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# Antimicrobial resistance in community-acquired enteric pathogens amongst children ≤10-years-old in low- and middle-income settings: a systematic review and meta-analysis

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 February 2024 and was last updated on 12 February 2024.

## INTRODUCTION

**Review question / Objective** What is the prevalence of antimicrobial resistance (AMR) in community-acquired enteric bacteria from children under 10 years living in low- and middle-income settings?

**Rationale** Children are at increased risk of community acquired infections due to exposure to contamination from the environment. Majority of such infections are associated with enteric bacteria that cause preventable diarrheal disease that has been implicated in high mortality and morbidity in this population. Higher incidence of diarrhea in children necessitates frequent use of antimicrobials both in community and hospital settings. This has seen a surge in studies seeking to demonstrate the occurrence of AMR carriage in these enteric bacterial isolates.
This study seeks to systematically review data published in peer reviewed journals between 2005 and 2023 on the AMR profile of community-acquired enteric bacteria causing infections in children under 10 years, living in low- and middle-income settings. The findings may help to inform public health policy pertaining to the management of enteric disease in populations at risk of community acquired infections and unresponsive to commonly used antibiotics.

**Condition being studied** Antimicrobial resistance in enteric bacteria isolated from children under 10 years.

## METHODS

**Search strategy** The search strategy is designed to identify observational or experimental studies conducted in low- and middle-income countries, reporting AMR in enteric bacteria isolated from samples obtained from children under 10 years of age.
A systematic search of scientific databases will be conducted to identify studies published in peer-reviewed journals.
1. Scientific databases: PubMed, Medline, Web of Science, Cochrane library, CABI and EMBASE. The Boolean logic will be used to construct search strings using a combination of keywords related to the following concepts:
i. Concept 1: Children
Keywords: child* OR infant* OR "infant, newborn" OR neonat* OR babies
ii. Concept 2: Antibiotic resistance
Keywords: ((Antibiotic AND Resistan*) OR (Antimicrobial AND Resistan*) OR (Drug AND Resistan*) OR (Antibacterial AND Resistan*))
iii. Concept 3: Low- and middle-income countries, as defined by World Bank, 2019 (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups).
2. Reference lists of selected papers will also be scanned, and authors' personal files will be searched to ensure all relevant material has been captured. Where necessary, authors will be contacted, and additional missing details of their studies requested.

**Participant or population** 1. Population/participantsInclusion: all studies investigating AMR in community-acquired enteric bacteria from children aged between 0 and 10 years living in low- and middle-income community settings as defined by World Bank, 2019. 'Community acquired AMR' is defined as:i. AMR reported in non-hospitalized children i.e. outside medical care facilities, primary care practices, walk-in centers, hospital accident and emergency departments, hospital outpatient departmentsii. AMR reported in 'within 48 hours hospital admissions' (treated as not hospital acquired). i.e. if a child (0-10 years) is admitted and a fecal sample taken within 48 hours of admission and screened for AMR.iii. Diarrhea and/or gastroenteritis as reasons for admission or hospitalization.

**Intervention** Intervention/exposure of interest in the reviewed studies will be treatment with antibiotics.

**Comparator** No comparison group/control.

**Study designs to be included** cross-sectional, case/control, prospective, cohort.

**Eligibility criteria** Exclusion: i. Articles reporting non-enteric isolates ii. Articles reporting isolates from hospitalized patients other than the given definition of 'community' in this context iii. Articles reporting mixed population (irrespective of age) iv. Articles reporting studies from high income countries (HICs) v. Articles written in other languages other than English.

**Information sources** Electronic databases, contact with authors, grey literature.

**Main outcome(s)** The expected outcome of the interventions in the reviewed studies will be phenotypic antibiotic resistance or sensitivity. As such the effect size estimate will be the proportion of resistance to each antibiotic.

**Quality assessment / Risk of bias analysis** The review authors will independently assess the methodological quality of all included full-text articles using the Newcastle-Ottawa quality Score (NOS) adapted for cross-sectional studies. Any disagreements will be resolved by consensus.

**Strategy of data synthesis** All articles retrieved from database searching will be exported into a reference manager (Mendeley) and duplicate articles removed. Data screening will follow a three-stage approach. Firstly, articles will be screened by title and ineligible articles excluded. The abstracts of the remaining articles will then be screened, and potentially eligible full text articles will be retrieved. Finally, these full text articles will be screened for inclusion using a checklist highlighting the main inclusion criteria of the review (against PECOS). i.e. does the paper report AMR in enteric bacteria isolated from children aged between 0 and 10 years. This screening process will be presented in a Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flowchart.
Data will be extracted in a standardized data extraction form. Data will be extracted from each article using a double-blind approach (i.e. each paper by two review authors independently). Any discrepancy will be resolved by discussion with a third author. In total, three review authors will be involved in extracting data.
The data points to be extracted will include:
i. Title
ii. Authors
iii. Study location (country/city) and region
iv. Year of publication
v. Study period

vi. Epidemiological study design
vii. Study participants (age, sex, health status)
viii. Sampling design/ recruitment procedure
ix. Sampling design
x. Sample processing methods
xi. Antimicrobial resistance (AMR) detection methods
xii. Type and number of isolates tested
xiii. Interpretive criteria (CLSI, EUCAST)
xiv. Measurement tool (epidemiological or clinical breakpoints)
xv. Antibiotic resistance rate
Data Analysis strategies
i. Characteristics of all included studies will be described. Proportions of bacteria resistant to a drug will be calculated as the effect size estimate. A random-effects meta-analysis model for proportions will be used to estimate the pooled prevalence of antimicrobial resistance if at least 2 relevant studies are identified. Studies will be stratified by antibiotic type, bacterial species, geographical setting (region).
ii. Heterogeneity will be assessed by Higgins & Thompson's I2 statistics (I2 >50% will be considered as evidence of significant heterogeneity).
iii. Publication bias will be assessed using funnel plot asymmetry and quantitative assessment of funnel plot asymmetry will be done by Egger's regression tests.

**Subgroup analysis** Where possible, we will look at prevalence of antimicrobial resistance in age group stratified at '0 to 5 years' and '5 to 10 years'. We may also carry out subgroup analyses based on geographical region and study period (5 or 10 yearly based on the number of studies).

**Sensitivity analysis** Sensitivity analysis will not be done.

**Country(ies) involved** International Livestock Research Institute, Kenya.

**Keywords** Antibiotic, antimicrobial, resistance, AMR, LMIC, children, limited-resource, community, Enterobacteriaceae.

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