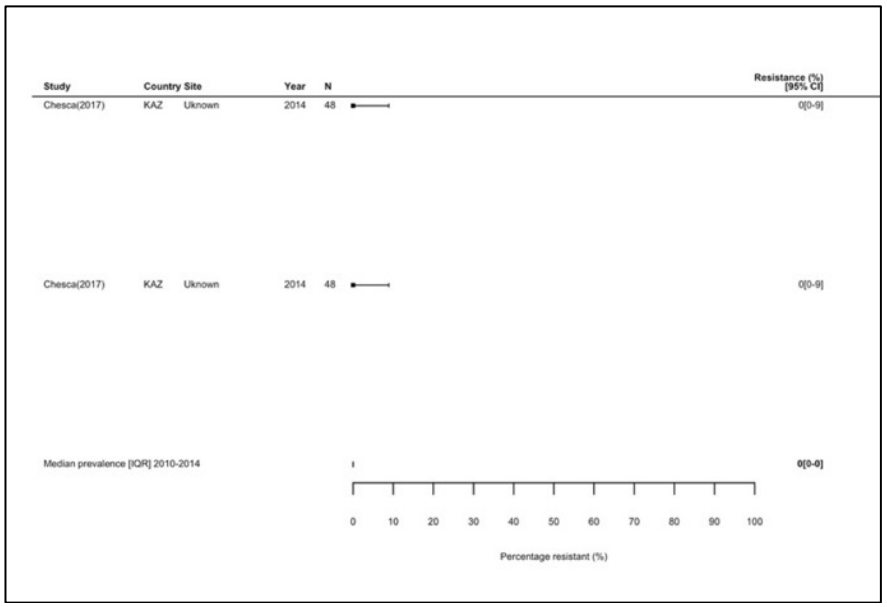
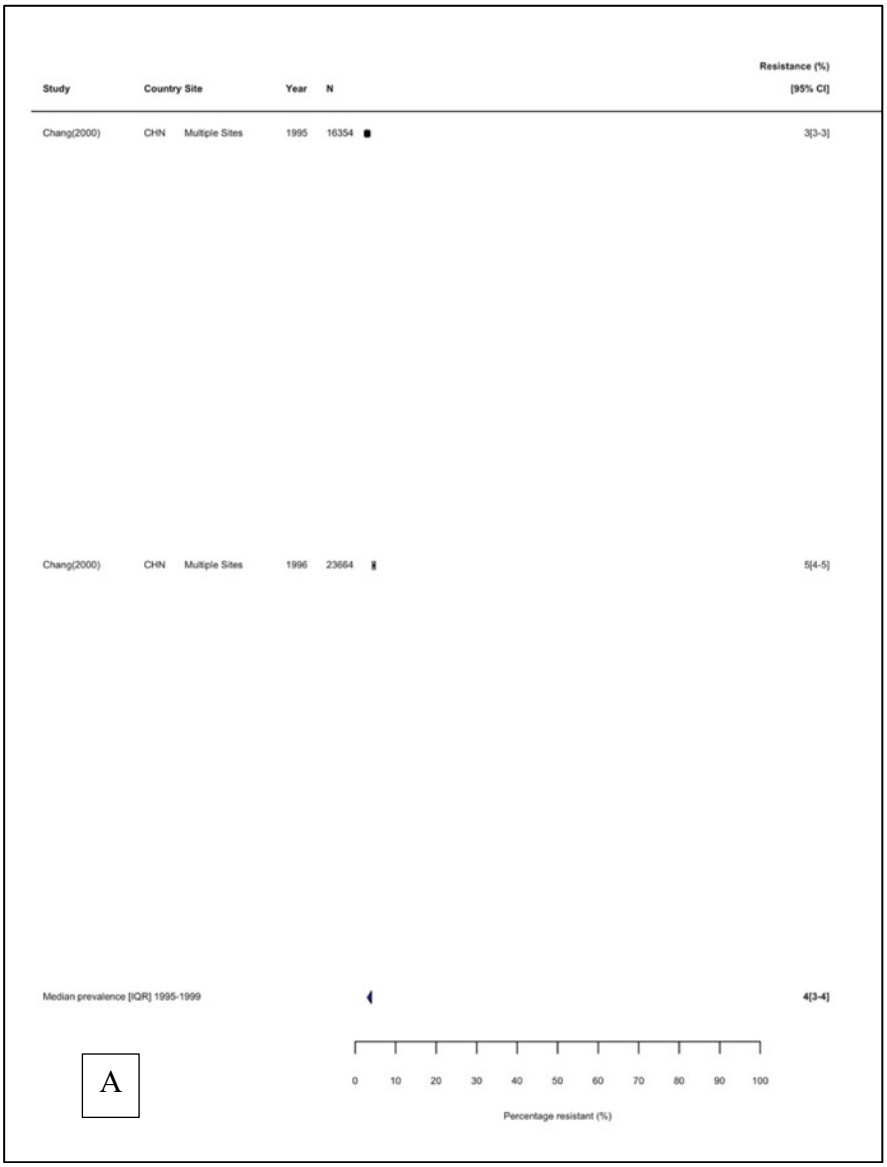
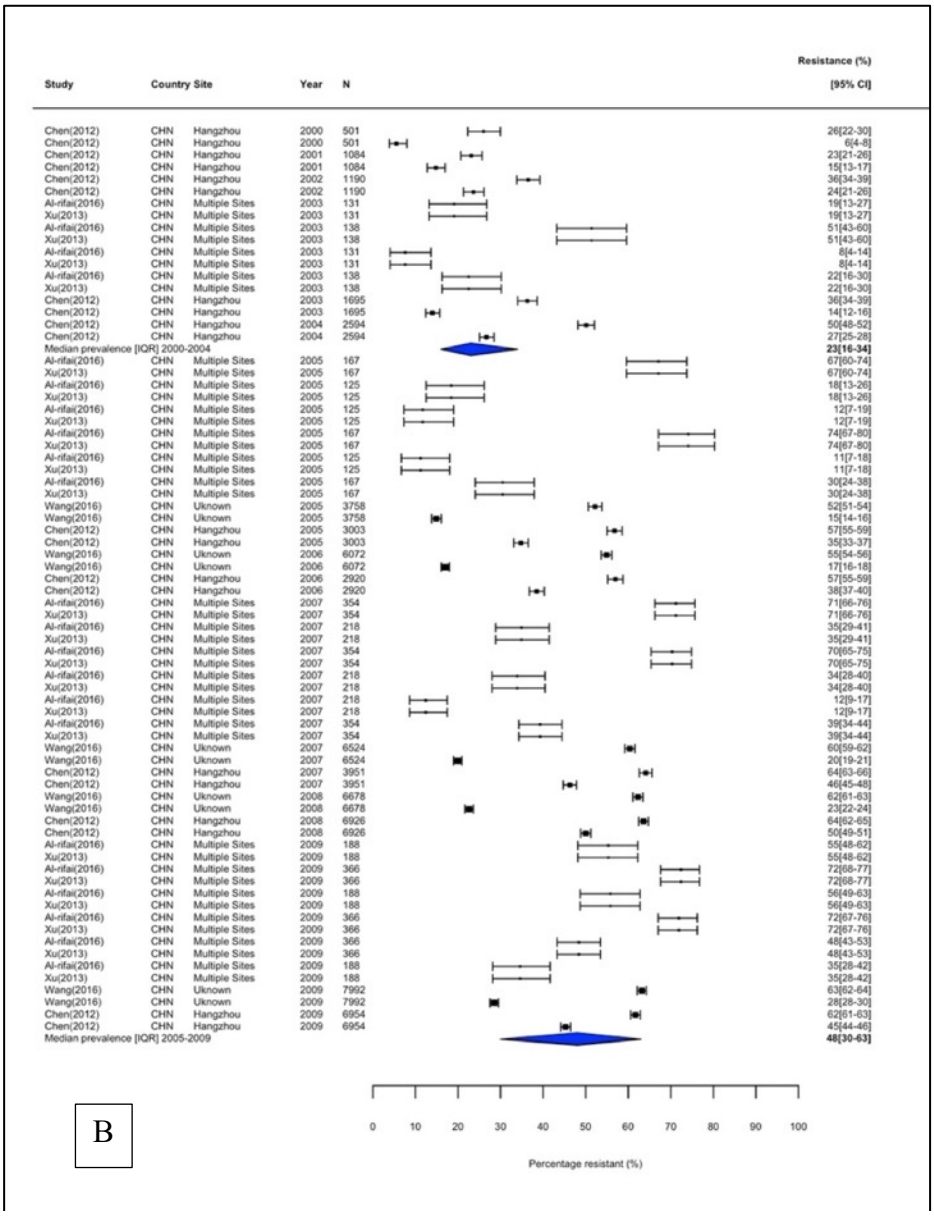


Figure C.68: Forest plot of third-generation cephalosporin resistance in Central Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.


Study
Country
Site
Year
N
Resistance (%) [95% CI]
Chang(2000) CHN Multiple Sites 1995 16354 3[3-3]
Chang(2000) CHN Multiple Sites 1996 23664 5[4-5]
Median prevalence [IQR] 1995-1999 4[3-4]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

A


Study
Country Site
Year
N
Resistance (%)
[95% CI]
Chen(2012) CHN Hangzhou 2000 501 26[22-30]
Chen(2012) CHN Hangzhou 2000 501 6[4-8]
Chen(2012) CHN Hangzhou 2001 1084 23[21-26]
Chen(2012) CHN Hangzhou 2001 1084 15[13-17]
Chen(2012) CHN Hangzhou 2002 1190 36[34-39]
Chen(2012) CHN Hangzhou 2002 1190 24[21-26]
Al-rifai(2016) CHN Multiple Sites 2003 131 19[13-27]
Xu(2013) CHN Multiple Sites 2003 131 19[13-27]
Al-rifai(2016) CHN Multiple Sites 2003 138 51[43-60]
Xu(2013) CHN Multiple Sites 2003 138 51[43-60]
Al-rifai(2016) CHN Multiple Sites 2003 131 8[4-14]
Xu(2013) CHN Multiple Sites 2003 131 8[4-14]
Al-rifai(2016) CHN Multiple Sites 2003 138 22[16-30]
Xu(2013) CHN Multiple Sites 2003 138 22[16-30]
Chen(2012) CHN Hangzhou 2003 1695 36[34-39]
Chen(2012) CHN Hangzhou 2003 1695 14[12-16]
Chen(2012) CHN Hangzhou 2004 2594 50[48-52]
Chen(2012) CHN Hangzhou 2004 2594 27[25-28]
Median prevalence [IQR] 2000-2004 23[16-34]
Al-rifai(2016) CHN Multiple Sites 2005 167 67[60-74]
Xu(2013) CHN Multiple Sites 2005 167 67[60-74]
Al-rifai(2016) CHN Multiple Sites 2005 125 18[13-26]
Xu(2013) CHN Multiple Sites 2005 125 18[13-26]
Al-rifai(2016) CHN Multiple Sites 2005 125 12[7-19]
Xu(2013) CHN Multiple Sites 2005 125 12[7-19]
Al-rifai(2016) CHN Multiple Sites 2005 167 74[67-80]
Xu(2013) CHN Multiple Sites 2005 167 74[67-80]
Al-rifai(2016) CHN Multiple Sites 2005 125 11[7-18]
Xu(2013) CHN Multiple Sites 2005 125 11[7-18]
Al-rifai(2016) CHN Multiple Sites 2005 167 30[24-38]
Xu(2013) CHN Multiple Sites 2005 167 30[24-38]
Wang(2016) CHN Uknown 2005 3758 52[51-54]
Wang(2016) CHN Uknown 2005 3758 15[14-16]
Chen(2012) CHN Hangzhou 2005 3003 57[55-59]
Chen(2012) CHN Hangzhou 2005 3003 35[33-37]
Wang(2016) CHN Uknown 2006 6072 55[54-56]
Wang(2016) CHN Uknown 2006 6072 17[16-18]
Chen(2012) CHN Hangzhou 2006 2920 57[55-59]
Chen(2012) CHN Hangzhou 2006 2920 38[37-40]
Al-rifai(2016) CHN Multiple Sites 2007 354 71[66-76]
Xu(2013) CHN Multiple Sites 2007 354 71[66-76]
Al-rifai(2016) CHN Multiple Sites 2007 218 35[29-41]
Xu(2013) CHN Multiple Sites 2007 218 35[29-41]
Al-rifai(2016) CHN Multiple Sites 2007 354 70[65-75]
Xu(2013) CHN Multiple Sites 2007 354 70[65-75]
Al-rifai(2016) CHN Multiple Sites 2007 218 34[28-40]
Xu(2013) CHN Multiple Sites 2007 218 34[28-40]
Al-rifai(2016) CHN Multiple Sites 2007 218 12[9-17]
Xu(2013) CHN Multiple Sites 2007 218 12[9-17]
Al-rifai(2016) CHN Multiple Sites 2007 354 39[34-44]
Xu(2013) CHN Multiple Sites 2007 354 39[34-44]
Wang(2016) CHN Uknown 2007 6524 60[59-62]
Wang(2016) CHN Uknown 2007 6524 20[19-21]
Chen(2012) CHN Hangzhou 2007 3951 64[63-66]
Chen(2012) CHN Hangzhou 2007 3951 46[45-48]
Wang(2016) CHN Uknown 2008 6678 62[61-63]
Wang(2016) CHN Uknown 2008 6678 23[22-24]
Chen(2012) CHN Hangzhou 2008 6926 64[62-65]
Chen(2012) CHN Hangzhou 2008 6926 50[49-51]
Al-rifai(2016) CHN Multiple Sites 2009 188 55[48-62]
Xu(2013) CHN Multiple Sites 2009 188 55[48-62]
Al-rifai(2016) CHN Multiple Sites 2009 366 72[68-77]
Xu(2013) CHN Multiple Sites 2009 366 72[68-77]
Al-rifai(2016) CHN Multiple Sites 2009 188 56[49-63]
Xu(2013) CHN Multiple Sites 2009 188 56[49-63]
Al-rifai(2016) CHN Multiple Sites 2009 366 72[67-76]
Xu(2013) CHN Multiple Sites 2009 366 72[67-76]
Al-rifai(2016) CHN Multiple Sites 2009 366 48[43-53]
Xu(2013) CHN Multiple Sites 2009 366 48[43-53]
Al-rifai(2016) CHN Multiple Sites 2009 188 35[28-42]
Xu(2013) CHN Multiple Sites 2009 188 35[28-42]
Wang(2016) CHN Uknown 2009 7992 63[62-64]
Wang(2016) CHN Uknown 2009 7992 28[28-30]
Chen(2012) CHN Hangzhou 2009 6954 62[61-63]
Chen(2012) CHN Hangzhou 2009 6954 45[44-46]
Median prevalence [IQR] 2005-2009 48[30-63]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)
B

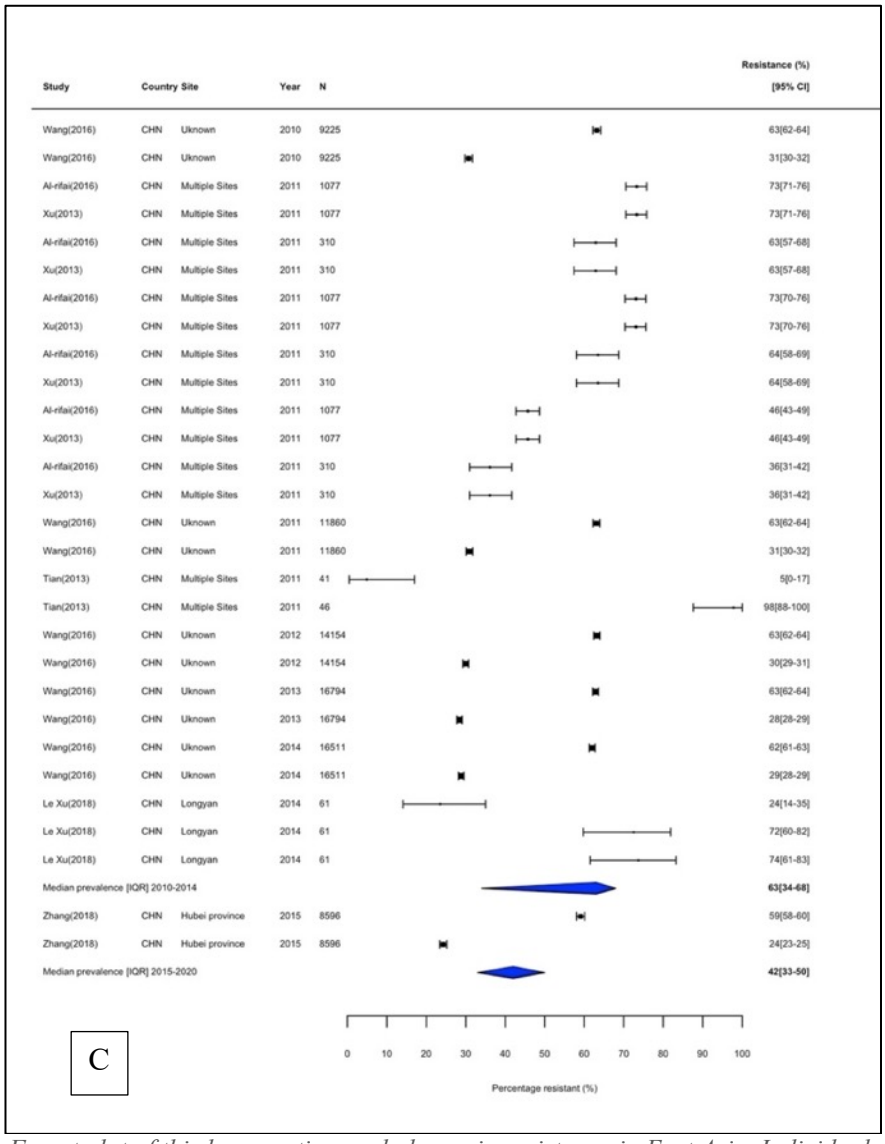


Figure C.69: Forest plot of third-generation cephalosporin resistance in East Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2018

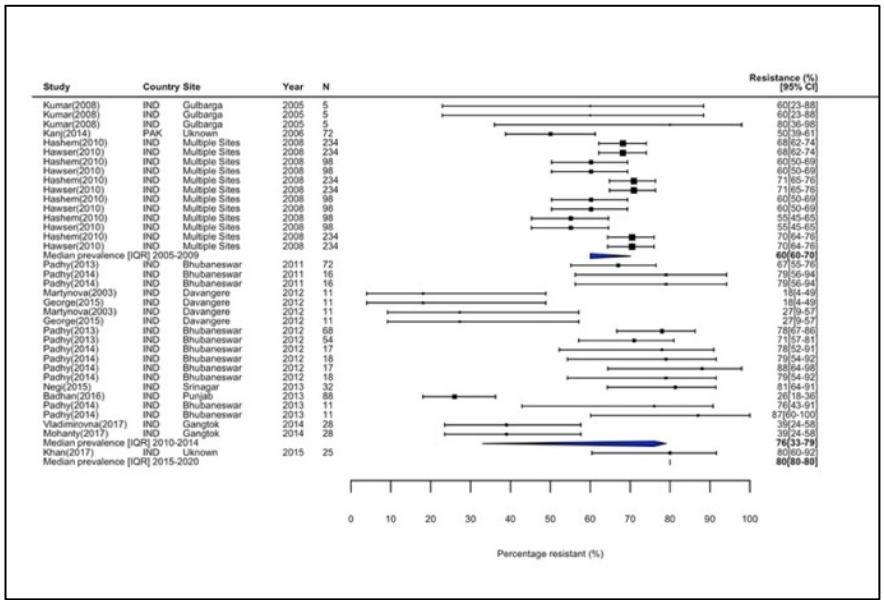


Figure C.70: Forest plot of third-generation cephalosporin resistance in South Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

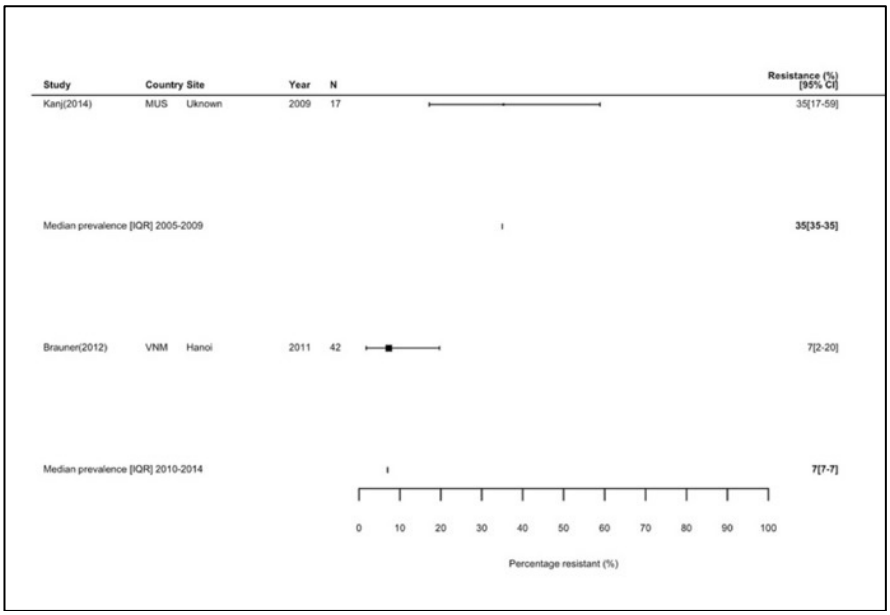


Figure C.71: Forest plot of third-generation cephalosporin resistance in Southeast Asia. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

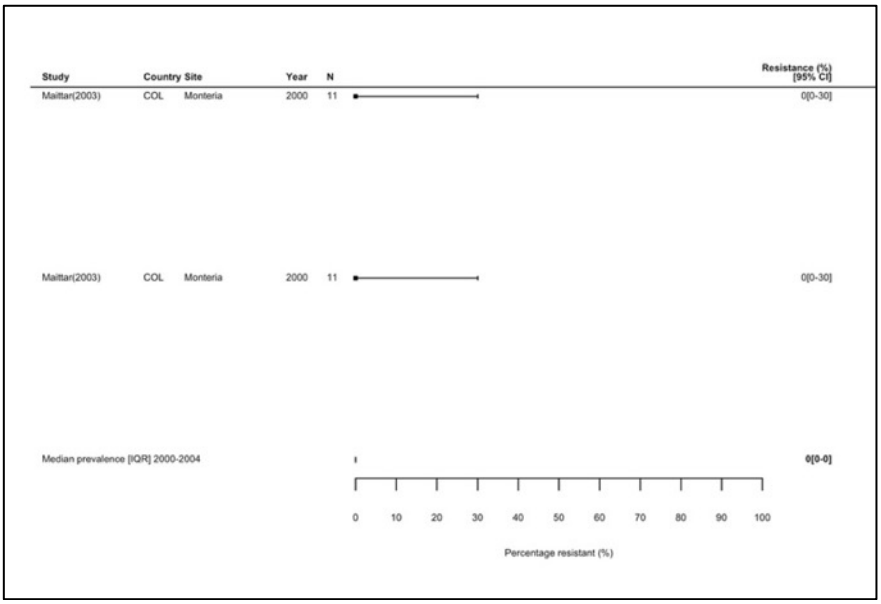


Figure C.72. Forest plot of third-generation cephalosporin resistance in Central Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

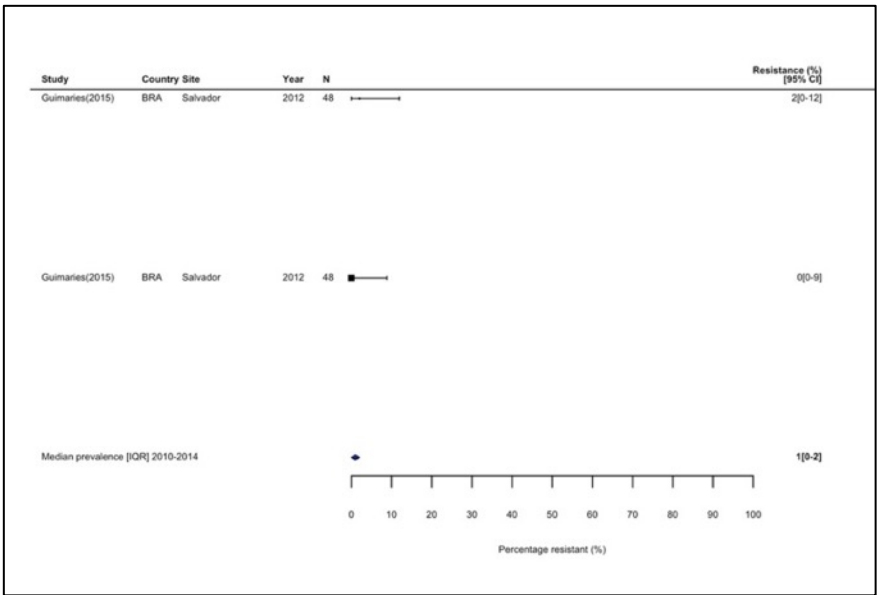


Figure C.73: Forest plot of third-generation cephalosporin resistance in Tropical Latin America. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

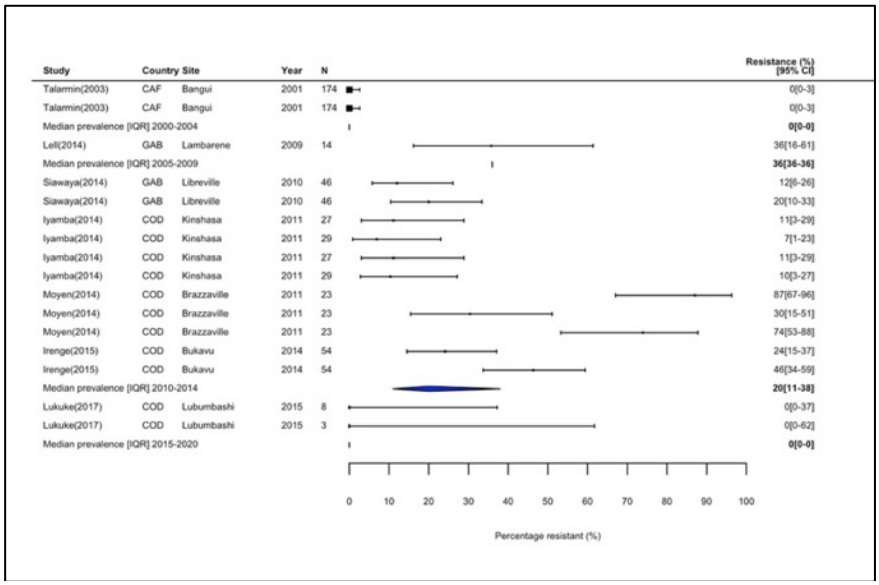
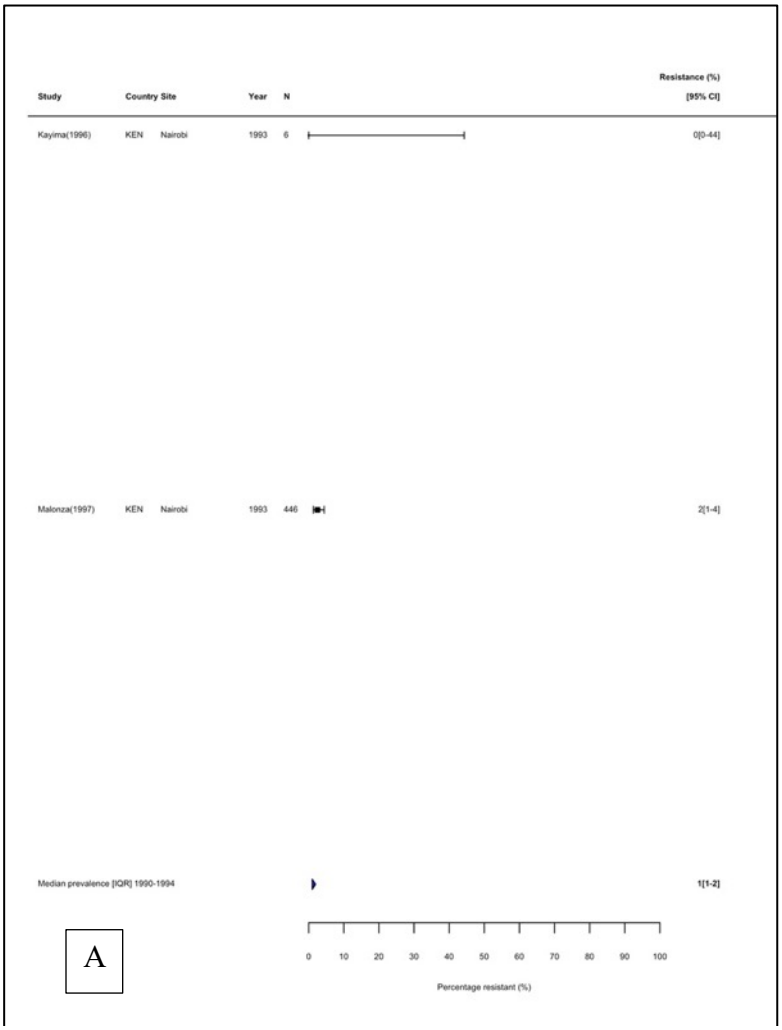
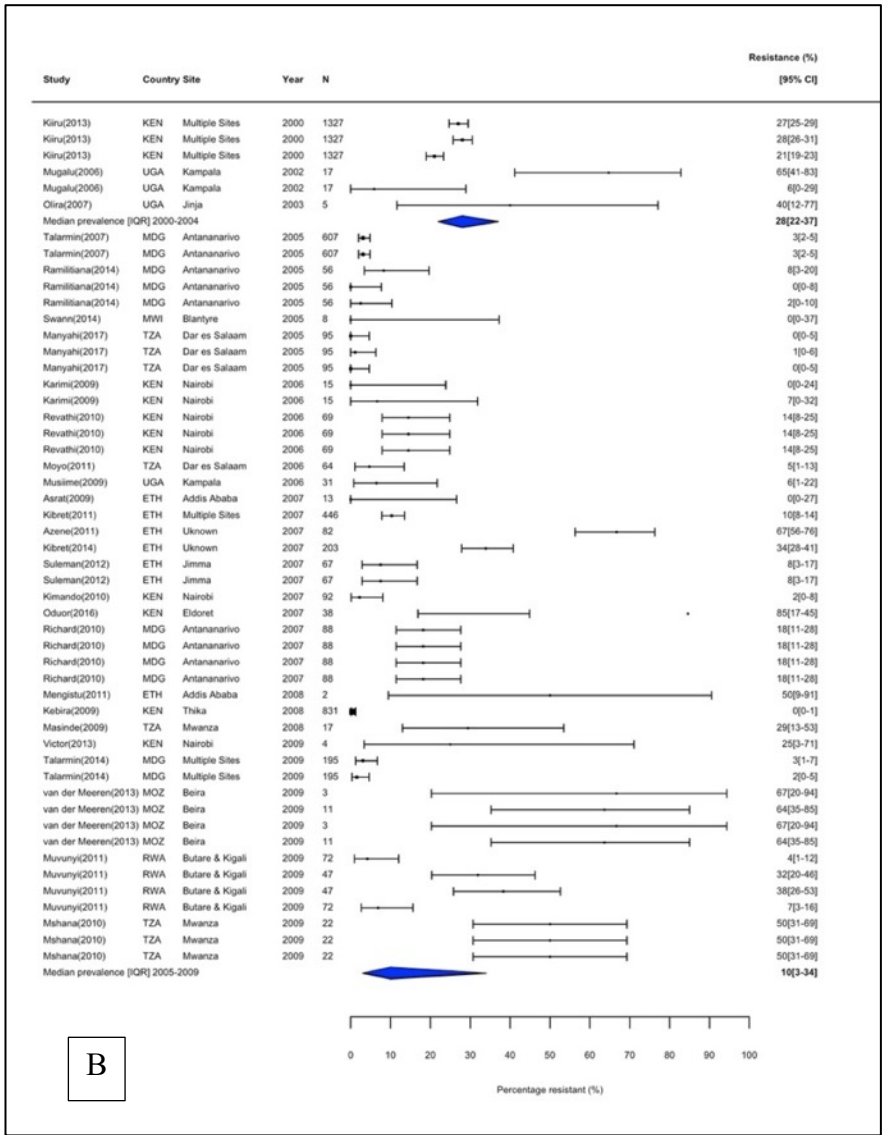
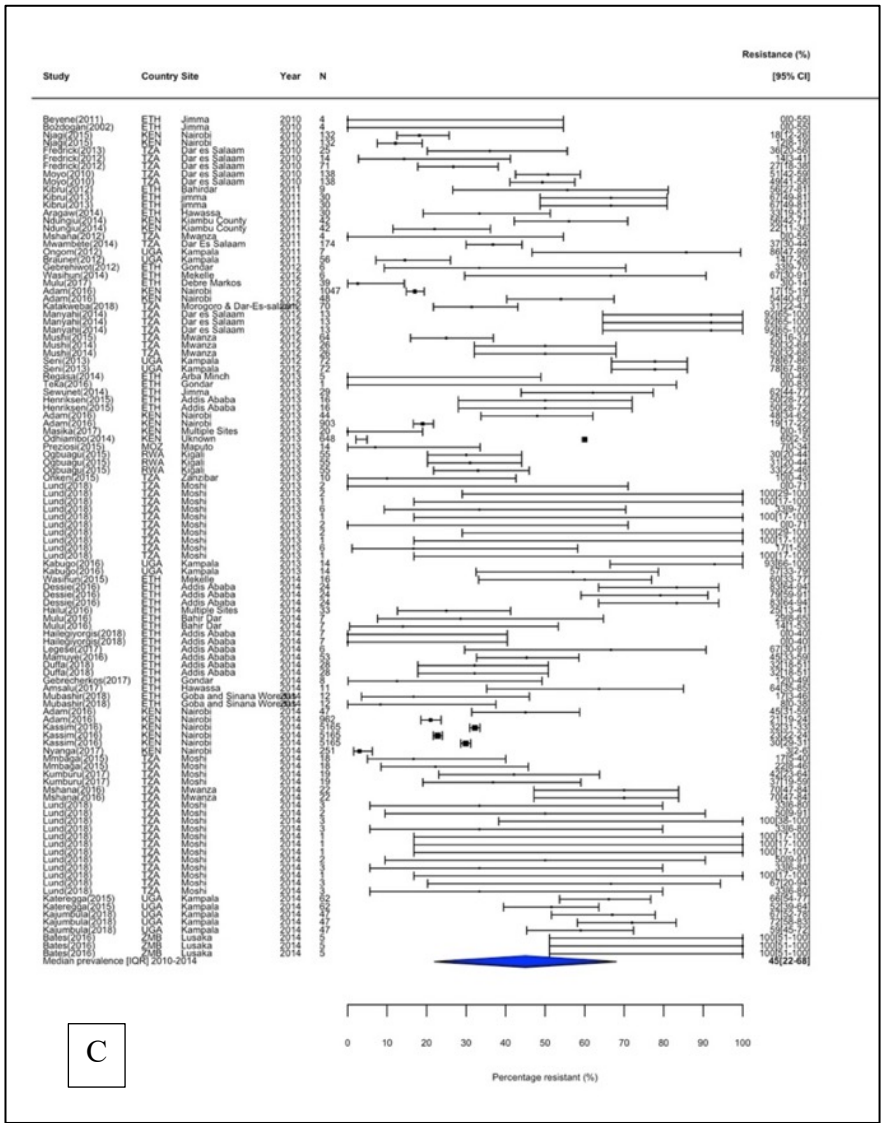


Figure C.74: Forest plot of third-generation cephalosporin resistance in Central sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.




Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Kiiru(2013) KEN Multiple Sites 2000 1327 27[25-29]
Kiiru(2013) KEN Multiple Sites 2000 1327 28[26-31]
Kiiru(2013) KEN Multiple Sites 2000 1327 21[19-23]
Mugalu(2006) UGA Kampala 2002 17 65[41-83]
Mugalu(2006) UGA Kampala 2002 17 6[0-29]
Olira(2007) UGA Jinja 2003 5 40[12-77]
Median prevalence [IQR] 2000-2004 28[22-37]
Talarmin(2007) MDG Antananarivo 2005 607 3[2-5]
Talarmin(2007) MDG Antananarivo 2005 607 3[2-5]
Ramilitiana(2014) MDG Antananarivo 2005 56 8[3-20]
Ramilitiana(2014) MDG Antananarivo 2005 56 0[0-8]
Ramilitiana(2014) MDG Antananarivo 2005 56 2[0-10]
Swann(2014) MWI Blantyre 2005 8 0[0-37]
Manyahi(2017) TZA Dar es Salaam 2005 95 0[0-5]
Manyahi(2017) TZA Dar es Salaam 2005 95 1[0-6]
Manyahi(2017) TZA Dar es Salaam 2005 95 0[0-5]
Karimi(2009) KEN Nairobi 2006 15 0[0-24]
Karimi(2009) KEN Nairobi 2006 15 7[0-32]
Revathi(2010) KEN Nairobi 2006 69 14[8-25]
Revathi(2010) KEN Nairobi 2006 69 14[8-25]
Revathi(2010) KEN Nairobi 2006 69 14[8-25]
Moyo(2011) TZA Dar es Salaam 2006 64 5[1-13]
Musiime(2009) UGA Kampala 2006 31 6[1-22]
Asrat(2009) ETH Addis Ababa 2007 13 0[0-27]
Kibret(2011) ETH Multiple Sites 2007 446 10[8-14]
Azene(2011) ETH Uknown 2007 82 67[56-76]
Kibret(2014) ETH Uknown 2007 203 34[28-41]
Suleman(2012) ETH Jimma 2007 67 8[3-17]
Suleman(2012) ETH Jimma 2007 67 8[3-17]
Kimando(2010) KEN Nairobi 2007 92 2[0-8]
Oduor(2016) KEN Eldoret 2007 38 85[17-45]
Richard(2010) MDG Antananarivo 2007 88 18[11-28]
Richard(2010) MDG Antananarivo 2007 88 18[11-28]
Richard(2010) MDG Antananarivo 2007 88 18[11-28]
Richard(2010) MDG Antananarivo 2007 88 18[11-28]
Mengistu(2011) ETH Addis Ababa 2008 2 50[9-91]
Kebira(2009) KEN Thika 2008 831 0[0-1]
Masinde(2009) TZA Mwanza 2008 17 29[13-53]
Victor(2013) KEN Nairobi 2009 4 25[3-71]
Talarmin(2014) MDG Multiple Sites 2009 195 3[1-7]
Talarmin(2014) MDG Multiple Sites 2009 195 2[0-5]
van der Meeren(2013) MOZ Beira 2009 3 67[20-94]
van der Meeren(2013) MOZ Beira 2009 11 64[35-85]
van der Meeren(2013) MOZ Beira 2009 3 67[20-94]
van der Meeren(2013) MOZ Beira 2009 11 64[35-85]
Muvunyi(2011) RWA Butare & Kigali 2009 72 4[1-12]
Muvunyi(2011) RWA Butare & Kigali 2009 47 32[20-46]
Muvunyi(2011) RWA Butare & Kigali 2009 47 38[26-53]
Muvunyi(2011) RWA Butare & Kigali 2009 72 7[3-16]
Mshana(2010) TZA Mwanza 2009 22 50[31-69]
Mshana(2010) TZA Mwanza 2009 22 50[31-69]
Mshana(2010) TZA Mwanza 2009 22 50[31-69]
Median prevalence [IQR] 2005-2009 10[3-34]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2010-2014
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

C

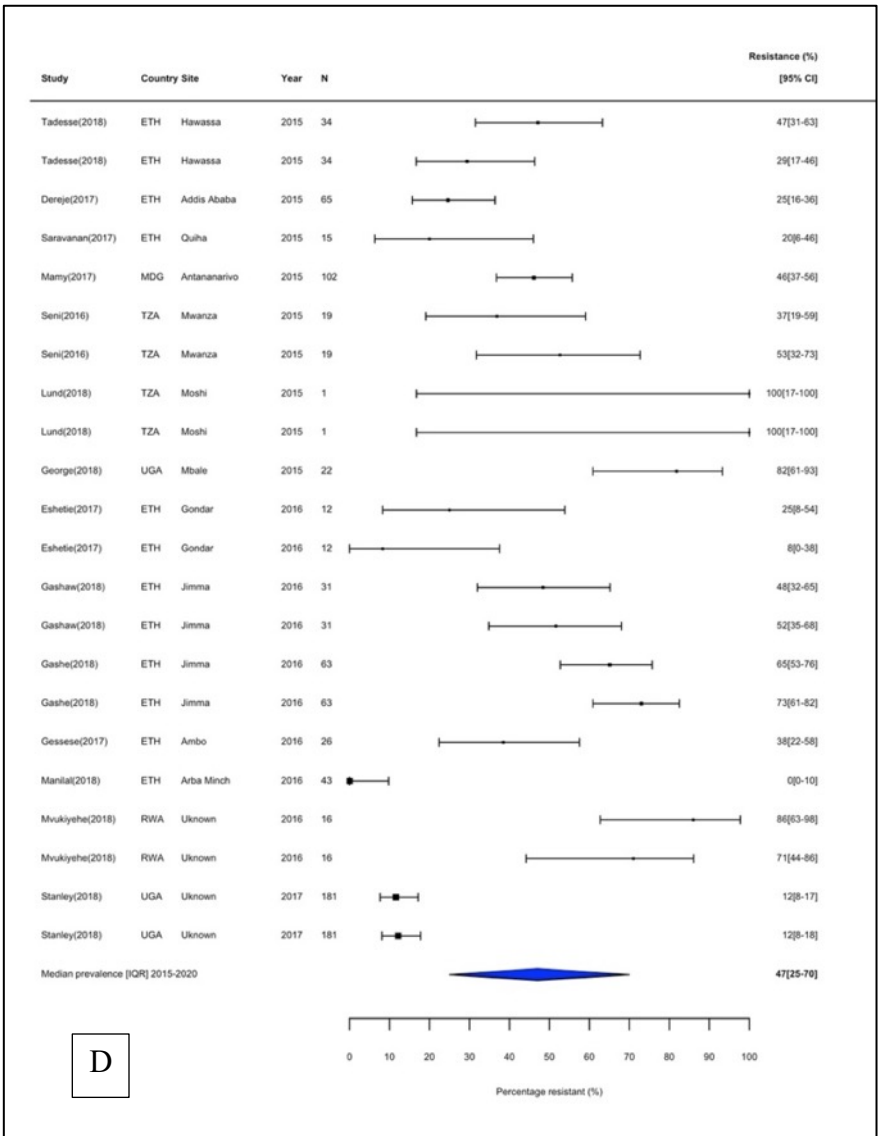


Figure C.75: Forest plot of third-generation cephalosporin resistance in Eastern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2014, D: 2015-2018

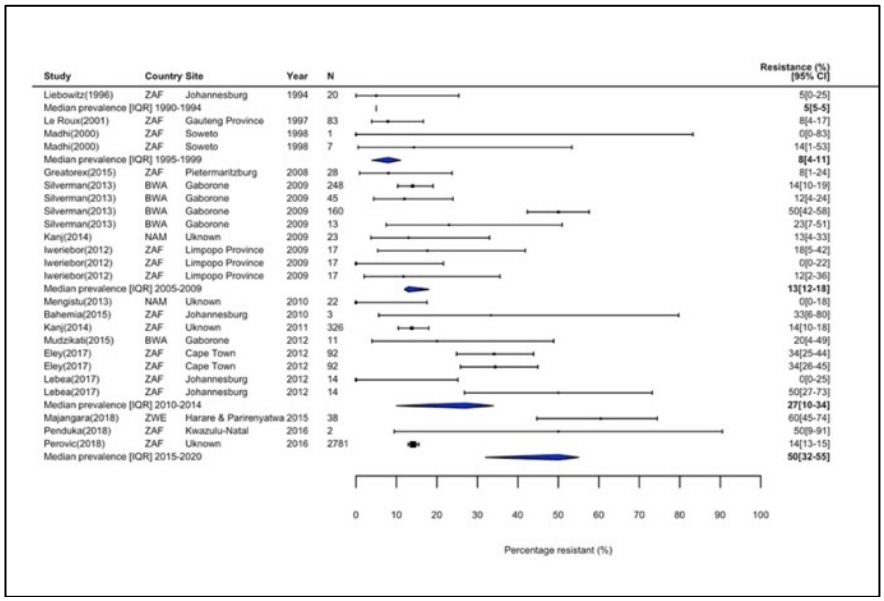
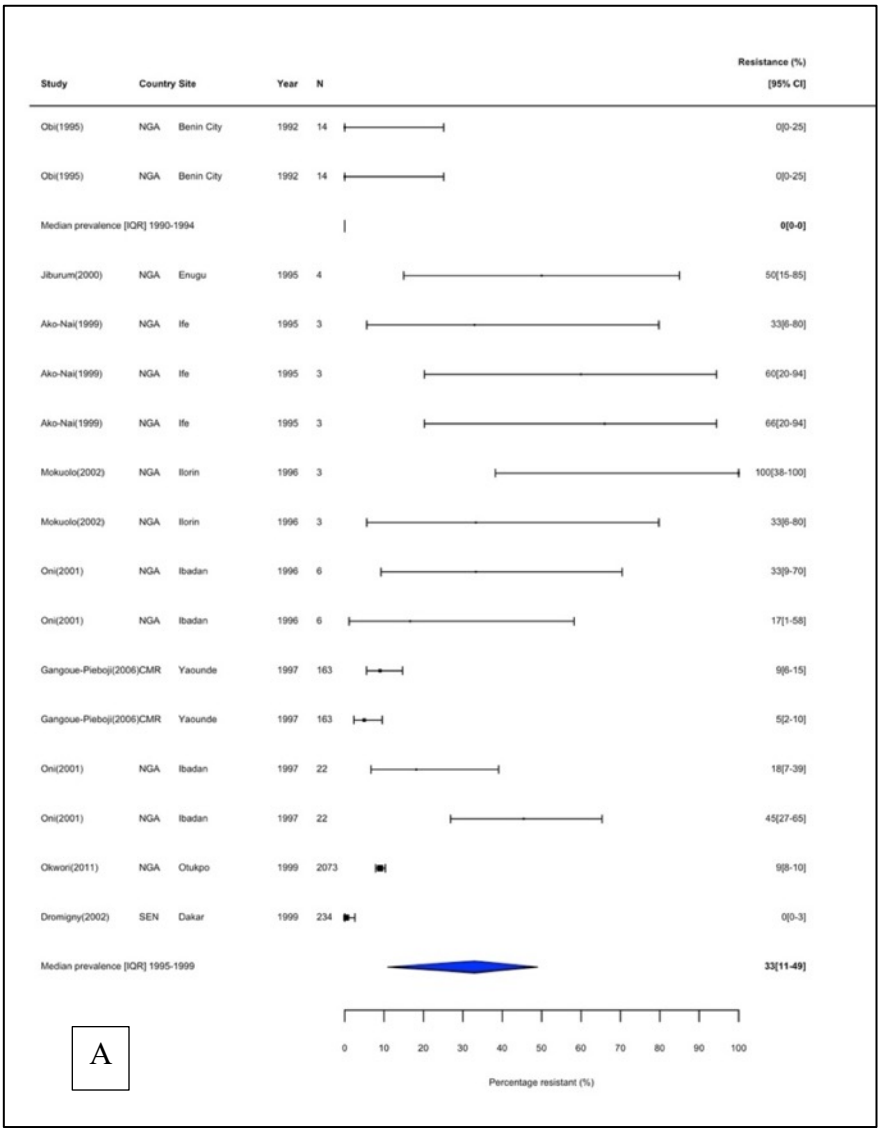
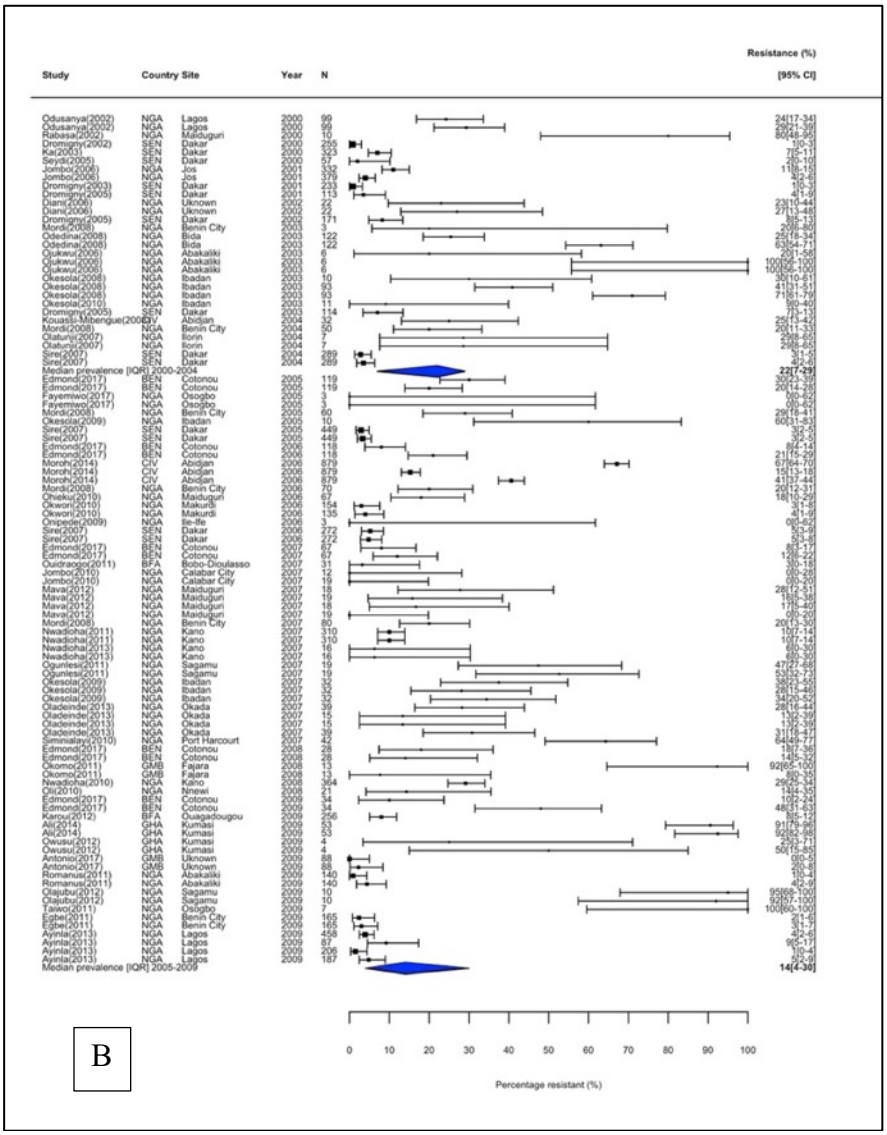
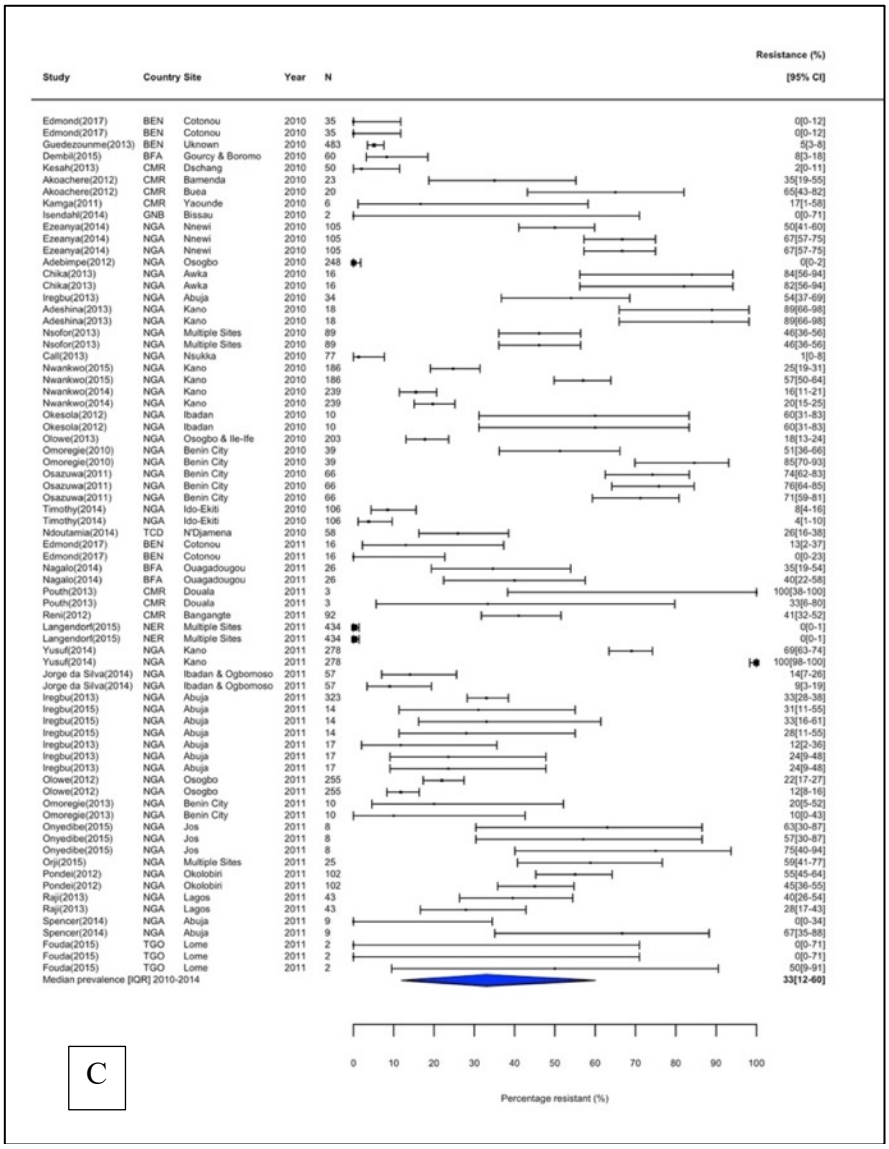


Figure C.76: Forest plot of third-generation cephalosporin resistance in Southern sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

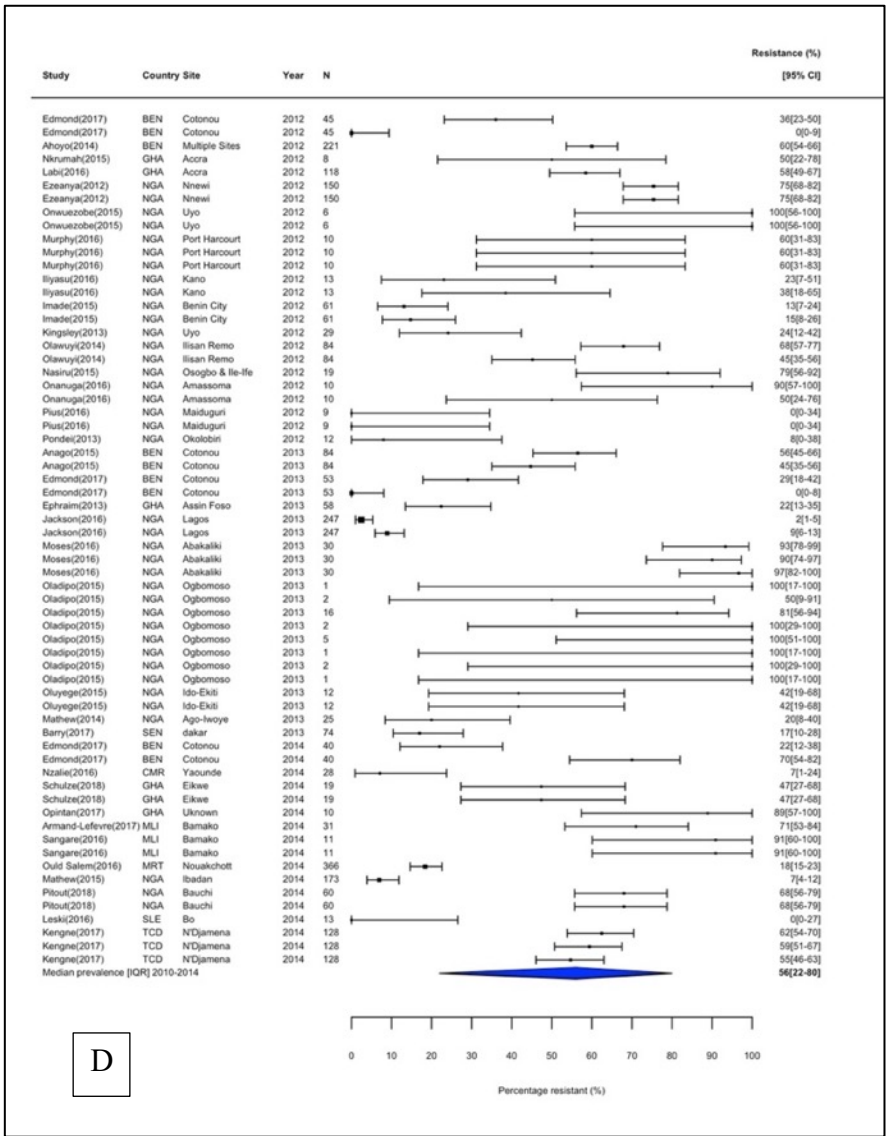

Study
Country
Site
Year
N
Resistance (%) [95% CI]
Obi(1995) NGA Benin City 1992 14 0[0-25]
Obi(1995) NGA Benin City 1992 14 0[0-25]
Median prevalence [IQR] 1990-1994 0[0-0]
Jiburum(2000) NGA Enugu 1995 4 50[15-85]
Ako-Nai(1999) NGA Ife 1995 3 33[6-80]
Ako-Nai(1999) NGA Ife 1995 3 60[20-94]
Ako-Nai(1999) NGA Ife 1995 3 66[20-94]
Mokuolo(2002) NGA Ilorin 1996 3 100[38-100]
Mokuolo(2002) NGA Ilorin 1996 3 33[6-80]
Oni(2001) NGA Ibadan 1996 6 33[9-70]
Oni(2001) NGA Ibadan 1996 6 17[1-58]
Gangoue-Pieboji(2006) CMR Yaounde 1997 163 9[6-15]
Gangoue-Pieboji(2006) CMR Yaounde 1997 163 5[2-10]
Oni(2001) NGA Ibadan 1997 22 18[7-39]
Oni(2001) NGA Ibadan 1997 22 45[27-65]
Okwori(2011) NGA Otukpo 1999 2073 9[8-10]
Dromigny(2002) SEN Dakar 1999 234 0[0-3]
Median prevalence [IQR] 1995-1999 33[11-49]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)
A


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Median prevalence [IQR] 2000-2004
Median prevalence [IQR] 2005-2009
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

B


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2010 35 0[0-12]
Edmond(2017) BEN Cotonou 2010 35 0[0-12]
Guedezounme(2013) BEN Uknown 2010 483 5[3-8]
Dembi(2015) BFA Gourcy & Boromo 2010 60 8[3-18]
Kesah(2013) CMR Dschang 2010 50 2[0-11]
Akoachere(2012) CMR Bamenda 2010 23 35[19-55]
Akoachere(2012) CMR Buea 2010 20 65[43-82]
Kamga(2011) CMR Yaounde 2010 6 17[1-58]
Isendahl(2014) GNB Bissau 2010 2 0[0-71]
Ezeanya(2014) NGA Nnewi 2010 105 50[41-60]
Ezeanya(2014) NGA Nnewi 2010 105 67[57-75]
Ezeanya(2014) NGA Nnewi 2010 105 67[57-75]
Adebimpe(2012) NGA Osogbo 2010 248 0[0-2]
Chika(2013) NGA Awka 2010 16 84[56-94]
Chika(2013) NGA Awka 2010 16 82[56-94]
Iregbu(2013) NGA Abuja 2010 34 54[37-69]
Adeshina(2013) NGA Kano 2010 18 89[66-98]
Adeshina(2013) NGA Kano 2010 18 89[66-98]
Nsofor(2013) NGA Multiple Sites 2010 89 46[36-56]
Nsofor(2013) NGA Multiple Sites 2010 89 46[36-56]
Call(2013) NGA Nsukka 2010 77 1[0-8]
Nwankwo(2015) NGA Kano 2010 186 25[19-31]
Nwankwo(2015) NGA Kano 2010 186 57[50-64]
Nwankwo(2014) NGA Kano 2010 239 16[11-21]
Nwankwo(2014) NGA Kano 2010 239 20[15-25]
Okesola(2012) NGA Ibadan 2010 10 60[31-83]
Okesola(2012) NGA Ibadan 2010 10 60[31-83]
Olowe(2013) NGA Osogbo & Ile-Ife 2010 203 18[13-24]
Omoregie(2010) NGA Benin City 2010 39 51[36-66]
Omoregie(2010) NGA Benin City 2010 39 85[70-93]
Osazuwa(2011) NGA Benin City 2010 66 74[62-83]
Osazuwa(2011) NGA Benin City 2010 66 76[64-85]
Osazuwa(2011) NGA Benin City 2010 66 71[59-81]
Timothy(2014) NGA Ido-Ekiti 2010 106 8[4-16]
Timothy(2014) NGA Ido-Ekiti 2010 106 4[1-10]
Ndoutamia(2014) TCD N'Djamena 2010 58 26[16-38]
Edmond(2017) BEN Cotonou 2011 16 13[2-37]
Edmond(2017) BEN Cotonou 2011 16 0[0-23]
Nagalo(2014) BFA Ouagadougou 2011 26 35[19-54]
Nagalo(2014) BFA Ouagadougou 2011 26 40[22-58]
Pouth(2013) CMR Douala 2011 3 100[38-100]
Pouth(2013) CMR Douala 2011 3 33[6-80]
Reni(2012) CMR Bangangte 2011 92 41[32-52]
Langendorf(2015) NER Multiple Sites 2011 434 0[0-1]
Langendorf(2015) NER Multiple Sites 2011 434 0[0-1]
Yusuf(2014) NGA Kano 2011 278 69[63-74]
Yusuf(2014) NGA Kano 2011 278 100[98-100]
Jorge da Silva(2014) NGA Ibadan & Ogbomoso 2011 57 14[7-26]
Jorge da Silva(2014) NGA Ibadan & Ogbomoso 2011 57 9[3-19]
Iregbu(2013) NGA Abuja 2011 323 33[28-38]
Iregbu(2015) NGA Abuja 2011 14 31[11-55]
Iregbu(2015) NGA Abuja 2011 14 33[16-61]
Iregbu(2015) NGA Abuja 2011 14 28[11-55]
Iregbu(2013) NGA Abuja 2011 17 12[2-36]
Iregbu(2013) NGA Abuja 2011 17 24[9-48]
Iregbu(2013) NGA Abuja 2011 17 24[9-48]
Olowe(2012) NGA Osogbo 2011 255 22[17-27]
Olowe(2012) NGA Osogbo 2011 255 12[8-16]
Omoregie(2013) NGA Benin City 2011 10 20[5-52]
Omoregie(2013) NGA Benin City 2011 10 10[0-43]
Onyedibe(2015) NGA Jos 2011 8 63[30-87]
Onyedibe(2015) NGA Jos 2011 8 57[30-87]
Onyedibe(2015) NGA Jos 2011 8 75[40-94]
Orji(2015) NGA Multiple Sites 2011 25 59[41-77]
Pondei(2012) NGA Okolobiri 2011 102 55[45-64]
Pondei(2012) NGA Okolobiri 2011 102 45[36-55]
Raji(2013) NGA Lagos 2011 43 40[26-54]
Raji(2013) NGA Lagos 2011 43 28[17-43]
Spencer(2014) NGA Abuja 2011 9 0[0-34]
Spencer(2014) NGA Abuja 2011 9 67[35-88]
Fouda(2015) TGO Lome 2011 2 0[0-71]
Fouda(2015) TGO Lome 2011 2 0[0-71]
Fouda(2015) TGO Lome 2011 2 50[9-91]
Median prevalence [IQR] 2010-2014 33[12-60]
0 10 20 30 40 50 60 70 80 90 100
Percentage resistant (%)

C


Study
Country
Site
Year
N
Resistance (%)
[95% CI]
Edmond(2017) BEN Cotonou 2012 45 36[23-50]
Edmond(2017) BEN Cotonou 2012 45 0[0-9]
Ahoyo(2014) BEN Multiple Sites 2012 221 60[54-66]
Nkrumah(2015) GHA Accra 2012 8 50[22-78]
Labi(2016) GHA Accra 2012 118 58[49-67]
Ezeanya(2012) NGA Nnewi 2012 150 75[68-82]
Ezeanya(2012) NGA Nnewi 2012 150 75[68-82]
Onwuezobe(2015) NGA Uyo 2012 6 100[56-100]
Onwuezobe(2015) NGA Uyo 2012 6 100[56-100]
Murphy(2016) NGA Port Harcourt 2012 10 60[31-83]
Murphy(2016) NGA Port Harcourt 2012 10 60[31-83]
Murphy(2016) NGA Port Harcourt 2012 10 60[31-83]
Iliyasu(2016) NGA Kano 2012 13 23[7-51]
Iliyasu(2016) NGA Kano 2012 13 38[18-65]
Imade(2015) NGA Benin City 2012 61 13[7-24]
Imade(2015) NGA Benin City 2012 61 15[8-26]
Kingsley(2013) NGA Uyo 2012 29 24[12-42]
Olawuyi(2014) NGA Ilisan Remo 2012 84 68[57-77]
Olawuyi(2014) NGA Ilisan Remo 2012 84 45[35-56]
Nasiru(2015) NGA Osogbo & Ile-Ife 2012 19 79[56-92]
Onanuga(2016) NGA Amassoma 2012 10 90[57-100]
Onanuga(2016) NGA Amassoma 2012 10 50[24-76]
Pius(2016) NGA Maiduguri 2012 9 0[0-34]
Pius(2016) NGA Maiduguri 2012 9 0[0-34]
Pondei(2013) NGA Okolobiri 2012 12 8[0-38]
Anago(2015) BEN Cotonou 2013 84 56[45-66]
Anago(2015) BEN Cotonou 2013 84 45[35-56]
Edmond(2017) BEN Cotonou 2013 53 29[18-42]
Edmond(2017) BEN Cotonou 2013 53 0[0-8]
Ephraim(2013) GHA Assin Foso 2013 58 22[13-35]
Jackson(2016) NGA Lagos 2013 247 2[1-5]
Jackson(2016) NGA Lagos 2013 247 9[6-13]
Moses(2016) NGA Abakaliki 2013 30 93[78-99]
Moses(2016) NGA Abakaliki 2013 30 90[74-97]
Moses(2016) NGA Abakaliki 2013 30 97[82-100]
Oladipo(2015) NGA Ogbomoso 2013 1 100[17-100]
Oladipo(2015) NGA Ogbomoso 2013 2 50[9-91]
Oladipo(2015) NGA Ogbomoso 2013 16 81[56-94]
Oladipo(2015) NGA Ogbomoso 2013 2 100[29-100]
Oladipo(2015) NGA Ogbomoso 2013 5 100[51-100]
Oladipo(2015) NGA Ogbomoso 2013 1 100[17-100]
Oladipo(2015) NGA Ogbomoso 2013 2 100[29-100]
Oladipo(2015) NGA Ogbomoso 2013 1 100[17-100]
Oluyege(2015) NGA Ido-Ekiti 2013 12 42[19-68]
Oluyege(2015) NGA Ido-Ekiti 2013 12 42[19-68]
Mathew(2014) NGA Ago-Iwoye 2013 25 20[8-40]
Barry(2017) SEN dakar 2013 74 17[10-28]
Edmond(2017) BEN Cotonou 2014 40 22[12-38]
Edmond(2017) BEN Cotonou 2014 40 70[54-82]
Nzalie(2016) CMR Yaounde 2014 28 7[1-24]
Schulze(2018) GHA Eikwe 2014 19 47[27-68]
Schulze(2018) GHA Eikwe 2014 19 47[27-68]
Opintan(2017) GHA Uknown 2014 10 89[57-100]
Armand-Lefevre(2017) MLI Bamako 2014 31 71[53-84]
Sangare(2016) MLI Bamako 2014 11 91[60-100]
Sangare(2016) MLI Bamako 2014 11 91[60-100]
Ould Salem(2016) MRT Nouakchott 2014 366 18[15-23]
Mathew(2015) NGA Ibadan 2014 173 7[4-12]
Pitout(2018) NGA Bauchi 2014 60 68[56-79]
Pitout(2018) NGA Bauchi 2014 60 68[56-79]
Leski(2016) SLE Bo 2014 13 0[0-27]
Kengne(2017) TCD N'Djamena 2014 128 62[54-70]
Kengne(2017) TCD N'Djamena 2014 128 59[51-67]
Kengne(2017) TCD N'Djamena 2014 128 55[46-63]
Median prevalence [IQR] 2010-2014 56[22-80]
0
10
20
30
40
50
60
70
80
90
100
Percentage resistant (%)

D

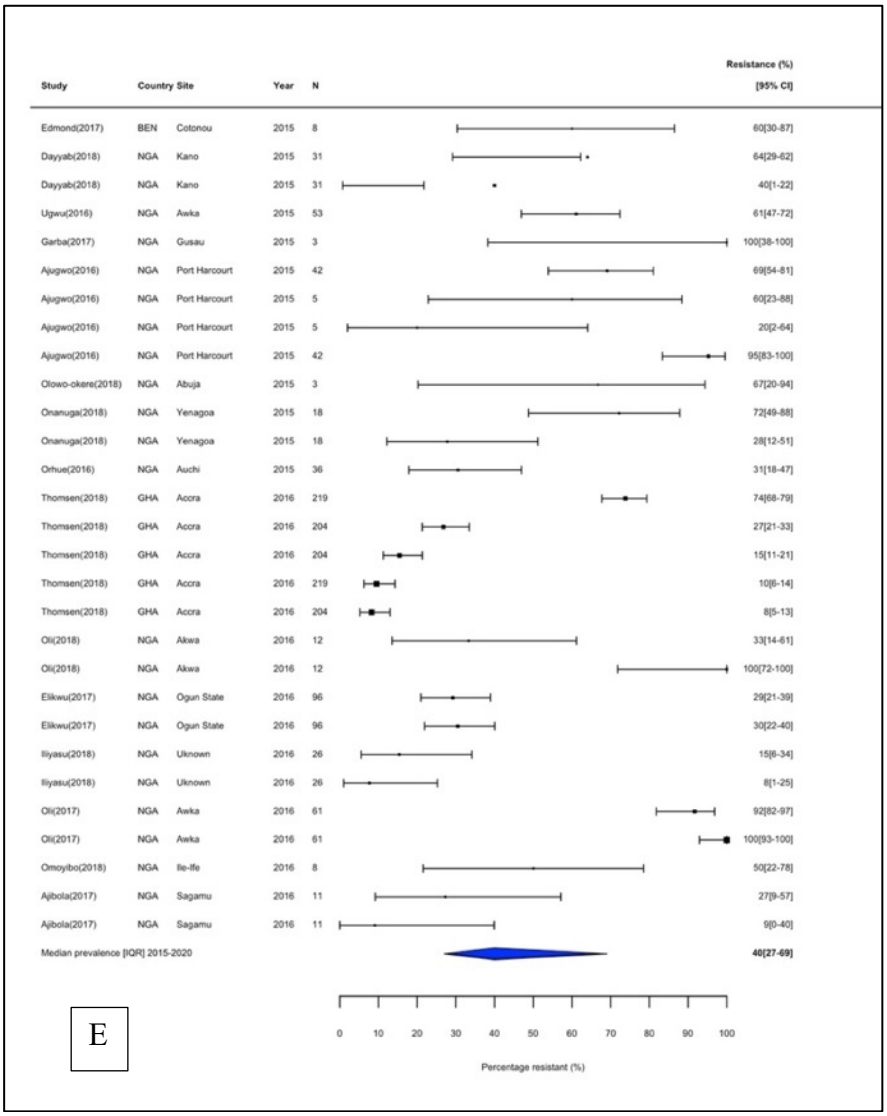


Figure C.77: Forest plot of third-generation cephalosporin resistance in Western sub-Saharan Africa. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup. A: 1990-1999, B: 2000-2009, C: 2010-2012, D: 2013-2014, E: 2015-2018

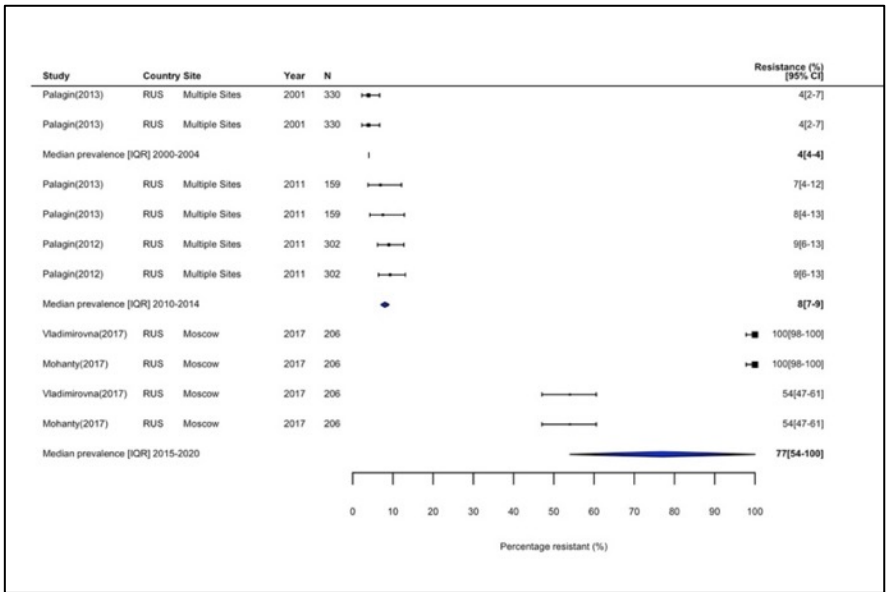


Figure C.78: Forest plot of third-generation cephalosporin resistance in Eastern Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

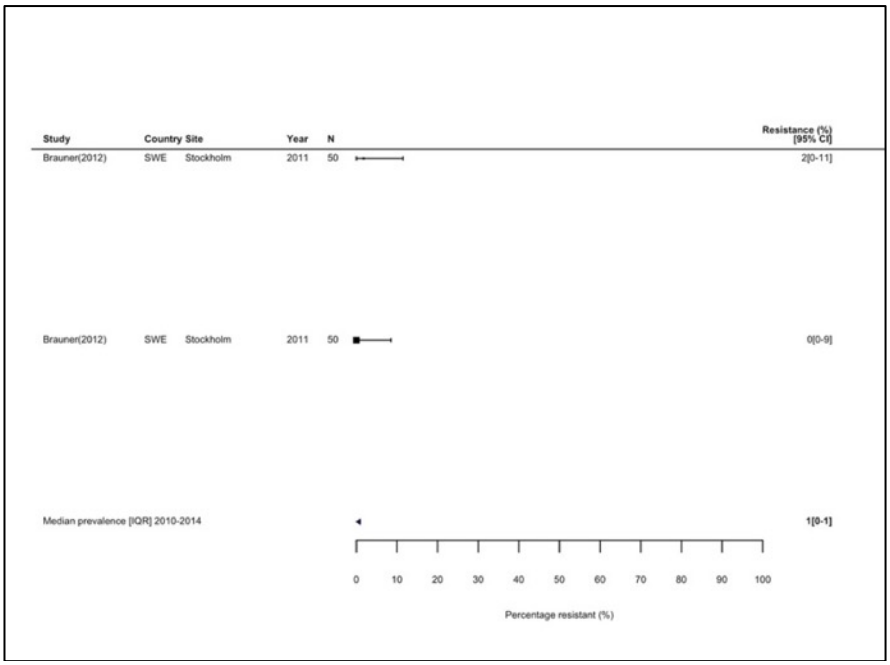


Figure C.79: Forest plot of third-generation cephalosporin resistance in Western Europe. Individual study results are provided with 95% confidence intervals aggregated by five-year time periods; the blue diamond reflects the pooled prevalence [95% CI] for each subgroup.

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Appendix to Chapter. 5

The appendix to Chapter 5 contains additional tables and figures. Chapter 5: Global Geospatial Modelling of Antimicrobial Drug Resistance in E. coli, 2000-2020. This section includes a table detailing the prevalence of resistance in *E.coli* in 2020, table describing the data sources types and finally the modeling validation statistics.

***E. coli* and 3rd Generation Cephalosporins**		
Country	Datapoints	Sample Size
Argentina	20	2,061
Australia	13	1,210
Austria	29	58,889
Bangladesh	1	3
Belarus	3	88
Belgium	38	47,274
Botswana	10	53
Brazil	19	1,653
Bulgaria	21	3,537
Cambodia	7	82
Canada	13	1,607
Central African Republic	3	116
Chile	17	1,353
China	10	1,662
Colombia	15	1,478
Costa Rica	3	145
Croatia	29	14,834
Cyprus	16	1,943
Czech Republic	36	47,172
Denmark	27	43,952
Ecuador	2	79
Egypt	3	91
El Salvador	2	79
Estonia	19	5,859
Ethiopia	1	10
Finland	26	51,798
France	36	149,749
Germany	39	111,712
Ghana	22	496
Greece	38	24,916
Guatemala	12	583
Honduras	3	78
Hong Kong	9	221
Hungary	35	24,574
India	10	332
Indonesia	1	19
Iran	2	134

Ireland	37	37,150
Israel	16	1,797
Italy	37	63,594
Jamaica	1	25
Japan	8	719
Jordan	6	144
Kenya	10	188
Kuwait	6	748
Latvia	20	2,182
Lebanon	1	27
Lithuania	18	6,703
Luxembourg	18	5,411
Malaysia	12	401
Malta	18	3,243
Mauritius	1	17
Mexico	19	3,233
Morocco	6	177
Mozambique	5	19
Namibia	2	23
Netherlands	33	69,723
Nicaragua	2	22
Nigeria	11	267
Norway	2	75
Oman	1	26
Pakistan	7	160
Panama	14	381
Peru	2	84
Philippines	11	1,057
Poland	32	17,799
Portugal	35	48,774
Puerto Rico	1	25
Romania	33	4,015
Russia	12	1,490
Rwanda	1	17
Saudi Arabia	6	174
Serbia	1	26
Singapore	12	357
Slovakia	18	7,705
Slovenia	28	15,895
South Africa	12	1,192
South Korea	18	1,654
Spain	37	90,807
Swaziland	7	34
Sweden	35	81,796
Switzerland	13	555
Taiwan	16	1,108
Thailand	14	1,041
The Gambia	18	158
Tunisia	3	100
Turkey	16	2,254
Uganda	7	52
Ukraine	2	25
United Kingdom	58	152,011
Unites States of America	27	815,179
Venezuela	15	1,314
Vietnam	4	91
Zambia	7	24

Table D.1 Data source type by country.

E. coli and Carbapenems		
Country	Datapoints	Sample Size
Afghanistan	1	10
Argentina	39	104,252
Australia	13	1,210
Austria	12	685
Bahrain	2	1,984
Bangladesh	2	312
Belarus	3	88
Belgium	20	2,772
Bosnia and Herzegovina	1	245
Botswana	8	90
Brazil	22	4,436
Bulgaria	5	317
Cambodia	2	237
Canada	19	28,969
Central African Republic	2	3
Chile	19	1,492
China	11	1,681
Colombia	17	11,927
Costa Rica	7	3,406
Croatia	12	565
Cuba	1	136
Czech Republic	18	1,337
Denmark	14	873
Dominican Republic	4	4,075
Ecuador	9	16,306
Egypt	4	273
El Salvador	5	8,495
Ethiopia	2	180
Finland	10	3,098
France	20	6,922
Georgia	1	48
Germany	20	6,678
Ghana	12	708
Greece	20	2,034
Guatemala	16	13,064
Honduras	6	2,095
Hong Kong	9	221
Hungary	17	1,185
India	10	332
Indonesia	3	2,804
Iran	6	1,910
Iraq	1	139
Ireland	20	1,874
Israel	16	1,797
Italy	20	7,081
Jamaica	1	25
Japan	16	2,180,802
Jordan	8	2,211
Kenya	16	826
Kuwait	6	748
Laos	2	111
Latvia	8	1,172
Lebanon	2	3,352
Lithuania	6	255
Macedonia	1	54
Madagascar	2	363
Malaysia	23	254,852
Mali	1	132
Malta	1	3,547

Mauritius	1	17
Mexico	22	4,729
Morocco	6	177
Mozambique	5	60
Myanmar	2	1,039
Namibia	2	23
Nepal	5	3,592
Netherlands	14	769
New Zealand	17	20,213
Nicaragua	8	2,986
Nigeria	12	661
Norway	3	1,498
Oman	2	1,165
Pakistan	15	63,678
Panama	18	8,446
Paraguay	7	5,592
Peru	9	5,716
Philippines	18	34,915
Poland	15	1,031
Portugal	17	2,062
Puerto Rico	1	25
Romania	16	702
Russia	13	1,571
Rwanda	1	17
Saudi Arabia	7	3,298
Serbia	1	26
Singapore	13	23,357
Slovakia	7	156
Slovenia	11	375
South Africa	14	9,377
South Korea	19	10,633
Spain	19	7,378
Sudan	1	326
Swaziland	7	59
Sweden	18	15,148
Switzerland	14	80,803
Taiwan	26	10,072
Thailand	18	18,971
Tunisia	4	9,585
Turkey	16	2,254
Uganda	8	217
Ukraine	2	25
United Arab Emirates	1	14,833
United Kingdom	42	370,595
Unites States of America	27	775,422
Uruguay	6	1,159
Venezuela	22	38,656
Vietnam	6	300
Zambia	7	74

Table D.2 Data source type by country.

E. coli and Fluoroquinolones		
Country	Datapoints	Sample Size
Afghanistan	1	61
Algeria	10	1,528
Argentina	47	390,651
Australia	26	321,144
Austria	31	64,413
Bahrain	2	1,715
Bangladesh	2	296
Belarus	8	517
Belgium	38	44,286
Benin	14	1,351
Bolivia	10	36,501
Bosnia and Herzegovina	4	817
Botswana	14	502
Brazil	32	13,352
Bulgaria	25	3,667
Burkina Faso	8	982
Cambodia	9	342
Cameroon	9	466
Canada	28	97,837
Central African Republic	5	295
Chad	2	256
Chile	19	1,491
China	47	164,525
Colombia	21	11,953
Costa Rica	12	14,028
Cote d'Ivoire	4	1,822
Croatia	29	15,923
Cuba	5	685
Cyprus	17	2,089
Czech Republic	37	50,783
Democratic Republic of the Congo	6	174
Denmark	28	52,436
Dominican Republic	4	11,494
Ecuador	15	54,532
Egypt	67	7,483
El Salvador	9	12,964
Estonia	19	5,914
Ethiopia	51	2,006
Fiji	1	40
Finland	28	139,460
France	38	161,816
Gabon	4	152
Georgia	3	85
Germany	40	133,129
Ghana	33	2,059
Greece	41	26,450
Guatemala	20	18,717
Honduras	8	8,010
Hong Kong Special Administrative Region of China	9	221
Hungary	35	24,251
India	53	5,548
Indonesia	3	3,883
Iran	13	3,193
Iraq	9	1,438
Ireland	38	40,488
Israel	17	2,448
Italy	38	79,371
Jamaica	1	25

Japan	16	2,416,577
Jordan	9	1,953
Kazakhstan	4	192
Kenya	54	12,013
Kosovo	2	37
Kuwait	10	766
Laos	16	1,199
Latvia	21	3,161
Lebanon	4	3,648
Lesotho	1	123
Libya	12	1,045
Lithuania	19	7,782
Luxembourg	19	5,793
Macedonia	6	354
Madagascar	10	2,953
Malawi	1	22
Malaysia	27	324,375
Mali	4	204
Malta	19	6,792
Mauritania	2	732
Mauritius	2	34
Mexico	26	4,899
Mongolia	6	248
Montenegro	2	39
Morocco	11	1,500
Mozambique	8	137
Myanmar	2	1,103
Namibia	4	59
Nepal	16	6,635
Netherlands	34	78,495
New Zealand	26	1,335,061
Nicaragua	10	5,741
Niger	2	868
Nigeria	203	26,451
Norway	3	3,952
Oman	10	4,056
Pakistan	22	90,244
Palestine	3	32
Panama	20	16,924
Paraguay	10	18,704
Peru	12	13,017
Philippines	21	46,109
Poland	38	19,137
Portugal	35	48,688
Puerto Rico	1	25
Romania	36	4,235
Russia	22	2,738
Rwanda	10	539
Saudi Arabia	11	5,120
Senegal	21	4,078
Serbia	8	1,434
Sierra Leone	1	13
Singapore	13	22,204
Slovakia	21	7,805
Slovenia	28	15,892
South Africa	70	697,931
South Korea	19	10,633
Spain	37	90,433
Sudan	21	979
Swaziland	7	19
Sweden	39	180,522
Switzerland	18	133,706

Syria	4	491
Taiwan	16	1,108
Tanzania	23	3,459
Thailand	21	35,961
The Gambia	3	110
Tunisia	24	14,132
Turkey	27	30,442
Uganda	21	585
Ukraine	3	36
United Arab Emirates	1	15,854
United Kingdom	60	974,890
Unites States of America	28	979,026
Uruguay	6	6,369
Venezuela	24	53,550
Vietnam	10	465
Yemen	3	1,288
Zambia	8	26
Zimbabwe	5	255

Table D.3 Data source type by country.

Stacked ensemble /ST-GPR	**Out of sample**		**In sample**	
Pathogen/ antimicrobial	**R2**	**RMSE**	**R2**	**RMSE**
E.coli fluoroquinolones	0.61	0.14	0.52	0.25
E.coli 3rd generation cephalosporins	0.34	0.20	0.47	0.20
E.coli carbapenems	0.61	0.14	0.76	0.11

Table D.4. E.coli and carbapenems, E.coli and 3rd generation cephalosporins, and E.coli fluoroquinolones model validation statistics. In- and out-of-sample validation metrics of RMSE and R^2.

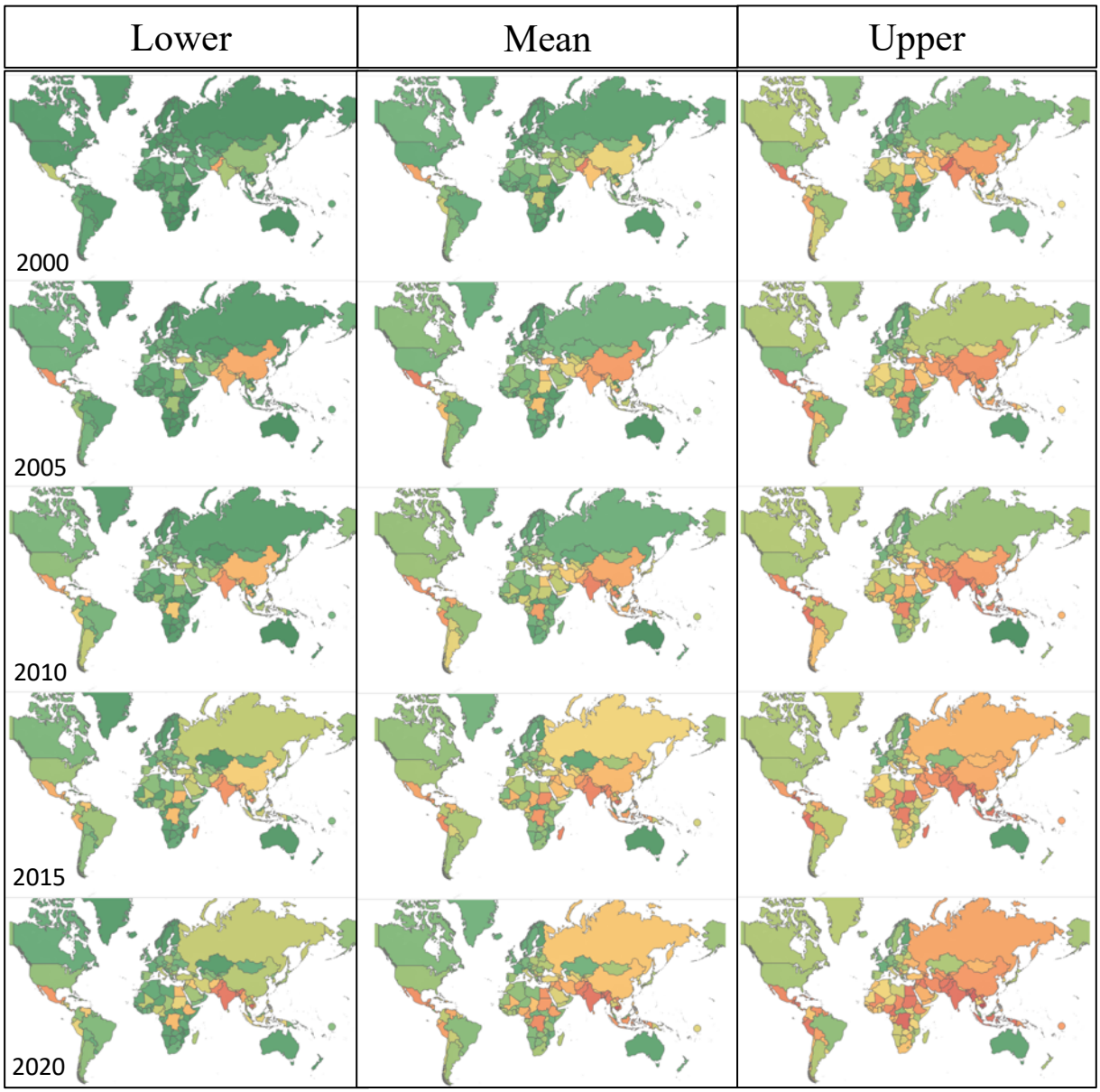

Figure D.1 Prevalence of FQR in E.coli in 2018, model uncertainty. The lower, median, and upper 95% uncertainty interval estimates for each country. Modeled estimates from the stacked ensemble and ST-GPR model.

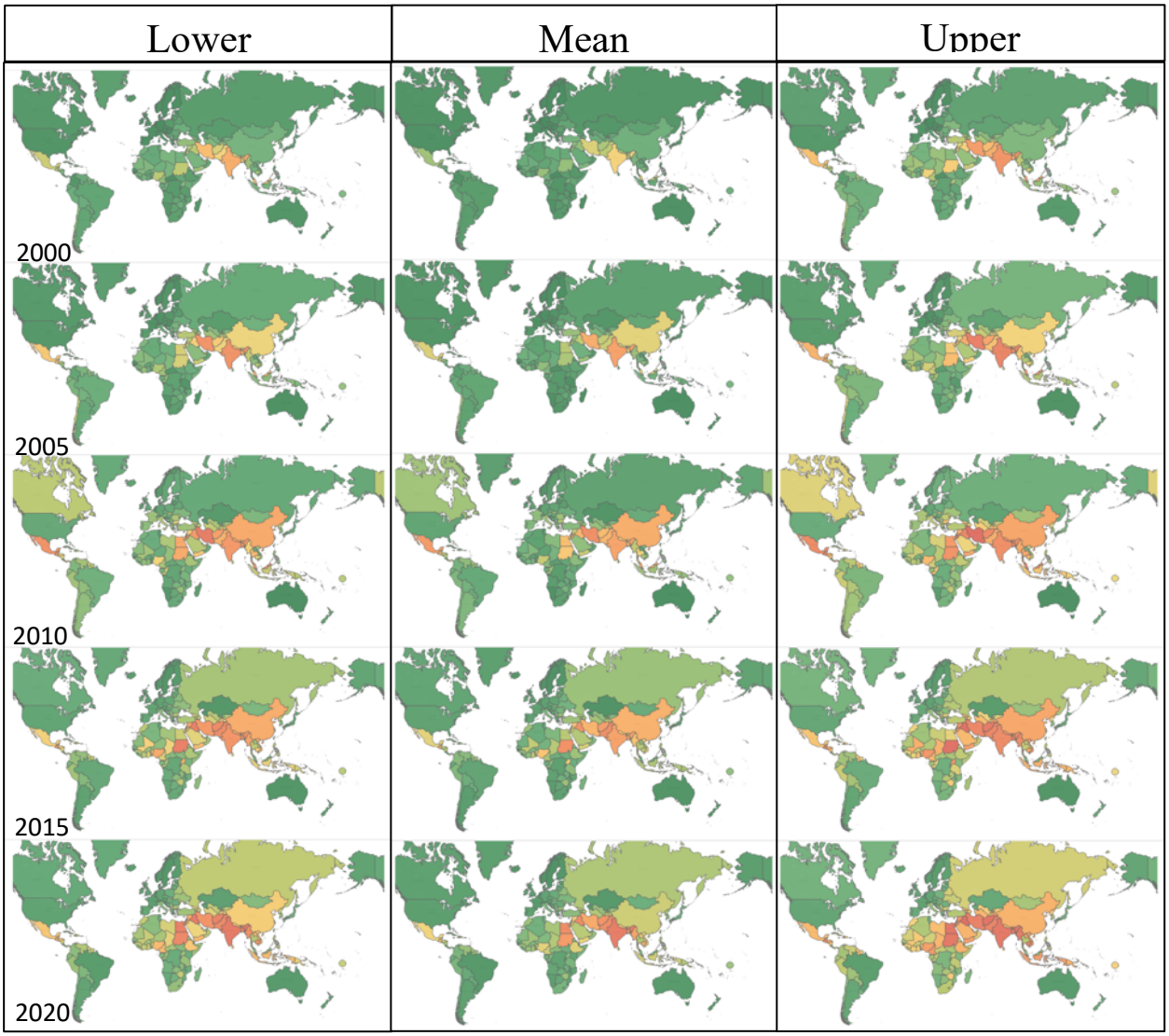

Figure D.2 Prevalence of 3GC in E.coli model uncertainty. The lower, median, and upper 95% uncertainty interval estimates for each country. Modeled estimates from the stacked ensemble and ST-GPR model.

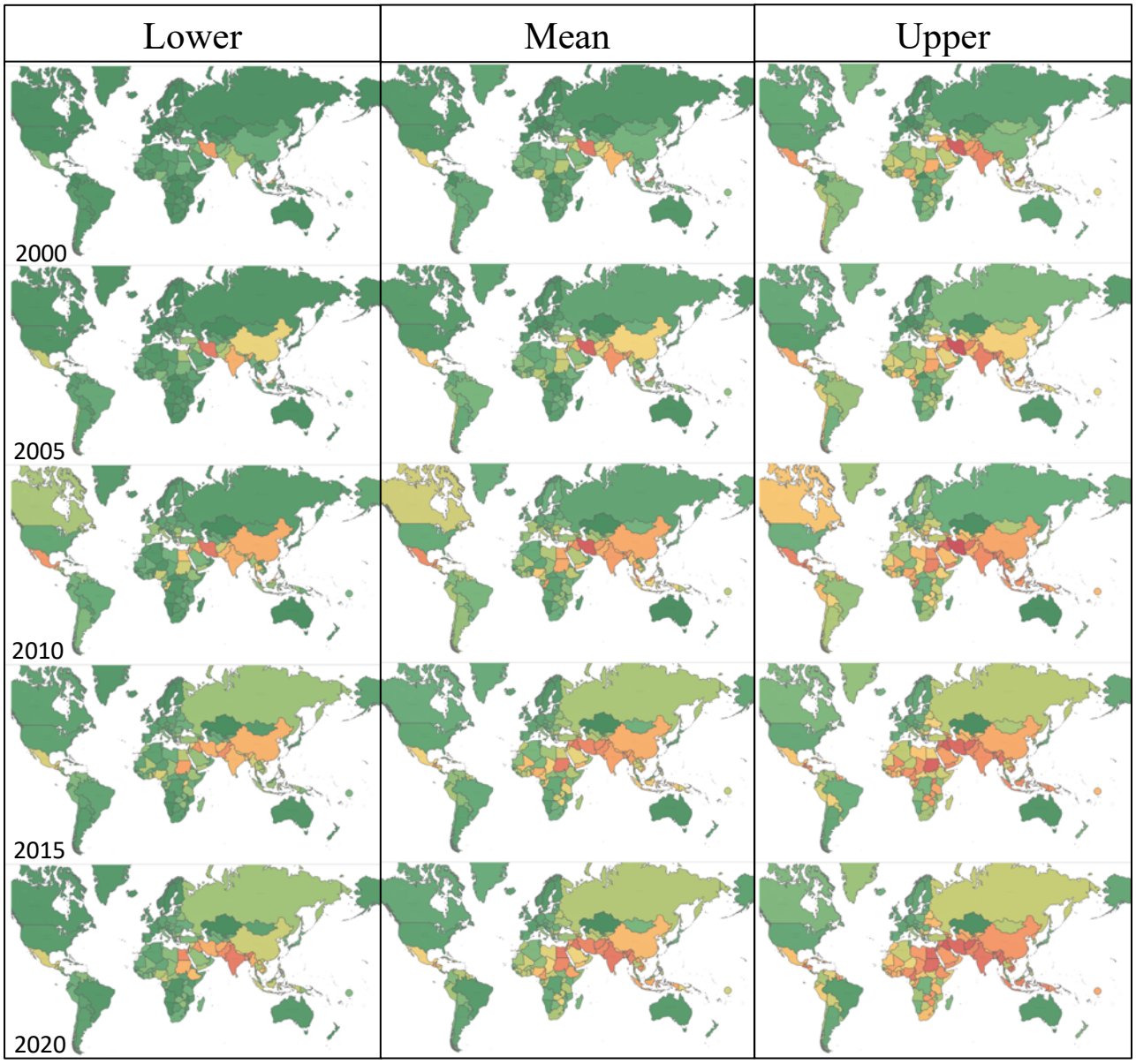

Figure D.3 Prevalence of Carbapenems in E.coli in model uncertainty. The lower, median, and upper 95% uncertainty interval estimates for each country. Modeled estimates from the stacked ensemble and ST-GPR model.

Prevalence of Resistance in 2020			
Country Name	**3GC**	**FQR**	**Carbapenems**
India	82%	83%	82%
Cambodia	71%	93%	71%
Pakistan	76%	81%	75%
Iraq	81%	67%	83%
Egypt	79%	70%	82%
Myanmar	73%	79%	76%
Afghanistan	79%	69%	78%
Bangladesh	72%	83%	70%
Sudan	76%	68%	76%
Bhutan	67%	76%	75%
Iran	72%	60%	77%
Guatemala	64%	70%	66%
Macedonia	55%	70%	67%
Syria	62%	63%	64%
Cameroon	57%	66%	65%
Vietnam	58%	72%	57%
Indonesia	56%	68%	61%
Ethiopia	53%	65%	64%
Mexico	53%	72%	51%
Honduras	54%	64%	57%
Jordan	64%	49%	62%
Nigeria	57%	60%	55%
Laos	58%	54%	60%
Sri Lanka	53%	63%	56%
Haiti	53%	56%	55%
China	52%	55%	57%
Nepal	56%	49%	56%
Nicaragua	46%	67%	46%
Yemen	58%	42%	56%
El Salvador	43%	67%	45%
Tajikistan	52%	57%	46%
Grenada	48%	55%	50%
Saint Lucia	48%	57%	47%
Chad	48%	55%	50%
Georgia	50%	49%	53%
Dominica	47%	53%	49%
Saudi Arabia	49%	47%	49%
Mali	43%	58%	45%

	51 - 100%
	21 - 50%
	0 - 20%

Papua New Guinea	48%	45%	49%
Country Name	**3GC**	**FQR**	**Carbapenems**
Turkmenistan	47%	51%	42%
Dominican Republic	41%	57%	41%
Venezuela	38%	62%	38%
Panama	36%	68%	34%
Guyana	45%	47%	45%
Vanuatu	45%	44%	47%
Tonga	43%	46%	46%
Armenia	43%	51%	40%
Kuwait	44%	44%	46%
North Korea	43%	48%	43%
Azerbaijan	44%	50%	39%
Peru	32%	66%	35%
Trinidad and Tobago	41%	48%	44%
Russia	41%	54%	38%
Kiribati	42%	46%	45%
Tokelau	41%	47%	44%
Suriname	41%	47%	44%
Philippines	39%	53%	40%
Lebanon	45%	42%	45%
Maldives	37%	55%	39%
Nauru	40%	46%	44%
Barbados	38%	53%	39%
Moldova	41%	43%	44%
Palestine	43%	41%	43%
Tuvalu	40%	45%	43%
Mauritius	37%	51%	39%
Benin	45%	35%	47%
Zimbabwe	42%	35%	49%
Jamaica	39%	47%	40%
Uzbekistan	41%	46%	38%
Taiwan	36%	55%	34%
Puerto Rico	38%	44%	41%
Thailand	38%	46%	39%
Timor-Leste	35%	50%	37%
Fiji	37%	45%	40%
Guinea	41%	38%	43%

Libya	46%	28%	47%
Country Name	**3GC**	**FQR**	**Carbapenems**
Rwanda	36%	45%	39%
Kyrgyzstan	41%	44%	35%
Ghana	42%	36%	42%
Bulgaria	38%	42%	40%
Cape Verde	40%	38%	42%
Cote d'Ivoire	41%	37%	41%
The Bahamas	36%	46%	37%
Morocco	42%	39%	38%
Belize	34%	49%	35%
Niue	35%	44%	38%
Samoa	36%	42%	38%
Congo	33%	38%	45%
Palau	31%	48%	36%
Uganda	34%	44%	37%
Turkey	33%	48%	33%
Guam	31%	49%	34%
Belarus	37%	36%	40%
Qatar	38%	36%	40%
Bahrain	41%	30%	41%
Oman	39%	32%	41%
United Arab Emirates	35%	44%	33%
Cyprus	33%	43%	34%
Togo	37%	34%	39%
South Korea	31%	46%	32%
Bermuda	31%	45%	33%
Ukraine	33%	39%	36%
Albania	33%	41%	34%
Ecuador	26%	56%	24%
Cuba	30%	44%	32%
Slovakia	30%	45%	30%
Liberia	35%	33%	36%
Cook Islands	28%	42%	33%
D.R.C	18%	74%	12%
Zambia	28%	30%	45%
South Africa	31%	36%	37%
Equatorial Guinea	34%	38%	30%
Eritrea	33%	37%	32%
Serbia	28%	44%	30%

Tanzania	31%	32%	38%
Country Name	**3GC**	**FQR**	**Carbapenems**
Burkina Faso	34%	33%	33%
Mauritania	35%	31%	34%
Central African Republic	35%	22%	43%
Italy	27%	44%	28%
Colombia	29%	41%	27%
Bolivia	24%	44%	26%
Niger	35%	28%	30%
Somalia	31%	29%	30%
Chile	21%	44%	24%
Gabon	27%	35%	27%
Montenegro	24%	39%	25%
Israel	24%	37%	25%
Singapore	23%	40%	23%
Madagascar	23%	39%	23%
Andorra	24%	35%	25%
Mongolia	26%	35%	23%
Paraguay	24%	38%	22%
South Sudan	28%	28%	27%
Algeria	28%	30%	25%
Malaysia	27%	28%	27%
Senegal	26%	32%	22%
Sierra Leone	28%	33%	19%
Guinea-Bissau	31%	26%	23%
Lesotho	26%	22%	30%
Japan	20%	37%	20%
Swaziland	23%	27%	27%
Hungary	20%	36%	21%
Djibouti	24%	28%	24%
Poland	19%	38%	19%
Botswana	21%	27%	24%
Burundi	24%	26%	22%
Bosnia and Herzegovina	21%	25%	21%
Greece	18%	30%	19%
Monaco	17%	30%	20%
Malta	13%	40%	13%
Romania	18%	30%	18%
Angola	20%	27%	18%
Croatia	15%	32%	16%
The Gambia	22%	19%	19%
Uruguay	15%	29%	17%

Tunisia	17%	27%	17%
Country Name	**3GC**	**FQR**	**Carbapenems**
Spain	14%	33%	13%
Mozambique	19%	21%	20%
Latvia	17%	26%	17%
Argentina	13%	33%	13%
Costa Rica	16%	30%	14%
Kenya	19%	21%	18%
Canada	16%	26%	15%
United States	12%	33%	12%
Ireland	14%	28%	14%
Portugal	15%	26%	14%
Lithuania	16%	23%	16%
Greenland	16%	21%	17%
Czech Republic	15%	24%	15%
Namibia	16%	26%	12%
Malawi	17%	20%	15%
Belgium	10%	29%	10%
Luxembourg	13%	23%	13%
Germany	13%	24%	13%
Brazil	9%	28%	8%
United Kingdom	12%	20%	12%
Austria	10%	23%	10%
New Zealand	10%	20%	12%
Slovenia	9%	24%	9%
Estonia	11%	20%	11%
Iceland	10%	18%	10%
France	10%	17%	10%
Kazakhstan	11%	21%	1%
Netherlands	8%	17%	8%
Sweden	6%	19%	7%
Switzerland	7%	17%	7%
Australia	8%	14%	8%
Denmark	8%	14%	8%
Finland	9%	12%	9%
Norway	7%	16%	7%

Table D.5 2020 prevelance of resistance to fluoroquinlolnes, 3GC and carbapenems. Dark green color shading indicates over 50% resistance, medium green indicates over 20% resistance and light green indicates below 20% resistance. Countries with resistacne to all three antibiotics are listed first.

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Publications and Posters

PUBLICATIONS RELATED TO THIS THESIS

Christopher J L Murray,…**Bahar H. Kashef Hamadani**,…Mohsen Naghavi "Articles Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis Antimicrobial Resistance." The Lancet. Jan 2022.

(Under Review) **Kashef Hamadani, Bahar H.,** Emmanuelle P. A. Kumaran, Georgina Haines-Woodhouse, Annie J. Browne, Michael G. Chipeta, Eli Harris, Nicholas P. J.Day, Paul Turner, Stephen Baker, Alan D. Lopez, Catrin E. Moore, Susanna Dunachie, and Christiane Dolecek. "Antimicrobial drug resistance in Shigella isolates globally, 1990 to 2018: A systematic review of the literature."

(Under Review) **Kashef Hamadani, Bahar H.,** Annie J. Browne, Susanna Dunachie, Catrin E Moore, Paul Turner, Benn Sartorius, Christiane Dolecek. "Estimating the global prevalence of antimicrobial resistance: challenges, biases and solutions."

Kashef Hamadani, Bahar H., Emmanuelle P. A. Kumaran, Georgina Haines-Woodhouse, Annie J. Browne, Michael G. Chipeta, Eli Harris, Nicholas P. J.Day, Paul Turner, Stephen Baker, Alan D. Lopez, Catrin E. Moore, Susanna Dunachie, and Christiane Dolecek. "Antimicrobial drug resistance in Shigella isolates globally, 1990 to 2018: A systematic review of the literature."

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Catrin E. Moore, Susanna Dunachie, **Bahar H. Kashef Hamadani**, Emmanuelle P. A. Kumaran, Georgina Haines-Woodhouse, Gisela Robles Aguilar, Michael G. Chipeta, Puja Rao, Andy Stergachis, Mohsen Naghavi, Christiane Dolecek, Nathaniel J. Henry, Aniruddha Deshpande, Robert C. Reiner Jnr, Nicholas P. J. Day, Alan, Christopher J L Murray. "Determining the global burden of antimicrobial resistance – The GRAM project." International Journal of Infectious Diseases. Dec 2020.

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