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Review

Impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review

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ABSTRACT

Antibiotic consumption is a key driver of antimicrobial resistance (AR), particularly in low- and middle-income countries (LMICs) where risk factors for AR emergence and spread are prevalent. However, the potential contribution of mass drug administration (MDA) and systematic drug administration (SDA) of antibiotics to AR spread is unknown. We conducted a systematic review to provide an overview of MDA/SDA in LMICs, 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, human immunodeficiency virus (HIV)-infected populations, and communities in outbreak settings. Available data suggest that MDA/SDA may lead to a significant increase in AR, especially following azithromycin administration. However, only 40% of studies evaluated AR. Integrative approaches that evaluate AR in addition to clinical outcomes are needed to understand the consequences of MDA/SDA implementation, combined with standardised AR surveillance for timely detection of AR emergence.

1. Introduction

Antimicrobial 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 failures, 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]. Although antibiotics are predominantly used for the treatment of bacterial infections, they are also used for prophylaxis both at 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, the World Health Organization (WHO) recommends azithromycin MDA for trachoma control in high-prevalence settings [3]. SDA aims to prevent specific health outcomes or complications by prescribing antibiotics to targeted groups. For example, co-trimoxazole (trimethoprim/sulfamethoxazole) can be given to human immunodeficiency virus (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.

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2. Methods

We systematically reviewed the literature for studies describing the 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 S1). The full study protocol was registered with PROSPERO (no. CRD42020140182).

2.1. Search strategy and selection criteria

PubMed, Web of Science, Scopus and Cochrane Library databases 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 and 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 target a substantial part of the population in at least one country defined as LMIC by the World Bank (2019) [8]. Exclusion criteria were systematic reviews and meta-analyses (only used as a source of references in snowball searches), data collected prior to 1 January 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 summarised 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.

3. Results

Overall, 2438 articles were identified (Fig. 1). After removal of duplicates, 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%) (Fig. 2). Moreover, 25 studies (69%) were randomised controlled trials and 26 (72%) were implemented in an urban setting. Other study characteristics are given in Supplementary Table S2.

3.1. Antibiotics administered

Overall, the most commonly used antibiotic was co-trimoxazole (16 studies, 14 of which were 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, antibiotics, doses and frequency, and main outcomes investigated are presented in Table 1 and Fig. 3.

3.2. Populations targeted

Of the 36 studies, 14 (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 2 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 morbimortality.

Eleven studies (31%) [41–59] evaluated the 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, cefalexin or penicillin [41], or ampicillin in combination or not with metronidazole [53]. Three studies targeted HIV-infected pregnant women [54–57] to prevent morbimortality 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 Caesarean 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 a high prevalence of meningitis [70] and azithromycin to members of villages with a high prevalence of yaws in Papua New Guinea [71,72].

3.3. Antimicrobial resistance (AR)

AR was evaluated post-baseline (after first antibiotic administration) in 14 studies (39%) [11,17,18,32,36,37,39,50,52,60,63,66–72]: in 36% of studies (5/14) 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 methods (11/14) [17,32,36,37,50,52,60,63,66–70] or molecular methods (4/14) [11,17,18,39,71,72], 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]

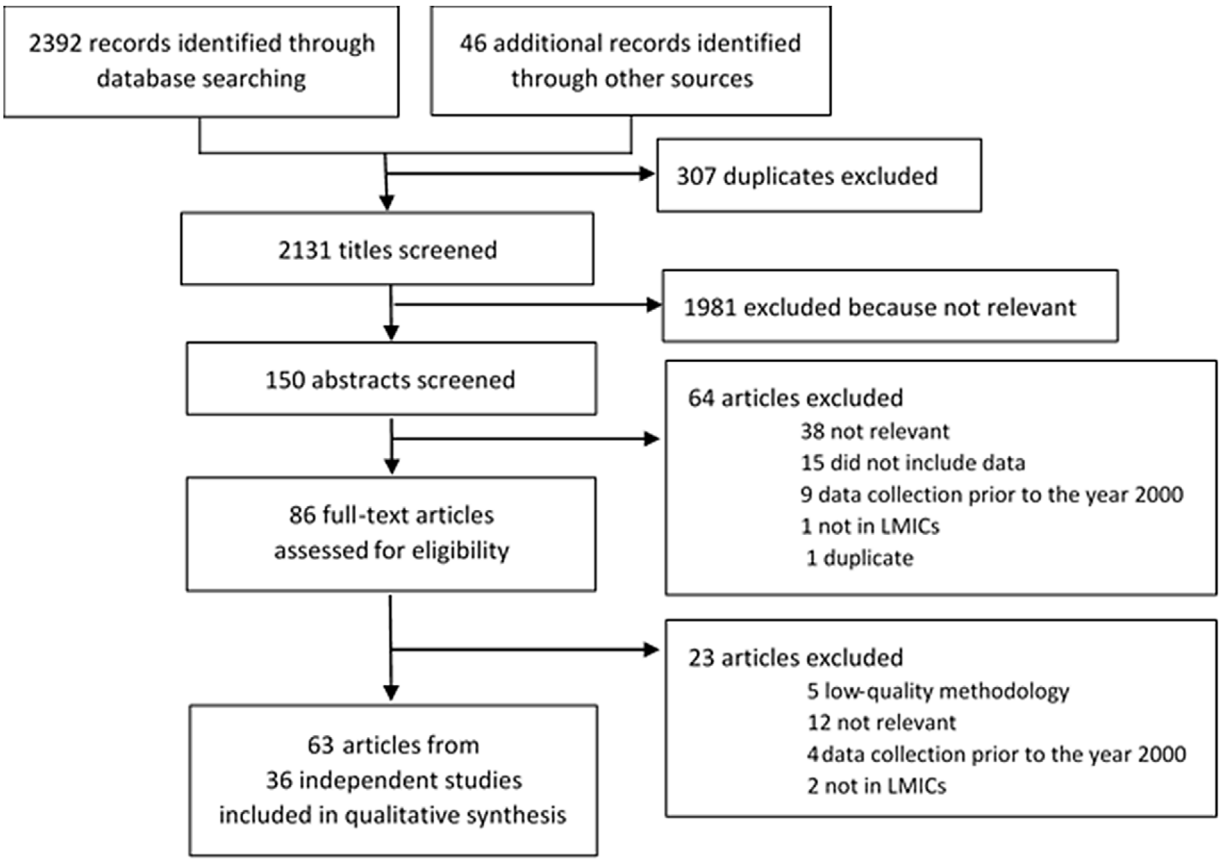

Fig. 1. PRISMA flow diagram. LMICs, low- and middle-income countries.

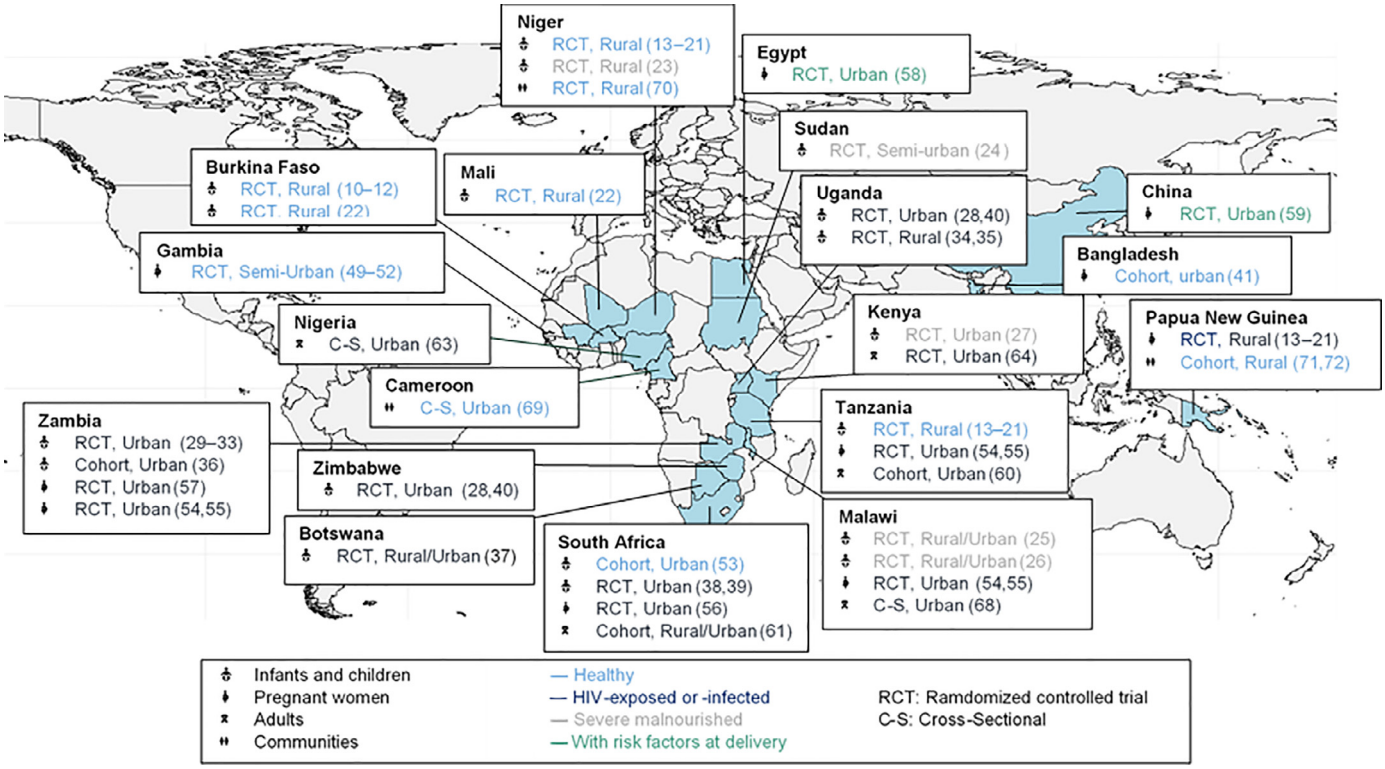

Fig. 2. Geographic distribution of the 63 included articles (36 studies).

Table 1
Mass or systematic administration of antibiotics among 63 included articles: target populations, 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[d], 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
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
• 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

(*continued on next page*)

Table 1 (*continued*)

Target population	MDA/SDA[a]	Dose (mg)	Frequency	Main outcomes investigated
Erythromicyn				
• HIV-infected [54,55]	SDA	500 + 250	3/d x7d	Mortality and morbidity[d]
Penicillin				
• Healthy [41]	SDA	500	1 at delivery	Early-onset neonatal sepsis

Legends
Infants and children d- day
Pregnant women w- week
HIV-infected individuals m- month
Communities 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

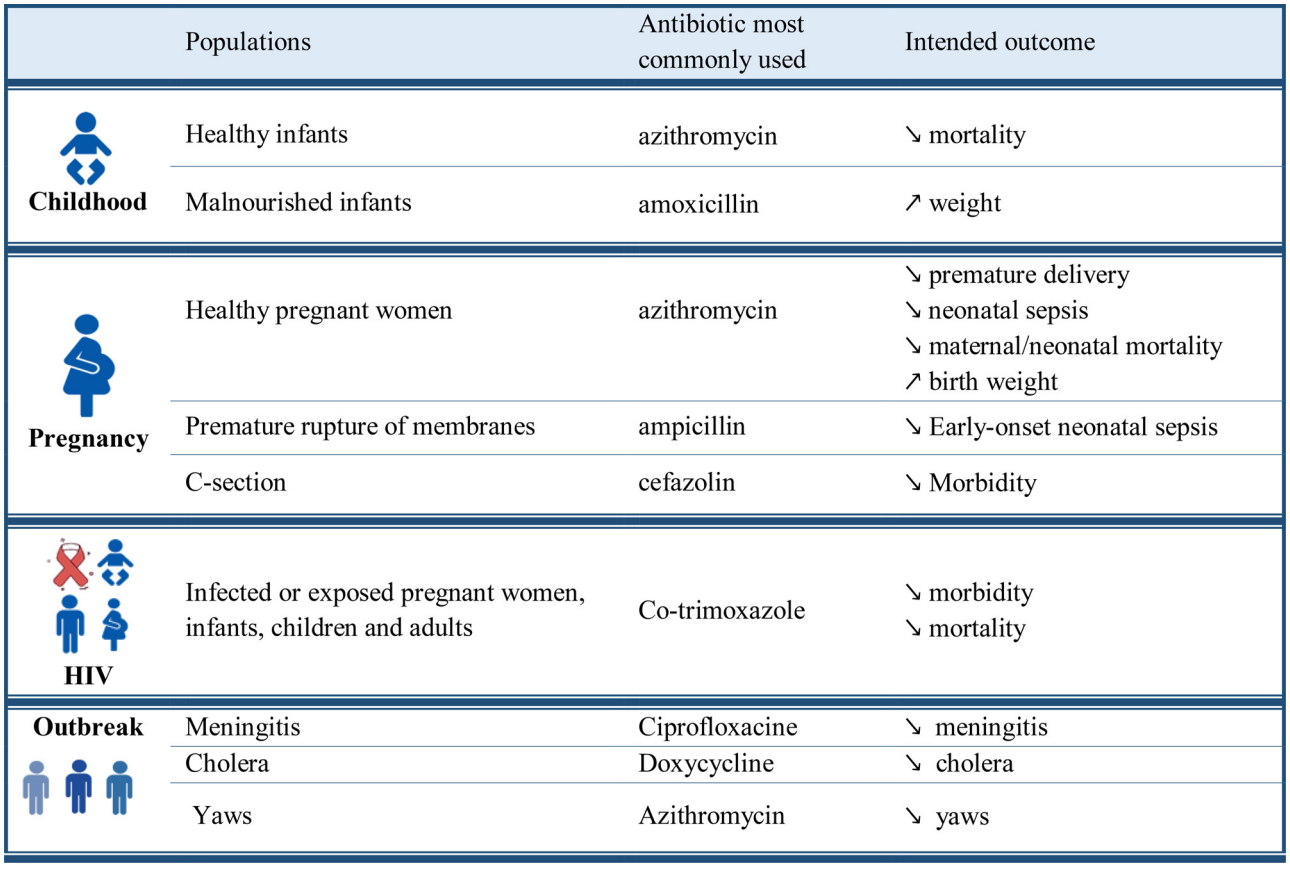

Fig. 3. Main populations, antibiotics used and indications for mass or systematic drug administration in low- and middle-income countries.

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

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 [11]	Rectal	MG	Macrolides	10		2.6	[1.5; 4.4]	<0.001
	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		1.6	[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	TZI project [36]	Nasal	PE	Chloramphenicol	42		0.8	[0.3; 2.3]	NS
pneumoniae	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

CI-Confidence Interval, MG – metagenomics, PDD - Phenotype disk diffusion, PE- Phenotype ellipsometry
1 – Time between first antibiotic administration and sampling, 2 – Control versus intervention, 3- Risk of non-susceptibility when co-trimoxazole non-susceptible

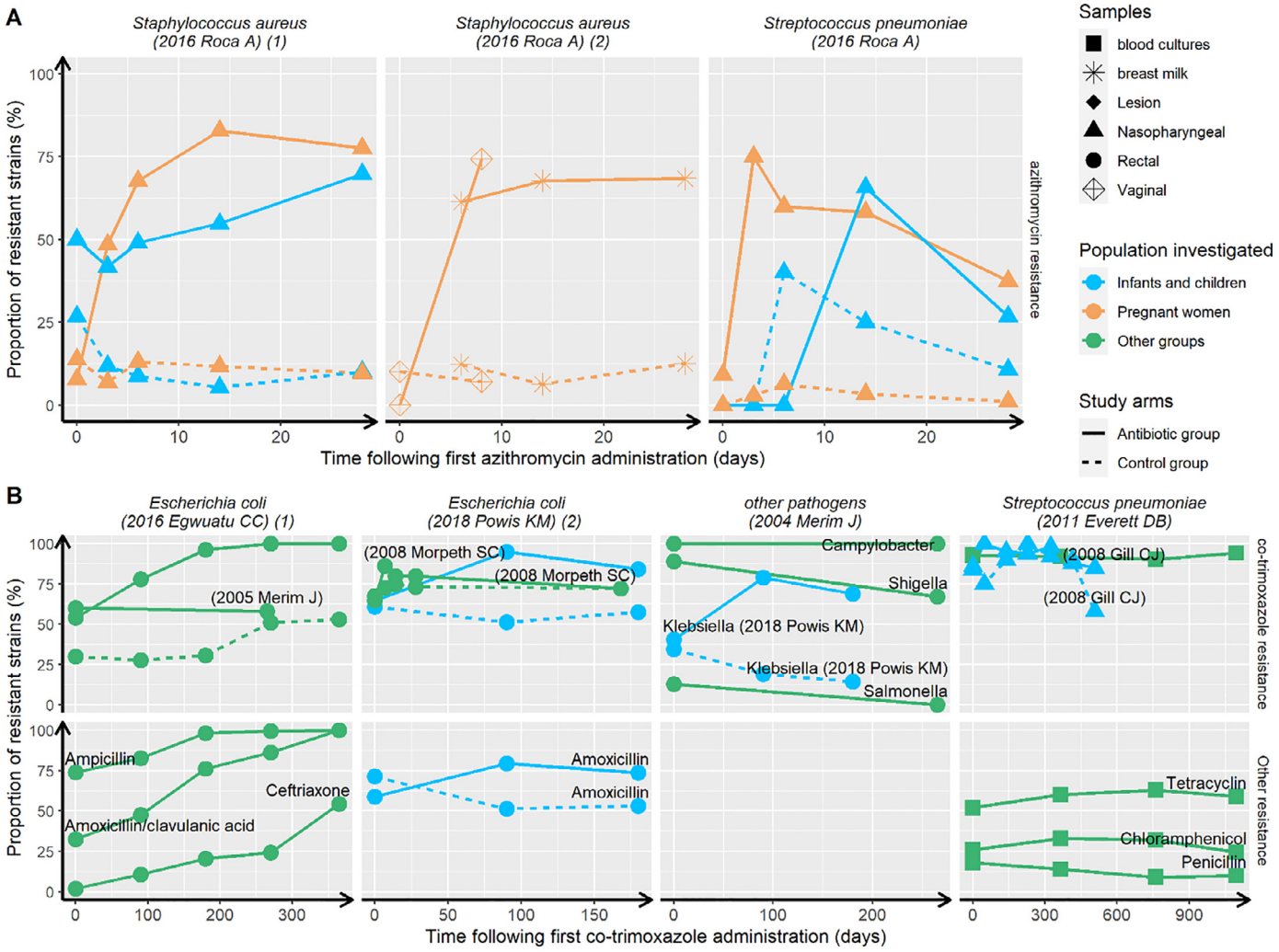

Fig. 4. Longitudinal evaluation of antimicrobial resistance with repeated measures. Resistance over time following (A) azithromycin and (B) co-trimoxazole administration.

(Table 2). Single sampling time points ranged from 6–730 days following first antibiotic administration. AR was evaluated longitudinally in ten studies [32,36,37,39,50,52,60,63,66–72] (Fig. 4). Follow-up ranged from 30 days to 10 years.

3.3.1. Azithromycin

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

Two studies, both among healthy children, investigated gut metagenomic resistance after MDA. In ARMCA, resistance determinants corresponding to each antibiotic class were identified using sequencing of DNA extracted from rectal swabs [11]. Five days after the last MDA, increases in the prevalence of macrolide and sulfonamide resistance genes were found [risk ratio (RR) = 3.6 ($P <$ 0.001) and RR = 16.0 ($P = 0.01$)] [11]. For resistance genes to other antibiotic classes, such as β-lactams and fluoroquinolones, the prevalence did not differ 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* and *msrD* [18]. Six months after the last MDA, determinants of macrolide resistance from metagenomic DNA sequencing were significantly higher in the antibiotic group than in the placebo group for the intestinal flora (12.3% vs. 2.9%; $P = 0.02$) and the nasopharyngeal flora (68.8% vs. 46.7%; $P = 0.002$) [17]. However, 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, 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 in controls (12.3% vs. 2.9%; $P = 0.02$) [17]. In pregnant women receiving antibiotics, proportions of *S. pneumoniae* and *Staphylococcus aureus* resistant to azithromycin were higher compared with 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 1 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]. The 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 following 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 Fig. S1).

3.3.2. Co-trimoxazole

Of the 16 studies in which co-trimoxazole was used as SDA, 9 evaluated AR.

AR was assessed using metagenomic analysis in two studies. In ARMCA, analysis of rectal swabs from healthy infants showed a significant increase in the risk of carrying sulfonamide (RR = 8.8; $P = 0.05$) and trimethoprim (RR = 3.3; $P = 0.04$) resistance determinants relative to the placebo group, while no difference was observed for β-lactam and macrolide resistance genes [11]. The second study targeted HIV-exposed uninfected infants [39]. In the group treated with co-trimoxazole compared with 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].

Streptococcus pneumoniae AR was investigated in three studies [32,36,68]. Based on a national surveillance system, Everett et al. 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 infections [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 both in 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 2 years, one study showed a higher level of co-trimoxazole-resistant *S. pneumoniae* in the co-trimoxazole arm than in the placebo arm (88% vs. 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 colonisation 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 faecal *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 with placebo, higher proportions of *E. coli* resistant to ampicillin [odds ratio (OR) = 10.2; $P < 0.001$], chloramphenicol (OR = 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 [at 3 months, 94% vs. 51% ($P < 0.0001$); at 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/mm^3, the resistant rate of *E. coli* to co-trimoxazole was 54% (vs. 29% in the control group) and reached 100% (vs. 53%) at 12 months [63]. Resistance rates were also higher compared with 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 diarrhoea, no difference in the proportion of resistance to co-trimoxazole was observed [66].

3.3.3. Amoxicillin

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

3.3.4. Ciprofloxacin

Faecal carriage of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae was evaluated in a cluster-randomised trial evaluating administration of a single oral dose of ciprofloxacin to prevent meningococcal meningitis [70]. Carriage of ciprofloxacin-resistant Enterobacteriaceae was >90% at baseline and at 28 days post-intervention with no significant change observed (Supplementary Fig. S1) [70].

3.3.5. Doxycycline

Doxycycline was administered to contacts of cholera patients and *Vibrio cholerae* resistance was tested in stool samples of cholera patients during an 8-month outbreak [69]. The authors reported stable susceptibility patterns, including high rates of resistance to co-trimoxazole and colistin and low rates to amoxicillin, clavulanic acid, cefotaxime, doxycycline and pefloxacin [69].

4. Discussion

MDA/SDA interventions can reduce the burden of infectious diseases and improve population health [73–75]. However, 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 (39%) of the 36 included studies evaluated AR following MDA/SDA. However limited, our findings are consistent with the expectation that MDA/SDA interventions lead to greater AR prevalence, especially following co-trimoxazole and azithromycin administration. Co-trimoxazole resistance was high at baseline in *E. coli* (>50%) [37,60,63,66,67] and *S. pneumoniae* (>75%) [36,68], 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, chloramphenicol 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* and *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. who found a transient or persistent increase in the proportion of *S. pneumoniae, E. coli* and *S. aureus* resistant to macrolides following MDA for trachoma control [9].

MDA/SDA is currently recommended by the WHO for various indications, so potentially large numbers of people are eligible recipients. For example, following recent updates to treatment

guidelines, the WHO now recommends SDA for children with uncomplicated severe acute malnutrition, both in hospital and community settings, without practical guidelines such as antibiotic class, dose or duration [82].

Since 2014, in settings with a high infectious disease prevalence, the WHO also recommends co-trimoxazole for all HIV-infected persons, irrespective of their CD4 cell count, as well as HIV-exposed neonates until 6 weeks of age [4]. With an 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 the WHO is evaluation of SDA for all women during the second or third trimesters of pregnancy to prevent infectious morbidity [83]. Several randomised controlled trials investigating azithromycin MDA are currently ongoing, targeting diverse populations including children following 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 patients with COVID-19 (coronavirus disease 2019) at the primary care level recommend azithromycin for mild symptomatic COVID-19 patients, asymptomatic contacts or 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 other 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 the 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 5 days to 10 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 in individuals and throughout communities. For example, among pregnant women receiving azithromycin MDA, a rise of AR in *S. aureus* was also observed in their untreated neonates [50]. Better understanding of the mechanisms of AR across species could help to better target particular bacteria while minimising bystander selection [75]. Microbiological assessment of AR was also highly heterogeneous and included phenotypic, molecular and metagenomic testing methods. Phenotypic methods can identify resistance of specific organisms to specific antibiotics and are commonly used to characterise AR both among 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 the risk of intestinal infection [5]. More studies are needed to better understand the 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 standardised methodologies for AR evaluation.

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2021.106364.

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