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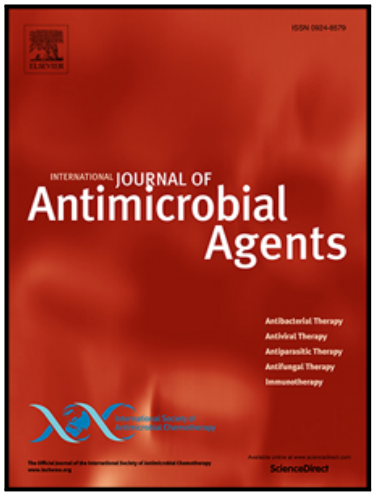


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**Highlights**:

- Mass and systematic antibiotic administration target a large portion of communities
- These interventions may increase the level of antibiotic resistance
- Particularly after azithromycin and co-trimoxazole administration
- More systematic and standardized surveillance of resistance is urgently needed

# Title page

**Title** What is the impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review

**Running Title:** AR after mass/systematic antibiotic administration

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**Key words**

Antibiotic resistance, prophylaxis, mass drug administration, systematic drug administration, Antibiotic usage, global health, Public health, low- and middle-income countries

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**Abstract**

Antibiotic consumption is a key driver of antibiotic resistance (AR), particularly in low- and middle-income countries, where risk factors for AR emergence and spread are rife. However, the potential contribution of mass and systematic antibiotic administration (MDA/SDA) to AR spread is unknown. We conducted a systematic review to provide an overview of MDA/SDA in low- and middle-income countries, including indications, antibiotics used and, if investigated, levels of AR over time. This systematic review is reported in accordance with the PRISMA statement. Of 2438 identified articles, 63 were reviewed: indications for MDA/SDA were various, and targeted populations were particularly vulnerable, including pregnant women, children, HIV-infected populations and communities in outbreak settings. Available data suggest MDA/SDA may lead to significant AR increase, especially after azithromycin administration. However, only 40% of studies evaluated AR. Integrative approaches that evaluate AR in addition to clinical outcomes are needed to understand consequences of MDA/SDA implementation, combined with standardized AR surveillance for timely detection of antibiotic resistance emergence.

**Units and Abbreviatons:**

AR: Antibiotic Resistance

MDA: Mass Drug Administration

SDA: Systematic Drug Adminitration

LMICs: Low- and Middle-income countries

## Introduction

Antibiotic resistance (AR) is one of the greatest threats to global health, particularly in low- and middle-income countries (LMICs) where risk factors for its emergence are widespread. Bacterial infections are already leading causes of death in LMICs, and further dissemination of AR could lead to increased mortality due to treatment failure, particularly in settings with restricted access to second-line drugs *[1]*.

Poor infection control, inadequate sanitation and poor living conditions have been identified as key drivers of AR in LMICs. Misuse, over-the-counter availability and low quality of antibiotics are also important contributors to AR in these settings *[2]*. Though antibiotics are predominantly used for treatment of bacterial infections, they are also used for prophylaxis at both the individual and population levels. Mass prophylactic use of antibiotics can broadly be classified as either mass drug administration (MDA) or systematic drug administration (SDA). MDA describes administration of antibiotics to entire communities to control the spread of particular infectious diseases. For instance, WHO (World Health Organization) recommends azithromycin MDA for trachoma control in high-prevalence settings *[3]*. Systematic drug administration (SDA) aims to prevent specific health outcomes or complications by prescribing antibiotics to targeted groups.

For example, co-trimoxazole can be given to HIV-infected individuals to prevent opportunistic infections *[4]*. Both of these repeated individual and/or large population exposures to antibiotics may play a critical role in the emergence and spread of AR *[5–7]*.

To our knowledge no systematic review has been conducted to describe antibiotic MDA/SDA interventions, despite their significance to public health and potentially important consequences for AR. The main objectives of this study were (i) to provide a descriptive overview of MDA/SDA interventions implemented in LMICs, including indications, targeted populations, antibiotics used and modes of administration, and (ii) to investigate their potential impact on AR.

## Methods

We systematically reviewed the literature for studies describing use of MDA/SDA in LMICs. This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Supplementary Table 1). The full study protocol was registered with PROSPERO, number CRD42020140182.

### Search strategy and selection criteria

PubMed, Web of Science, Scopus and Cochrane Library were searched for articles published between January 2000 and January 2019. Additional searches were conducted monthly until March 2020 to capture recently published literature. Further information was obtained using snowball searching by screening references identified from articles.

We used comprehensive Boolean search strategies with search terms pertaining to antibiotics, MDA, SDA and corresponding English MeSH headings for each database (Supplementary Text 1).

Articles included were original research articles describing antibiotic MDA or SDA interventions, with indication of administration that could potentially targeted a substantial part of the population in at least one countries defined as LMICs by the World Bank *[8]* (2019). Exclusion criteria were systematic reviews and meta-analyses articles (only used as a source of references in snowball searches), data collection prior to January 1 2000 and studies on MDA for trachoma control, owing to a recently updated systematic review and meta-analysis investigating AR following azithromycin MDA for trachoma control *[9]*. No language restrictions were applied.

Three researchers were involved in the review process (LR, BTH and EDA). One reviewer (LR) assessed article titles for relevance. Two of the three investigators (LR and BTH or EDA) independently reviewed all potentially relevant abstracts. The same process was used for full text screening and quality assessment. Disagreements were resolved by consensus among all parties.

For all eligible studies, we extracted details on objectives, methods and MDA/SDA characteristics. If AR was evaluated, epidemiological and microbiological methods were extracted. We stratified studies by target populations and types of antibiotic, and summarized data on AR when evaluated (resistant pathogen prevalence, measures of association).

The Critical Appraisal Skills Programme tools based on Cochrane guidelines were used to assess study quality. To assess data extraction quality, two investigators (LR and BTH or EDA) reviewed extracted data for selected articles.

**Findings**

Overall, 2438 articles were identified (Figure 1). After duplicate removal, 2131 articles were eligible for title screening, of which 150 were eligible for abstract screening. Of 86 full-text

articles assessed, 63 met our inclusion criteria. These 63 articles described 36 different studies across 19 countries. The majority of studies were from Africa (32 studies, 89%), in particular Southern Africa (17 studies, 47%) (Figure 2). Twenty-five studies (69%) were randomized controlled trials and 26 (72%) were implemented in an urban setting. Other study characteristics are available in supplementary Table 2.

**Antibiotics administered**

Overall, the most commonly used antibiotic was co-trimoxazole (16 studies, 14 of which among HIV-exposed or –infected individuals), with dosing consistent with international recommendations. Other common antibiotics under study were azithromycin (seven studies) and amoxicillin (six studies), with variable dosing. Details of populations, antibiotic, doses and frequency, and main outcomes investigated are presented in Table 1 and Figure 3.

**Populations Targeted**

Fourteen of the 36 studies (39%) assessed MDA/SDA in children *[10–40]*.

MDA was administered to healthy infants in three studies *[10–22]*. First, ARMCA investigated the impact of amoxicillin, co-trimoxazole or azithromycin MDA on infant weight gain *[10–12]*. Second, MORDOR assessed the effect of azithromycin MDA on infant morbidity and mortality *[13–21]*. The last study investigated the effect on infant morbidity and mortality of adding azithromycin to seasonal malaria chemoprophylaxis *[22]*.

Five studies targeted severely malnourished infants under two years old *[23–27]*. Among them, four investigated the impact of amoxicillin as SDA on nutritional recovery *[23–26]*, of which two further included arms with ceftriaxone *[24]* or cefdinir *[25]*. The fifth assessed the impact of co-trimoxazole as SDA on mortality *[27]*.

Six studies targeted HIV-exposed or -infected children *[28–40]*, all in the context of co-trimoxazole as SDA to decrease morbi-mortality.

Eleven studies [41–59] (31%) evaluated efficacy of SDA in pregnant women.

Six studies targeted healthy pregnant women [41–53], of which four evaluated azithromycin to decrease maternal/infant morbidity, preterm birth or low birth weight, or to improve gestational weight gain [42–51]. Two studies evaluated antibiotic SDA to prevent early neonatal sepsis, using either amoxicillin, cephalexin or penicillin [41], or ampicillin in combination or not with metronidazole [53].

Three studies targeted HIV-infected pregnant women [54–57] to prevent morbi-mortality using either co-trimoxazole [57], cefoxitin [56], or metronidazole in combination with erythromycin or ampicillin [54,55].

The remaining two studies targeted women with risk factors at delivery [58,59]. The first administered ampicillin to women with premature rupture of fetal membranes to prevent early onset neonatal sepsis [58]. The other assessed cefazolin administration at cord clamping to prevent maternal infections among women who underwent Caesarian section [59].

Eight studies (22%) investigated co-trimoxazole as SDA in HIV-infected adults [60–68] (or adults and children) and its potential to decrease mortality rates, infections or malaria incidence.

The remaining three studies (8%) described MDA in outbreak settings [69–72] which administered : doxycycline to contacts of cholera patients in Cameroon [69]; ciprofloxacin to members of Nigerien villages with high prevalence of meningitis [70]; and azithromycin to members of villages with high prevalence of yaws in Papua New Guinea [71,72].

**Antibiotic resistance**

AR was evaluated post-baseline (after first antibiotic administration) in 39% of studies [11,17,18,32,36,37,39,50,52,60,63,66–72] (14/36): in 36% (5/14) of studies among children

[11,17,18,32,36,37,39], in 18% (2/11) among pregnant women [50,52], in 50% (4/8) among HIV-infected adults [60,63,66–68], and in 100% (3/3) in outbreak settings [69–72]. Of note, two additional studies investigated AR at baseline without post-exposure follow-up and were thus excluded from the following results [23,48]. AR was detected with either phenotypic [17,32,36,37,50,52,60,63,66–70] (11/14) or molecular methods [11,17,18,39,71,72] (4/14) with one study using both methods [17].

Four studies with both intervention and control groups evaluated carriage of resistant bacteria cross-sectionally *[11,17,18,36,60]* (table 2). Single sampling time points ranged from 6 to 730 days following first antibiotic administration. AR was evaluated longitudinally in ten studies [32,36,37,39,50,52,60,63,66–72] (Figure 4). Follow-up ranged from 30 days to ten years.

**Azithromycin**

Of seven studies investigating azithromycin MDA/SDA, four evaluated AR.

Two studies, both among healthy children, investigated gut meta-genomic resistance after MDA. In ARMCA, antibiotic resistance determinants corresponding to each antibiotic class were identified using DNA-seq extracted from rectal swabs [11]. Five days after last MDA, increases in prevalence of macrolide and sulfonamide resistance genes were found (RR=3.6, $p<0.001$ and RR=16.0, $p=0.01$) [11]. For resistance genes for other antibiotic classes, such as beta-lactams and fluoroquinolones, prevalence was not different between antibiotic and placebo groups [11]. In MORDOR, antibiotic resistance determinants/genes identified were Ls, ermA, ermB, ermF, ermT, ermX, lnuA, lnuC, Lsa, macB, mefA, MEL, mphA, msrD [18]. Six months after last MDA, determinants of macrolide resistance from metagenomic DNA sequencing were significantly higher in the antibiotic group than in placebo in the intestinal flora (12.3% vs. 2.9%, $p= 0.02$) and in the nasopharyngeal flora (68.8% vs. 46.7%, $p=0.002$) [17]. The presence of genetic resistance determinants at the DNA level is not always associated with phenotypic

resistance. This requires analysis of gene expression at the RNA level. In MORDOR, the expression of macrolide resistance genes in the gut was also significantly higher in the antibiotic group than in the placebo group (16.7% vs. 2.7%, p=0.001 [18]).

Two studies, one in infants (MORDOR) [17] and the other in pregnant women [50], assessed *Streptococcus pneumoniae* resistance. In MORDOR, the proportion of resistance to erythromycin in nasopharyngeal samples was higher in the antibiotic group than controls (12.3% vs. 2.9%, p=0.02) [17]. In pregnant women receiving antibiotics, proportions of *S. pneumoniae* and *S. aureus* resistant to azithromycin were higher compared to the control group in nasopharyngeal, breast milk and vaginal samples at day 28 [50]. While antibiotics were administered only to mothers, infants born to mothers in the antibiotic group had higher rates of *S. aureus* resistant to azithromycin in nasopharyngeal samples taken at one month of age (4.5% vs 16.7%, p<0.001), but rates were similar to controls at 12 months (3.1% vs. 2.6%, p=0.724) [50,52]. Prevalence of resistant *S. pneumoniae* and *S. aureus* to other antibiotic classes (such as erythromycin, chloramphenicol, and clindamycin) was similar between both arms at 28 days and 12 months [52].

In a study evaluating *Treponema pallidum* resistance after azithromycin MDA in residents of yaws-endemic villages [71,72], rates of macrolide resistance genes (*A2058G* and *A2059G*) did not change over time and remained below 10% [71] (Supplementary Figure 1).

**Co-trimoxazole**

Of the sixteen studies in which co-trimoxazole was used as SDA, nine evaluated AR.

AR was assessed using meta-genomic analysis in two studies. Analysis of rectal swabs from healthy infants from ARMCA showed a significant increase in risk of carrying sulfonamide (RR=8.8, p=0.05) and trimethoprim (RR=3.3, p=0.04) resistance gene determinants relative to the placebo group, while no difference was observed for beta-lactam and macrolide resistance

genes [11]. The second study targeted HIV-exposed uninfected infants [39]. In the group treated with co-trimoxazole compared to placebo, the authors showed a decrease of gut microbiome β-diversity (diversity in resistance gene composition), increased AR gene α-diversity (resistance gene richness) (p=0.0045) and increased overall resistance gene prevalence (p=0.007) [39].

*S. pneumoniae* AR was investigated in three studies [32,36,68]. Based on a national surveillance system, Everett and colleagues reported a high rate of co-trimoxazole resistance (>90%) in *S. pneumoniae* cultures of cerebrospinal fluid and blood from adults and children admitted to hospital for severe bacterial infection [68]. No resistance to other antibiotics such as tetracycline, chloramphenicol or penicillin was reported [68]. The two remaining studies investigated AR in nasopharyngeal samples of HIV-infected children: high levels of co-trimoxazole resistance were observed at baseline in both antibiotic (85.2% [36] and 58% [32]) and control groups (83.3% [36] and 60% [32]), with an increase in both groups observed in the first months of administration [36]. Over two years, one study showed a higher level of co-trimoxazole resistant *S. pneumoniae* in the co-trimoxazole arm than in the placebo arm (88%/72% $p < 0.0001$) [32]. The proportion of *Haemophilus influenzae* resistant to co-trimoxazole was also higher in the co-trimoxazole arm [32]. The second study found an increase in nasopharyngeal colonization with *S. pneumoniae* resistant to co-trimoxazole (RR=3.2, p=0.04) and clindamycin (RR=1.6, p=0.04) [36]. However, no increase was detected for resistance to penicillin, erythromycin, tetracycline or chloramphenicol [36].

Four studies investigated phenotypic AR of fecal *Escherichia coli*: all in HIV-infected or -exposed populations.

In adults, proportions of *E. coli* resistant to co-trimoxazole were similar at 24 weeks in both groups. In the co-trimoxazole arm compared to placebo higher proportions of *E. coli* resistant to ampicillin (OR=10.2, p<0.001), chloramphenicol (0R=7.8, p<0.001), ciprofloxacin (OR=17.1,

p=0.006) and nalidixic acid (OR=26.4, p=0.001) were found [60]. In HIV-exposed but uninfected infants, the proportion of *E. coli* resistant to co-trimoxazole was higher in co-trimoxazole recipients compared with placebo (3 months: 94% vs. 51% p<0.0001, 6 months: 84% vs. 57% p=0.01); as well as in *Klebsiella spp.* at 3 months (94% vs. 51% p<0.0001) and 6 months (69% vs. 14% p=0.002)[37]. In HIV-infected patients with CD4-cell counts <350 cell/mm3, the resistant rate of *E. coli* to co-trimoxazole was 54% (29% in the control group) and reached 100% (53%) at 12 months [63]. Resistance rates were also higher when compared to baseline for ampicillin (from 74% to 100%), amoxicillin/clavulanic acid (from 33% to 100%) and ceftriaxone (from 2% to 54%) [63]. In the remaining study, 76% of bacterial isolates (*E. coli*, *Shigella spp.*, *Campylobacter spp.* or *Salmonella spp.*) were classified as resistant before, and 83% after co-trimoxazole use among HIV-infected adults [67]. In their HIV-negative family members with diarrhea, no difference in the proportion of resistance to co-trimoxazole was observed [66].

**Amoxicillin**

Of the five studies using amoxicillin as MDA, AR was evaluated in only one study [11]. While prevalence of beta-lactam, macrolide and trimethoprim resistance genes were not significantly different, prevalence of sulfonamide resistance was higher in the amoxicillin arms compared to control (RR=15.3, p=0.01) [11].

**Ciprofloxacin**

Fecal carriage of extended-spectrum beta-lactamase producing *Enterobacteriaceae* was evaluated in a cluster-randomized trial evaluating administration of a single oral dose of ciprofloxacin to prevent meningococcal meningitis [70]. Carriage of ciprofloxacin-resistant *Enterobacteriaceae* was higher than 90% at baseline and at 28 days post-intervention without significant change observed (Supplementary Figure 1) [70].

**Doxycycline**

Doxycycline was administered to contacts of cholera patients and *Vibrio cholerae* resistance was tested in stool samples of cholera patients during the eight months of outbreak [69]. The authors reported stable susceptibility patterns, including high rates of resistance for co-trimoxazole and colistin, and low rates for amoxicillin, clavulanic acid, cefotaxime, doxycycline, and perfloxacin [69].

## Discussion

MDA/SDA interventions can reduce the burden of infectious diseases and improve population health [73–75]. Yet MDA/SDA may also contribute to the mounting global health crisis posed by AR [5–7]. We conducted an exhaustive review of published MDA/SDA studies conducted in LMICs since 2000 and, when evaluated, their impacts on AR.

We found that MDA/SDA interventions targeted a diverse range of particularly vulnerable populations, including severely malnourished infants, pregnant women, young children, HIV-exposed and -infected individuals, and communities in outbreak settings. These populations are over-represented in many LMICs [76–79] and sometimes overlap, such that the same individuals may be targeted by more than one MDA/SDA. Three main families of antibiotics were administered for three main purposes: amoxicillin and azithromycin administration for weight gain, ampicillin to prevent neonatal sepsis, and co-trimoxazole to decrease mortality and morbidity. Despite potentially important consequences for AR, only 14 of 36 included studies (40%) evaluated AR following MDA/SDA. However limited, our findings are consistent with the expectation that MDA/SDA interventions lead to greater AR prevalence, especially after co-trimoxazole and azithromycin administration. Co-trimoxazole resistance was high at baseline in *E. coli* [37,60,63,66,67](>50%) and *S. pneumoniae* [36,68] (>75%), yet increased further in

several populations receiving co-trimoxazole MDA/SDA. In some included studies, co-trimoxazole prophylaxis was followed by increased resistance to other antibiotic classes such as aminopenicillins, chloramphenicols and quinolones [60]. It is possible that co-trimoxazole induces cross-resistance, although there is currently no scientific consensus [80]. One alternative explanation is that co-trimoxazole resistance genes can be found alongside other resistance genes, for example on the same plasmid [80]. Another explanation for co-trimoxazole favouring resistance to unrelated antibiotics, such as clindamycin, is co-selection of related antibiotic resistance genes [80].

Azithromycin MDA/SDA was associated with increased macrolide resistance in *S. pneumoniae*, *S. aureus* [50,52,81], and increased resistance genes among microbiota [11,17,18]. These results are concordant with those reported by O'brien *et al.* that found a transient or persistent increase in the proportion of *S. pneumoniae*, *E. coli* and *S. aureus* resistant to macrolides after MDA for trachoma control [9].

MDA/SDA is currently recommended by WHO for various indications, so potentially large numbers of people are eligible recipients. For example, following recent updates to treatment guidelines, WHO now recommends SDA for children with uncomplicated severe acute malnutrition, both in hospital and community settings, without practical guideline such as antibiotic class, dose or duration [82].

Since 2014, in settings with high infectious disease prevalence, WHO also recommends co-trimoxazole for all HIV-infected persons, irrespective of their CD4 count, as well as HIV-exposed neonates until 6 weeks of age [4]. With HIV prevalence above 20% in some LMICs [78], significant proportions of the population may be eligible for SDA under these guidelines.

Guidelines for other uses of MDA/SDA will likely evolve as more evidence from current and future studies becomes available. This has potential to further expand populations targeted by

these interventions. For instance, a research priority identified by WHO is evaluation of SDA for all women during the second or third trimesters of pregnancy to prevent infectious morbidity [83]. Several randomized controlled trials investigating azithromycin MDA are currently ongoing, targeting diverse populations including children after discharge from hospital, children with non-severe diarrhoea and malnourished children [84–86]. Moreover, in several low-income countries the official guidelines for treatment of Covid-19 patients at the primary care level recommend azithromycin for mild symptomatic Covid-19 patients, asymptomatic contacts or for prophylaxis [87].

The vast majority of included studies were set in Africa, thus limiting information regarding the indications and populations targeted by MDA/SDA and their potential impact on AR in others continents.

Epidemiological methods were heterogeneous without systematic evaluation of AR over time. AR can be transient [88–90] or may remain elevated for long periods because of low fitness costs of resistance [91] and/or continued selection pressure from other sources of antibiotic consumption. Temporal dynamics of AR were often poorly described or difficult to interpret, largely owing to variability in study design and duration of follow-up, which varied from five days to ten years.

Most studies investigated AR only in the treatment group, and evaluated AR only to the focal antibiotic and among few bacterial species. In addition, AR was evaluated only in bacteria specifically targeted by MDA/SDA, yet antibiotic exposure broadly selects for resistance across human microflora, particularly in the digestive tract [7,92]. In addition to the focal pathogen, assessment of resistance across non-focal species and across multiple antibiotic classes will be necessary to assess the overall impact of broad-spectrum antibiotic use on pathogenic bacterial species. AR is a concern not only for individuals targeted by MDA/SDA, but also their contacts

and environments, raising concerns about propagation of multidrug-resistant bacteria both within individuals and throughout communities. For example, among pregnant women receiving azithromycin MDA, rise of AR in *S. aureus* was also observed in their untreated neonates [50]. Better understanding of mechanisms of AR across species could help to better target particular bacteria while minimizing bystander selection [75]. Microbiological assessment of AR was also highly heterogeneous, and included phenotypic, molecular or metagenomic testing methods. Phenotypic methods can identify resistance of specific organisms to specific antibiotics, and are commonly used to characterize AR among both gram-positive and gram-negative bacteria. Metagenomic methods can detect resistance determinants in several types of organisms at the same time, but cannot determine whether this affects pathogenic or non-pathogenic bacteria. These complementary methods should be considered simultaneously for future cross-assessments. Moreover, the microbiome can be affected in terms of bacterial abundance, richness and diversity [5]. It may take long periods for microbiota to recover and return to a species composition similar to baseline, particularly in the context of repeated administration during vulnerable time periods, such as childhood [5,7]. Disruption of the microbiome can further select for emergence of resistant pathogens responsible for acute disease and increase risk of intestinal infection [5]. More studies are needed to better understand potentially far-reaching consequences of MDA/SDA on the microbiome.

To our knowledge, this review is the first to provide a global overview of MDA/SDA administration and its potential impact on AR. Our findings suggest that MDA/SDA with antibiotics such as azithromycin and co-trimoxazole may lead to significant increases in AR levels across bacterial species. Guidelines for AR evaluation in the context of MDA/SDA are sorely needed, including integrative approaches that incorporate standardized methodologies for AR evaluation.

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**Declarations**

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**Ethical Approval:** Not required

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691 # Table

692

693 **Table 1: Mass or systematic administration of antibiotics among 63 included articles: target populations,**

694 **antibiotics used, antibiotic dosing and frequency, and main outcomes investigated.**

| Target population | MDA/SDA[a] | Dose (mg) | Frequency | Main outcomes investigated |
|---|---|---|---|---|
| **Amoxicillin** | | | | |
| 1-59m healthy [10–12] | MDA | 25/kg | 2/d[b] x 5d | Weight gain |
| 1-59m malnourished [23] | SDA | 80/kg | 2/d x7d | Nutritional recovery |
| 1-59m malnourished [24] | SDA | 12.5 | 1/d x5d | Weight gain |
| 1-59m malnourished [25] | SDA | 80/kg | 2/d x2w[c] | Mortality and nutritional recovery |
| 6-59m malnourished [26] | SDA | 60/kg | 1/d x7d | Nutritional recovery |
| Healthy [41] | SDA | 500 | 1 at delivery | Early-onset neonatal sepsis |
| **Ampicillin** | | | | |
| Vaginal delivery [53] | SDA | 1000 | 1/6h before delivery | Early-onset neonatal sepsis |
| HIV-infected [54,55] | SDA | 500 + 250 | 3/d x7d | Mortality and morbidity[d] |
| Pre-labor SROM[e] [58] | SDA | 1500 | 1 at delivery | Early-onset neonatal sepsis |
| **Azithromycin** | | | | |
| 1-59m healthy[13–21] | MDA | 20/kg | 2/y[f] x3y | Mortality, morbidity and resistance gene abundance |
| 1-59m healthy [10–12] | MDA | 5/kg | 1/d x5d | Mortality, hospital admission |
| 3-59m healthy [22] | MDA | 100 or 200 | 1/d x3d | Weight gain |
| Healthy [42] | SDA | 1000 | 1 at 2nd and 3rd trimester | Preterm-birth |
| Healthy [43–45] | SDA | 500 | 2 at 3rd trimester | Preterm deliveries, fetal and neonatal weight |
| Healthy [29–33] | SDA | 500 | 2/d x2d up to 3 times | Gestational weight gain, birth weight |
| Healthy [49–52] | SDA | 2000 | 1 at delivery | Mortality and morbidity**, infant weight gain |
| Yaws outbreak [71,72] | MDA | 30/kg | 1 dose | Prevalence of yaws |
| **Cefazolin** | | | | |
| C-section [59] | SDA | 2000 | 1 at cord clamping | Maternal infections |

| Target population | MDA/SDA[a] | Dose (mg) | Frequency | Main outcomes investigated |
|---|---|---|---|---|
| **Cefdinir** | | | | |
| 1-59m malnourished [25] | MDA | 14/kg | 2/d x2w | Mortality and nutritional recovery |
| **Cefoxitin** | | | | |
| HIV-infected, vaginal delivery [56] | SDA | 2000 | 1 at delivery | Maternal infections |
| **Ceftriaxone** | | | | |
| 1-59m malnourished [24] | SDA | 50/kg | 1/d x5d | Weight gain |
| **Cephalexin** | | | | |
| Healthy [41] | SDA | 500 | 1 at delivery | Early-onset neonatal sepsis |
| **Ciprofloxacin** | | | | |
| Previous meningitis outbreak [70] | MDA | 250 or 500 | 1 dose | Meningitis attack rate |
| **Co-trimoxazole** | | | | |
| 1-59m healthy [10–12] | MDA | 240 | 2/d x5d | Weight gain |
| 2-59m malnourished [27] | SDA | 120 or 240 | 1/d x1y | Mortality |
| 3-17y HIV-infected [28,40] | SDA | 480 or 960 | 1/d x96w or x200w | Mortality, hospital admission, skin infection |
| 3-14y HIV-infected [29–33] | SDA | 240 or 480 | 1/d x4y | Mortality, hospital admission, antibiotic consumption and pneumococcal colonization |
| 2-5y HIV-infected [34,35] | SDA | 60/kg | 1/d x4y | Malaria incidence |
| 0-1y HIV-exposed [36] | SDA | 60/kg | 1/d x1y | Pneumococcal colonization |
| 0-15m HIV-exposed [37] | SDA | 120 or 240 | 1/d x15m[g] | Colonization of resistant Enterobacteriaceae |
| 0-1y HIV-exposed [38,39] | SDA | 120 or 240 | 1/d | Morbidity and resistance gene abundance |
| HIV-infected [57] | SDA | 480 | 2/d x16d | Mortality and hospital admission |
| HIV-infected [60] | SDA | 960 | 2/d | Colonization of resistant *E. coli* |
| HIV-infected [61] | SDA | 960 | 1/d | Mortality |
| HIV-infected [62] | SDA | 960 | 1/d | Mortality and malaria incidence |
| HIV-infected [63] | SDA | 960 | 1/d | Colonization of resistant *E. coli* |
| HIV-infected with immune recovery [64] | SDA | 960 | 1/d | Mortality and morbidity |
| HIV-infected with immune recovery [64] | SDA | 960 | 1/d | Incidence of co-trimoxazole-preventable events or death |

| Target population | MDA/SDA[a] | Dose (mg) | Frequency | Main outcomes investigated |
|---|---|---|---|---|
| And children HIV-infected [66,67] | SDA | 960 | 1/d | Mortality and morbidity |
| >15y HIV-infected [68] | SDA | 960 | 1/d | Pneumococcal colonization |
| **Doxycycline** | | | | |
| contacts of infected Cholera patients [69] | MDA | 5/kg | 1 dose | Cholera incidence and rate of *V. cholerae* resistance |
| **Erythromicyn** | | | | |
| HIV-infected [54,55] | SDA | 500 + 250 | 3/d x7d | Mortality and morbidity (pregnant women and neonates) |
| **Penicillin** | | | | |
| Healthy [41] | SDA | 500 | 1 at delivery | Early-onset neonatal sepsis |

**Legends**

Infants and children
Pregnant women
HIV-infected individuals
Communities

d- day
w- week
m- month
y- year

a- MDA/SDA: Mass or systematic drug administration
b- d: day
c- w: week
d- of pregnant women and their neonate
e- SROM : Spontaneous Rupture of Membranes
f- y: year
g- m: month

[10–12] – 3 arms : co-trimoxazole, azithromycin, amoxicillin
[41] – 3 arms : amoxicillin, cephalexin, penicillin
[24] – 2 arms : amoxicillin, ceftriaxone
[25] – 2 arms : amoxicillin, cefdinir
[54,55] – 3 arms : ampicillin + metronidazole or erythromycin + metronidazole
[53] – 2 arms : ampicillin or ampicillin + metronidazole

718 **Table 2: Single time-point evaluation of antibiotic resistance following antibiotic administration**

719 CI-Confidence Interval, MG – metagenomics, PDD - Phenotype disk diffusion, PE- Phenotype ellipsometry

720 1 – Time between first antibiotic administration and sampling, 2 – Control versus intervention, 3- Risk of non-

721 susceptibility when co-trimoxazole non-susceptible

| Outcome evaluated | Study name | Sample | Method | Class or antibiotic evaluated | Time[1] (days) | Prevalence exposed / unexposed | Association measure[2] | CI 95% | pvalue |
|---|---|---|---|---|---|---|---|---|---|
| **Amoxicillin** | ARMCA [11] | Rectal | MG | Beta-lactam | 10 | | 3.1 | [0.7 ; 13.3] | NS |
| Resistome | ARMCA [11] | Rectal | MG | Macrolide | 10 | | 1.24 | [0.6 ; 4.4] | NS |
| | ARMCA [11] | Rectal | MG | Sulfonamide | 10 | | 15.3 | [1.8 ; 129.1] | 0.01 |
| | ARMCA [11] | Rectal | MG | Trimethoprim | 10 | | 1.4 | [0.5 ; 4.0] | NS |
| **Azithromycin** | MORDOR [18] | Rectal | MG | Aminoglycosides | 730 | 1.3 / 2.7 | | [0.0 ; 2.7] / [1.0 ; 5.0] | NS |
| Resistome | MORDOR [17] | Rectal | MG | Aminoglycosides | 730 | 38.0 / 31.3 | | [29.2 ; 44.7] / [24.7 ; 36.7] | NS |
| | ARMCA [11] | Rectal | MG | Beta-lactam | 10 | | 1.9 | [0.5 ; 6.6] | NS |
| | MORDOR [18] | Rectal | MG | Beta-lactam | 730 | 36.0 / 34.0 | | [27.3 ; 43.3] / [24.0 ; 44.0] | NS |
| | MORDOR [17] | Rectal | MG | Beta-lactam | 730 | 68.0 / 63.3 | | [60.0 ; 74.0] / [56.3 ; 70.7] | NS |
| | MORDOR [18] | Rectal | MG | Fluoroquinolones | 730 | 4.7 / 2.0 | | [1.3 ; 9.3] / [0.0 ; 5.0] | NS |
| | MORDOR [17] | Rectal | MG | Fluoroquinolones | 730 | 27.3 / 28.7 | | [19.3 ; 35.3] / [22.0 ; 35.3] | NS |
| | MORDOR [17] | Rectal | MG | Glycopeptides | 730 | 1.3 / 1.3 | | [0.0 ; 2.7] / [0.0 ; 2.7] | NS |
| | ARMCA | Rectal | MG | Macrolides | 10 | | 2.6 | [1.5 ; 4.4] | <0.001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [11] | | | | | | | | |
| | MORDOR [18] | Rectal | MG | Macrolides | 730 | 16.7 / 2.7 | | [9.3 ; 24.7] / [1.0 ; 5.0] | 0.001 |
| | MORDOR [17] | Rectal | MG | Macrolides | 730 | 68.0 / 46.7 | | [61.3 ; 74.0] / [36.0 ; 54.0] | 0.002 |
| | MORDOR [18] | Rectal | MG | Metronidazole | 730 | 30.0 / 23.3 | | [18.7 ; 39.3] / [16.0 ; 30.7] | NS |
| | MORDOR [17] | Rectal | MG | Metronidazole | 730 | 31.3 / 23.3 | | [20.7 ; 42.0] / [16.0 ; 29.3] | NS |
| | ARMCA [11] | Rectal | MG | Sulfonamides | 10 | | 16.0 | [1.9 ; 133.5] | 0.01 |
| | MORDOR [18] | Rectal | MG | Sulfonamides | 730 | 0.7 / 2.0 | | [0.0 ; 2.0] / [0.0 ; 4.0] | NS |
| | MORDOR [17] | Rectal | MG | Sulfonamides | 730 | 16.7 / 22.7 | | [9.3 ; 24.0] / [17.3 ; 29.6] | NS |
| | MORDOR [17] | Rectal | MG | Tetracyclines | 730 | 75.3 / 74.0 | | [66.3 ; 80.0] / [68.7 ; 78.7] | NS |
| | MORDOR [18] | Rectal | MG | Tetracyclines | 730 | 27.3 / 30.7 | | [20.7 ; 34.7] / [22.7 ; 39.3] | NS |
| | ARMCA [11] | Rectal | MG | Trimethoprim | 10 | | 1.8 | [ 0.7 ; 5.1 ] | NS |
| | MORDOR [17] | Rectal | MG | Trimethoprim | 730 | 51.3 / 48.7 | | [44.0 ; 58.0] / [38.7 ; 57.3] | NS |
| | MORDOR [18] | Rectal | MG | Trimethoprim | 730 | 2.0 / 2.0 | | [0.0 ; 4.0] / [0.0 ; 4.0] | NS |
| *Streptococcus* | MORDOR [17] | Nasal | PDD | Co-trimoxazole | 730 | 84.7 / 77.1 | | [76.4 ; 92.4] / [65.4 ; 88.1] | NS |
| *pneumoniae* | MORDOR [17] | Nasal | PDD | Clindamycin | 730 | 9.0 / 1.7 | | [4.3 ; 14.1] / [0.0 ; 4.3] | NS |
| | MORDOR [17] | Nasal | PDD | Doxycycline | 730 | 60.1 / 50.1 | | [50.8 ; 70.5] / [33.7 ; 66.0] | NS |
| | MORDOR [17] | Nasal | PDD | Erythromycin | 730 | 12.3 / 2.9 | | [5.7 ; 20.0] / [0.0 ; 6.1] | 0.02 |
| | MORDOR [17] | Nasal | PDD | Penicillin | 730 | 18.7 / 22.3 | | [8.2 ; 30.6] / [10.2 ; 37.6] | NS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Co-trimoxazole** | ARMCA [11] | Rectal | MG | Beta-lactam | 10 | 1.8 | [0.5 ; 6.4] | NS |
| Resistome | ARMCA [11] | Rectal | MG | Macrolides | 10 | 8.9 | [0.9 ; 3.0] | NS |
| | ARMCA [11] | Rectal | MG | Sulfonamides | 10 | 8.8 | [1 ; 77.0] | 0.05 |
| | ARMCA [11] | Rectal | MG | Trimethoprim | 10 | 3.3 | [1.1 ; 10.0] | 0.04 |
| *Escherichia coli* | [60] | Rectal | PDD | Ampicillin | 7 to 168 | 10.2[3] | [5.9 ; 17.8] | <0.001 |
| | [60] | Rectal | PDD | Azithromycin | 7 to 168 | 1.2[3] | [0.71 ; 1.9] | NS |
| | [60] | Rectal | PDD | Chloramphenicol | 7 to 168 | 7.8[3] | [3.0 ; 20.2] | <0.001 |
| | [60] | Rectal | PDD | Ciprofloxacin | 7 to 168 | 17.1[3] | [2.3 ; 127.7] | 0.006 |
| *Streptococcus pneumoniae* | TZI project [36] | Nasal | PE | Chloramphenicol | 42 | 0.8 | [0.3 ; 2.3] | NS |
| | TZI project [36] | Nasal | PE | Clindamycin | 42 | 1.6 | [1.0 ; 2.6] | 0.04 |
| | TZI project [36] | Nasal | PE | Erythromycin | 42 | 1.0 | [0.6 ; 1.7] | NS |
| | TZI project [36] | Nasal | PE | Penicillin | 42 | 1.1 | [0.7 ; 1.7] | NS |
| | TZI project [36] | Nasal | PE | Tetracycline | 42 | 0.9 | [0.6 ; 1.5] | NS |

722

723 **Figures**

724 **Figure 1 : PRISMA flow diagram**

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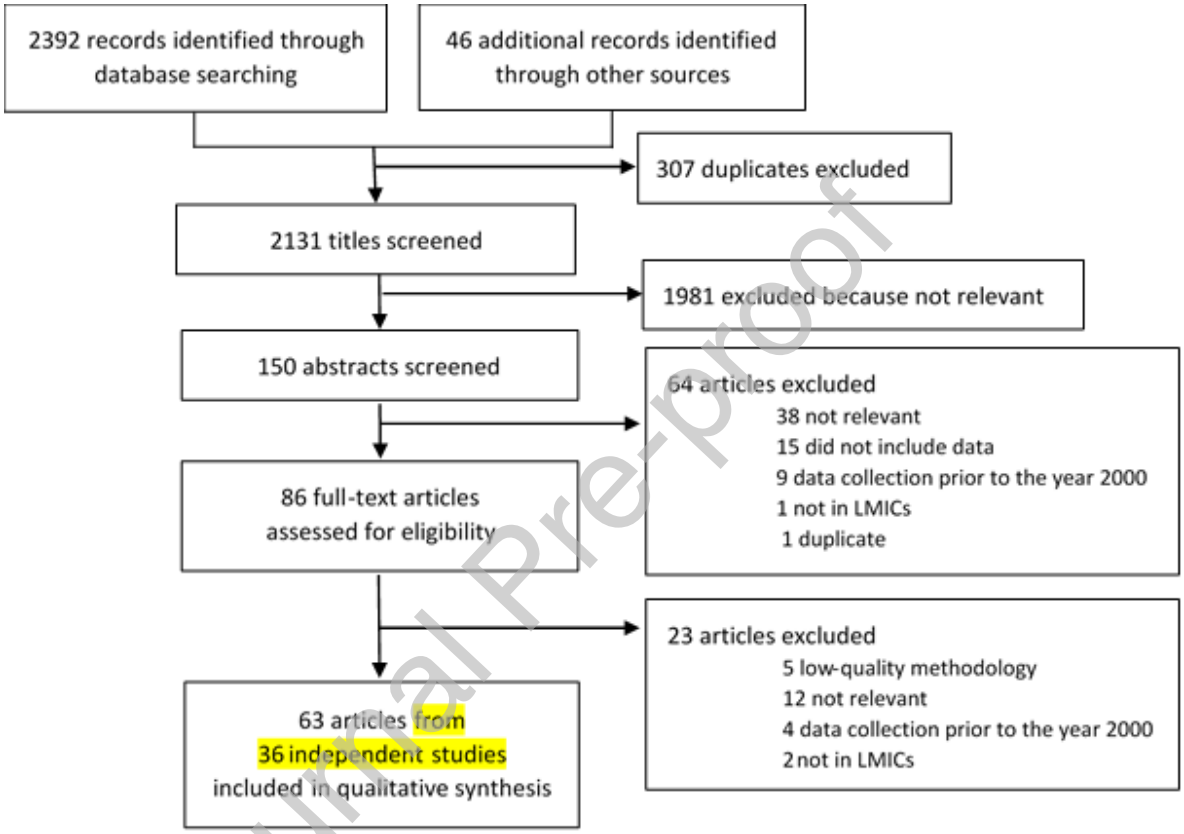


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727 **Figure 2 : Geographic distribution of the 63 included articles (36 studies)**

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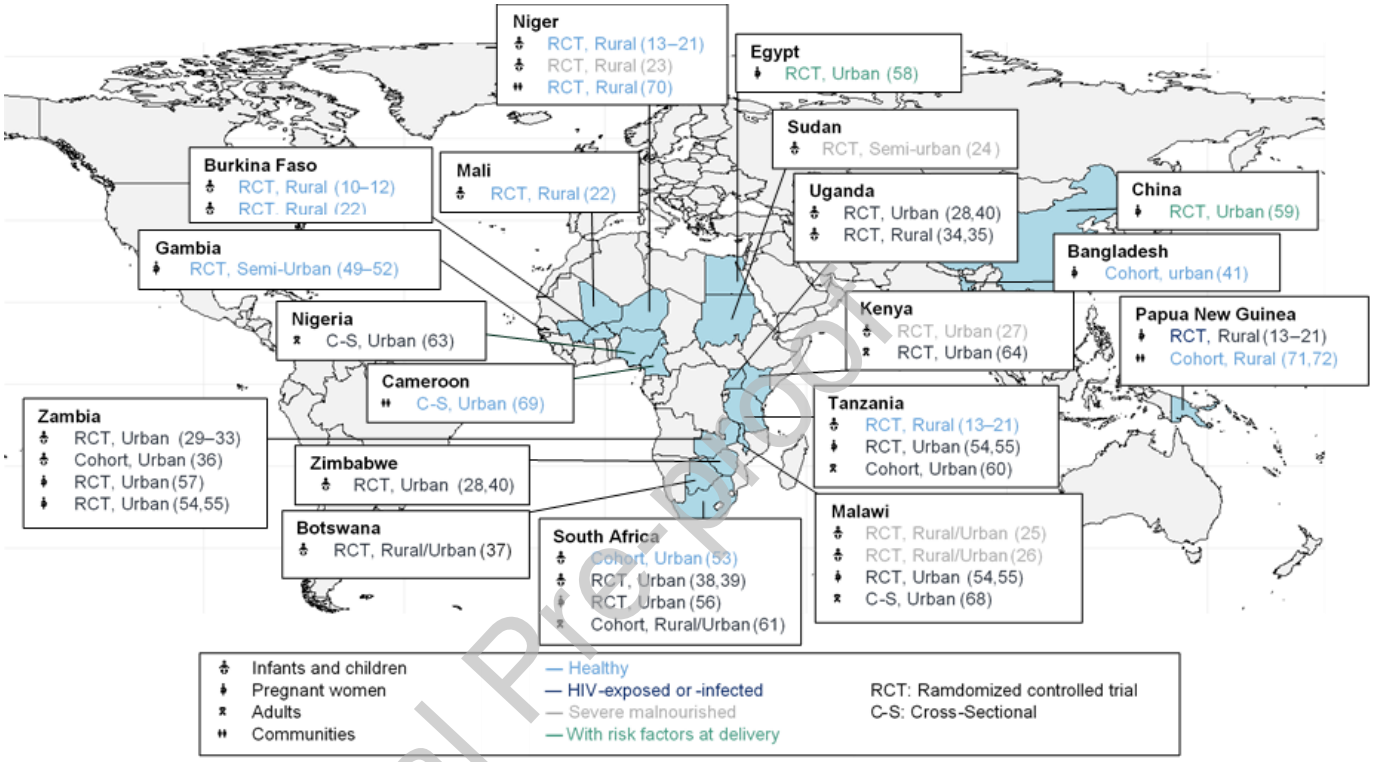


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731 **Figure 3 : Main populations, antibiotics used and indications for MDA/SDA in LMICs**

| | Populations | Antibiotic most commonly used | Intended outcome |
|---|---|---|---|
|  **Childhood** | Healthy infants | azithromycin | ↘ mortality |
| | Malnourished infants | amoxicillin | ↗ weight |
|  **Pregnancy** | Healthy pregnant women | azithromycin | ↘ premature delivery<br>↘ neonatal sepsis<br>↘ maternal/neonatal mortality<br>↗ birth weight |
| | Premature rupture of membranes | ampicillin | ↘ Early-onset neonatal sepsis |
| | C-section | cefazolin | ↘ Morbidity |
|  **HIV** | Infected or exposed pregnant women, infants, children and adults | Co-trimoxazole | ↘ morbidity<br>↘ mortality |
|  **Outbreak** | Meningitis | Ciprofloxacine | ↘ meningitis |
| | Cholera | Doxycycline | ↘ cholera |
| | Yaws | Azithromycin | ↘ yaws |

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733 **Figure 4: Longitudinal evaluation of antibiotic resistance with repeated measures**

734 Legend

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736 **4A** – Resistance over time after azitromycin administration, **4B**-Resistance over time after co-trimocazole administra

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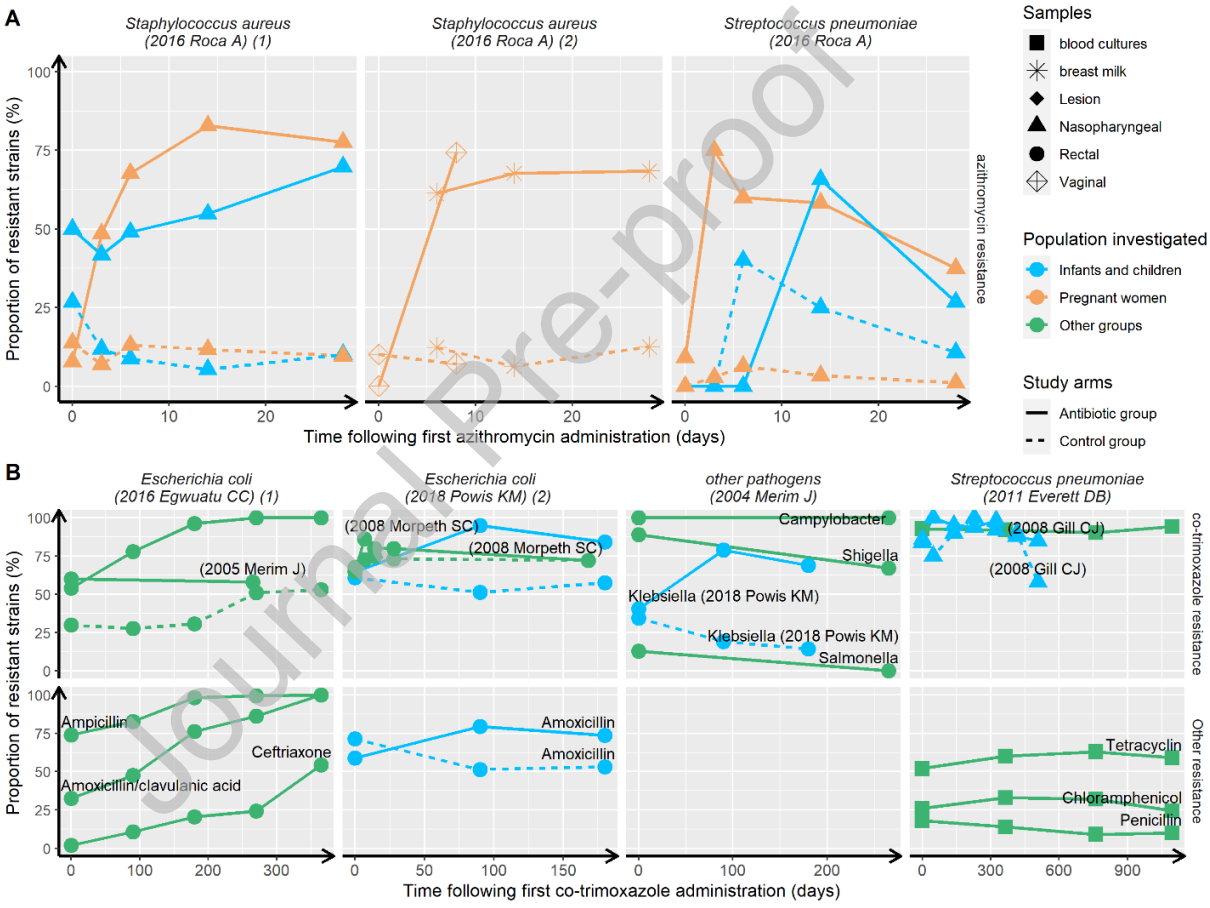


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