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Systematic review

Exposure to World Health Organization's AWaRe antibiotics and isolation of multidrug resistant bacteria: a systematic review and meta-analysis

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ABSTRACT

Background: Antibiotic use drives antibiotic resistance.
Objectives: To systematically review the literature and estimate associations between prior exposure to antibiotics across World Health Organization's (WHO) AWaRe categories (Access, Watch, Reserve) and isolation of critical and high-priority multidrug resistant organisms (MDROs) on the WHO priority pathogen list.
Data Sources: Embase, Ovid Medline, Scopus, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (from inception to 20/08/2020).
Study eligibility criteria: Case-control, cohort, or experimental studies that assessed the risk of infection/colonization with MDROs.
Participants: Inpatients or outpatients of any age and sex.
Interventions: Prior exposure to antibiotics that could be categorized into the AWaRe framework.
Data analysis: Tailored design-specific checklists applied to each included study. For each antibiotic/class, crude odds ratios (ORs) were pooled through random-effects meta-analyses, both overall and by MDRO. Heterogeneity was examined.
Results: We identified 349 eligible studies. All were observational, prone to bias due to design and lack of adjustment for confounding, and not primarily designed to compare associations across AWaRe categories. We found statistically significant associations between prior exposure to almost all antibiotics/classes across AWaRe categories and colonization/infection with any MDRO. We observed higher ORs for Watch and Reserve antibiotics than with Access antibiotics. First generation cephalosporins (Access) had the least association with any MDRO colonization/infection (58 studies; OR = 1.2 [95% CI: 1.0–1.4]), whereas strongest associations were estimated for linezolid (Reserve) (22 studies; OR = 2.6 [95% CI: 2.1

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−3.1]), followed by carbapenems (Watch) (237 studies; OR = 2.3 [95% CI: 2.1−2.5]). There was high heterogeneity for all antibiotic/MDRO associations.
Conclusions: Optimising use of Access antibiotics is likely to reduce the selection of MDROs and global antibiotic resistance. Despite data limitations, our study offers a strong rationale for further adoption of AWaRe as an important tool to improve antibiotic use globally. **Giorgia Sulis, Clin Microbiol Infect 2022;28:1193**

Introduction

Increasing rates of antibiotic resistance are a serious threat to humanity [1]. Reduction of total and inappropriate broad-spectrum antibiotic use in humans is a critical step to decreasing overall rates of resistance [2]. In an effort to optimize antibiotic use, the World Health Organization (WHO) created a new classification in 2017 in which antibacterial medicines were stratified into three groups—Access, Watch, and Reserve (AWaRe) based on their spectrum, anticipated risk of resistance development, risk of toxicity, and clinical utility [3]. The classification has been revised in 2019 and 2021 [4,5].

The AWaRe classification was developed using expert consensus of the literature but has not been empirically evaluated for validity [6]. Although other systematic reviews have analysed the association between antibiotic exposure and risk for specific multidrug-resistant organisms (MDROs) [7−10], our meta-analysis is the first designed to examine overall risks associated with each AWaRe antibiotic group while taking into account select MDROs of high clinical and public health interest. We collated the evidence on the association between prior exposure to antibiotics belonging to each AWaRe category and documented subsequent detection of colonization/infection with antibiotic-resistant bacteria. We hypothesized that the use of Access-group antibiotics is less likely to be associated with subsequent patient MDRO colonization/infection than the use of Watch- or Reserve-group antibiotics.

Methods

The protocol for this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; identifier: CRD42020206508) and is reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [11].

Search strategy, selection criteria, and screening process

We performed a systematic review of studies concerning MDROs that pose the greatest threat to human health and are considered as “critical” or “high” priority in the 2017 WHO priority pathogen list [12]: carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), extended-spectrum beta-lactamase (ESBL)−producing Enterobacterales (EB), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* spp. (VRE). A medical librarian searched the literature for records including critical Gram-negative MDROs, high priority Gram-positive MDROs, and antibiotics belonging to each of the WHO AWaRe categories both as individual drugs and as classes. We searched Embase.com, Ovid Medline, Scopus, The Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to August 20, 2020. Fully reproducible search strategies are provided in the appendix.

Eligible studies were any case-control, cohort, or experimental study that compared the risk of resistance in patients treated with different antibiotics and contrasted the risk profiles of antibiotics for antibiotic-resistant bacteria. Studies had to: include at least ten participants of any age, sex, or race from the same healthcare settings or geographical location; report the number of individuals who were exposed or unexposed to a given antibiotic/class for any clinical reason and, within each exposure category, the proportion of patients who were subsequently identified with colonization/infection with a given MDRO. Articles in Chinese, Japanese, or Korean were excluded as we had limited confidence in fully assessing the content based on machine translation.

We accepted definitions of infection and/or colonization as reported by study authors at face value; antibiotics were defined as any agents categorized as oral or parenteral antibacterial within the Anatomical Therapeutic Chemical classification system (2020 version) [13]. Studies restricted to travellers and those solely focused on patients with relapsing MDRO infections were excluded, as well as case reports, review articles, qualitative studies, ecological studies, economic analyses, mathematical modelling studies, commentaries, and conference abstracts. All records were screened independently by two investigators, first by title and abstract and then by full text.

Multiple pairs of reviewers among G.S., S.S., S.K., N.B., I.G., E.T., M.A.C., S.Y., and S.G. independently assessed titles and abstracts for inclusion, followed by full text screening and data extraction from selected studies.

Data extraction

We used a standardized Microsoft Excel (Redmond, WA, USA) form that was tested on ten randomly selected articles. One investigator extracted data, and a second investigator checked the primary extraction for correctness and completeness. Disagreements were resolved by arbitration including a third investigator. We extracted information on the study setting, characteristics of the study population at recruitment, type, and timing of prior antibiotic exposure, methods of exposure and outcome ascertainment, and the number of individuals who were exposed/unexposed to specific antibiotics/antibiotic classes by outcome status. For studies that reported on multiple MDROs, we extracted data for each pathogen separately. Since a small number of studies included more than one control group, we only utilized the one that was deemed to be better representative of the exposure distribution in the source population. Most notably, if patients infected with a susceptible pathogen (e.g. methicillin-susceptible *S. aureus* where the case group consisted of MRSA-infected patients) and uninfected hospitalized patients were included in the study as distinct control groups, we selected the latter [8,14]. In studies that utilized healthy population-based controls in addition to a group of

hospitalized individuals (either uninfected or infected with a susceptible pathogen), we disregarded healthy controls to mitigate the potential for selection bias.

During data extraction, all antibiotics or antibiotic classes reported were categorized using the 2019 WHO AWaRe framework (Table S1) [4]. As our primary aim was to determine how associations between prior antibiotic exposure and outcomes varied by AWaRe category, antibiotic classes that include agents belonging to two or more AWaRe categories and that were reported as a single group (e.g. cephalosporins with no further break down) were not considered. However, we extracted data on aminoglycosides even if reported as a single class because the most utilized agents in this class (i.e. amikacin, gentamicin) belong to the Access group; a similar approach was adopted for tetracyclines.

Risk of bias assessment

Building on the Cochrane's Risk Of Bias In Non-randomized Studies of Interventions tool and the Scottish Intercollegiate Guideline Network checklist [15,16], we developed tailored checklists to assess the risk of bias in included studies, addressing key bias sources that we deemed particularly relevant to the evaluation of the association of interest. Our checklists, one for case-control studies and the other for observational and experimental cohort studies, included four domains (participant selection, exposure assessment, outcome assessment, confounding) consisting of various subdomains. Two independent investigators judged each subdomain to be at low, high, or unclear risk of bias. The full checklists are provided in the appendix (Tables S2, S3).

Analysis

We conducted distinct meta-analyses of studies reporting on each MDRO-antibiotic combination of interest. Although we originally planned to compare outcomes among individuals exposed to "Access" versus "Watch" antibiotics within the same study, this analysis could not be performed because participants exposed to multiple antibiotics would have to be counted multiple times thus leading to a biased sample. Moreover, none of the included studies performed head-to-head comparisons of associations of Access versus Watch/Reserve-group antibiotics and the outcome. Prior antibiotic exposure was treated as a dichotomous variable; duration of treatment and dosages could not be examined. Our primary outcome was the odds of colonization/infection with any MDRO of interest among those exposed to a given antibiotic or antibiotic class across AWaRe groups relative to the odds among the unexposed. Our secondary outcomes were the odds of colonization/infection with specific MDROs (as defined above) among the exposed relative to the unexposed.

Based on findings from previous reviews [7–10], we reasoned a priori that adjustment for key demographic and clinical factors (e.g. age, sex, date of hospital admission, hospital ward/unit of recruitment) would have been seldomly and inconsistently used/reported. Therefore, determining whether the distribution of underlying medical conditions and other factors that could affect both the likelihood of receiving antibiotic treatment and the risk of acquiring a given MDRO differed according to the exposure and/or outcome status was prevented. For each included study we therefore preferred to consistently use the unadjusted odds ratios (ORs) of colonization and/or infection with any MDRO, if reported. Otherwise, when possible, we calculated the crude OR. Where data for two or more antibiotics belonging to the same class were reported separately, we produced class-specific pooled estimates by applying the Mantel-Haenszel method within the study, an approach that also allowed handling sparse data [17]. Owing to the observational nature of the included studies and the anticipated levels of between-study heterogeneity, we ultimately pooled class-specific log-transformed ORs from individual studies using random effects meta-analyses weighted by the DerSimonian-Laird method. Heterogeneity was assessed through visual inspection of forest plots and via the Higgins test [18]. As we expected substantial variability between specific pathogens, we also conducted subgroup analyses for each MDRO of interest.

For sensitivity analysis, we ran similar models after restricting to: 1) case-control studies; 2) studies including only adult participants; 3) studies conducted in either high-income or low- and middle-income countries; 4) studies conducted solely in intensive care unit(s) (ICUs); 5) studies focused on community-acquired infections and/or colonisations (only for ESBL-EB and MRSA); 6) studies focused on hospital-acquired infections and/or colonisations (only for CRAB, CRE, and ESBL-EB); 7) studies with different case types (e.g. only patients with clinically significant infections due to CRAB, CRE, or ESBL-EB; only patients colonized with VRE).

These analyses were carried out when at least five studies were available for a specific pathogen and antibiotic/class. Finally, we conducted analyses by omitting one study at a time to detect studies that were particularly influential and had a major impact on the pooled estimate. All analyses were conducted in Stata (version 17.0; StataCorp, College Station, TX, USA).

Given the fact that many studies selectively reported exposure to certain antibiotics but not others, we did not undertake a formal assessment of publication bias through funnel plots or statistical tests for asymmetry.

Results

Of the 179 869 unique records identified through our search, 2030 were selected for full-text review; 349 studies met the eligibility criteria, including 8 reporting on 2 different MDROs (Fig. 1). The list of studies excluded because of the publication language is shown in the appendix (Table S4), along with the references and main characteristics of each included study (Tables S5, S6). Most eligible studies dealt with ESBL-EB ($n = 133$), followed by CRE ($n = 79$), VRE ($n = 59$), CRAB ($n = 34$), MRSA ($n = 32$), and CRPA ($n = 20$) (Table 1). The vast majority were case-control studies (231, 64.7%), conducted in either high-income (218, 61.1%) or upper-middle-income countries (89, 24.9%), predominantly in inpatient care settings (307, 86.0%, of which 65 in ICU only), and involved only adult participants (242, 67.8%). Approximately two thirds of the studies (248, 69.5%) either did not specify whether the colonization/infection was hospital- or community-acquired or included a mix of patients belonging to both categories without providing disaggregated data. Among studies focusing on critical priority pathogens (ESBL-EB, CRE, CRAB, CRPA), over 50% defined cases as individuals diagnosed with clinically significant infection caused by the MDRO of interest, whereas 15.2% to 41.2% of the studies (depending on the pathogen) included a mix of colonized and infected cases. Colonized individuals (often identified through systematic screening) were used as cases in about half of the studies on high-priority pathogens (MRSA, VRE). With respect to the timing of antibiotic exposure relative to outcome onset/detection, we observed substantial heterogeneity across studies. Most notably, this information was not reported or unclear in approximately one third of the studies (100, 28.0%) and even more frequently among studies focused on CRAB, MRSA, and VRE. Among the remaining studies, antibiotic exposure assessment was most often restricted to the 30 days (68, 19.0%) or the 3 months (69, 19.3%) preceding the detection of MDRO colonization/infection. However, data were insufficient to determine the actual timing of antibiotic treatment for individual patients within the chosen exposure window.

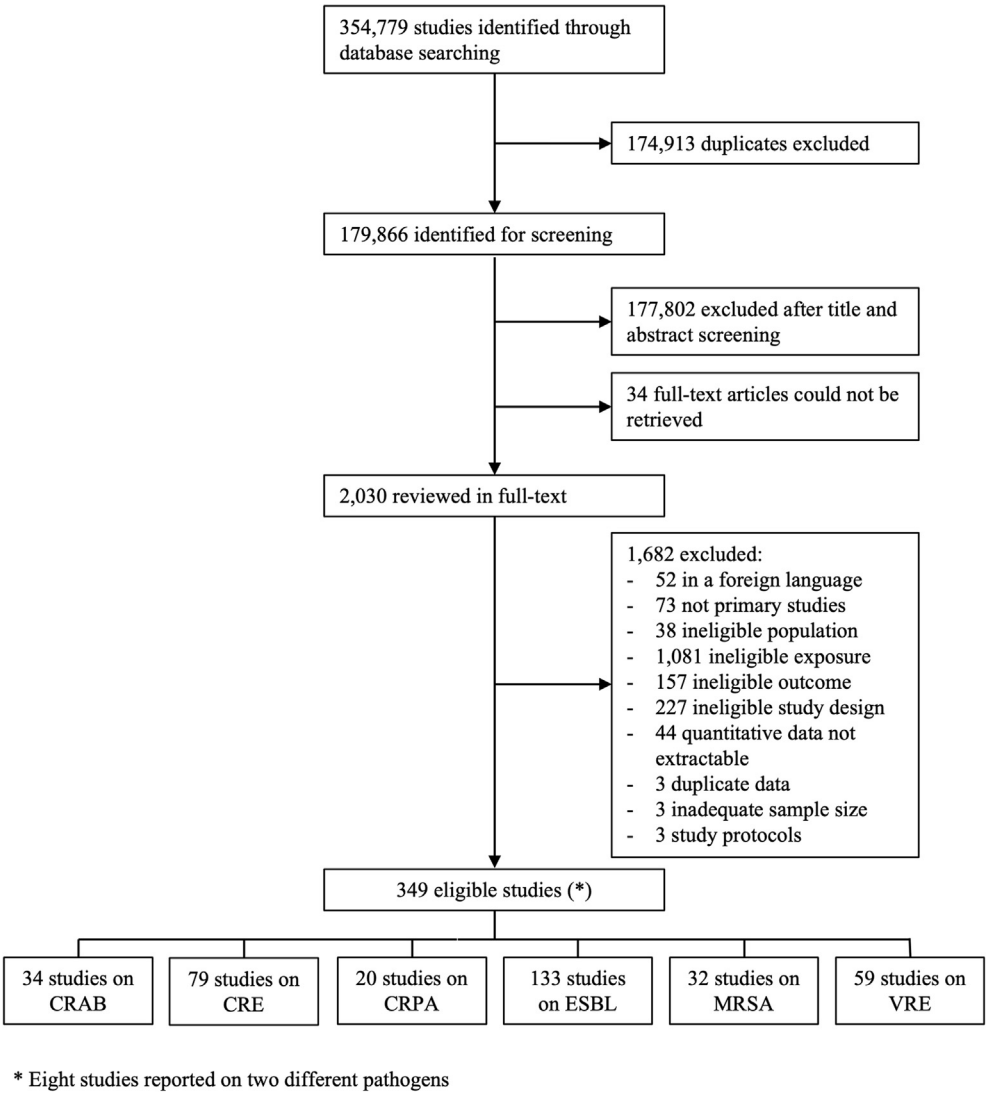


Fig. 1. Study selection process.

A graphical summary of studies' risk of bias evaluation is presented in Fig. 2, whereas study-specific assessments are provided in the appendix (Tables S7, S8). Participants' selection criteria and sampling methods were deemed to be at low risk of bias in most studies. Given the uncertainty about which controls are ideal to address our research question [14,19], we assigned an unclear risk of bias to all case-control studies concerning the chosen type of controls. The definition and ascertainment method of the exposure status were often deemed to be at high or unclear risk of bias due to the timing of antibiotic treatment relative to the outcome onset/detection (either too close or too far away from one another) and because a large proportion of patients in many studies were likely exposed to more than one antibiotic concomitantly or sequentially. The risk of misclassification of the outcome status was judged at low risk of bias because diagnostic tests are well-standardized and accurate; nonetheless, there might be potential bias in the identification of carriers unless systematic screening was performed. However, confounding was a major concern for all studies, leading to high risk of bias.

Pooled estimates suggest that almost all antibiotics/classes belonging to each AWaRe category were significantly associated with an increased risk of colonization/infection with any MDRO. However, ORs were more frequently higher for Watch and Reserve antibiotics (Fig. 3). First-generation cephalosporins (1GC) had the weakest association with any MDRO (58 studies; OR = 1.2 [95% CI: 1.0–1.4]), whereas stronger associations were estimated for linezolid (Reserve) (22 studies; OR = 2.6 [95% CI: 2.1–3.1]), followed by carbapenems (Watch) (237 studies; OR = 2.3 [95% CI: 2.1–2.5]), and tigecycline (Reserve) (15 studies; OR = 2.3 [95% CI: 1.8–3.1]).

Prior use of several Watch-group antibiotics was significantly associated with infection/colonization with CRAB, CRE, and CRPA (Table 2, Figures S1–S22); however, across AWaRe categories, use of carbapenems was most strongly associated with selection of CRAB (34 studies; OR = 2.2 [95% CI: 1.8–2.6]), CRE (74 studies; OR = 2.5 [95% CI: 2.2–2.7]), and CRPA (19 studies; OR = 3.2 [95% CI: 2.5–4.2]).

The use of any antibiotic/class, irrespective of AWaRe category, was significantly associated with colonization/infection with ESBL-EB (Table 2), with monobactams (Reserve) most strongly associated (8 studies; OR = 2.9 [95% CI: 1.7–5.0]), followed by 3GC (Watch) (63 studies; OR = 2.5 [95% CI: 2.2–2.9]) and 4GC (Watch) (17 studies; OR = 2.4 [95% CI: 1.6–3.8]).

Exposure to several antibiotics/classes belonging to Access and Watch groups was significantly associated with MRSA and VRE colonization/infection (Table 3, Figures S23–S40). Prior exposure to

Table 1
Summary characteristics of included studies

Characteristic	All N (%)	Critical priority pathogens				High priority pathogens	
		CRAB N (%)	CRE N (%)	CRPA N (%)	ESBL-EB N (%)	MRSA N (%)	VRE N (%)
All included studies	**357**	**34 (100)**	**79 (100)**	**20 (100)**	**133 (100)**	**32 (100)**	**59 (100)**
Study design							
Case-control	231 (64.7)	19 (55.9)	66 (83.5)	12 (60.0)	76 (57.1)	21 (65.6)	37 (62.7)
Prospective cohort	62 (17.4)	7 (20.6)	3 (3.8)	3 (15.0)	26 (19.6)	7 (21.9)	16 (27.1)
Retrospective cohort	64 (17.9)	8 (22.5)	10 (12.7)	5 (25.0)	31 (23.3)	4 (12.6)	6 (10.2)
Study country income level[a]							
High	218 (61.1)	16 (47.1)	40 (50.36)	9 (45.0)	86 (64.7)	23 (71.9)	44 (74.6)
Upper-middle	89 (24.9)	11 (32.4)	29 (36.7)	8 (40.0)	29 (21.8)	5 (15.6)	7 (11.9)
Lower-middle	47 (13.2)	7 (20.6)	10 (12.7)	3 (15.0)	16 (12.0)	3 (9.4)	8 (13.6)
Low	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (3.1)	0 (0.0)
Multiple countries with different income level	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Clinical setting							
ICU and non-ICU ward(s)	207 (58.0)	18 (52.9)	57 (72.2)	14 (70.0)	75 (56.4)	16 (50.0)	27 (45.7)
ICU only	65 (18.2)	14 (41.2)	13 (16.5)	5 (25.0)	12 (9.0)	5 (15.6)	16 (27.1)
Non-ICU ward(s) only	35 (9.8)	2 (5.9)	4 (5.1)	0 (0.0)	12 (9.0)	7 (21.9)	10 (17.0)
Mix of inpatient and outpatient services	22 (6.2)	0 (0.0)	3 (3.8)	1 (5.0)	16 (12.0)	0 (0.0)	2 (3.4)
Outpatient service(s)	18 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (9.0)	4 (12.5)	2 (3.4)
Unclear	10 (2.8)	0 (0.0)	2 (2.5)	0 (0.0)	6 (4.5)	0 (0.0)	2 (3.4)
Context of probable MDRO acquisition							
Hospital-acquired	76 (21.3)	14 (41.2)	25 (31.6)	5 (25.0)	14 (10.5)	10 (31.3)	8 (13.6)
Community-acquired	33 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)	26 (19.6)	6 (18.7)	1 (1.7)
Not reported or mixed (healthcare- and community-acquired)	248 (69.5)	20 (58.8)	54 (68.3)	15 (75.0)	93 (69.9)	16 (50.0)	50 (84.7)
Outbreak context							
Yes	20 (5.6)	3 (8.8)	2 (2.5)	0 (0.0)	1 (0.7)	1 (3.1)	13 (22.0)
No	337 (94.4)	31 (91.2)	77 (97.5)	20 (100)	132 (99.3)	31 (96.9)	46 (78.0)
Population age group							
Adults	242 (67.8)	22 (64.7)	57 (72.2)	17 (85.0)	84 (63.2)	23 (71.9)	39 (66.1)
Children	38 (10.6)	5 (14.7)	4 (5.1)	1 (5.0)	18 (13.5)	3 (9.4)	7 (11.9)
Both adults and children	52 (14.6)	4 (11.8)	13 (16.5)	1 (5.0)	22 (16.5)	4 (12.5)	8 (13.6)
Not reported	25 (7.0)	3 (8.8)	5 (6.3)	1 (5.0)	9 (6.8)	2 (6.2)	5 (8.5)
Type of cases							
Infected	191 (53.5)	18 (52.9)	50 (63.3)	15 (75.0)	88 (66.2)	11 (34.4)	9 (15.3)
Colonized	90 (25.2)	2 (5.9)	17 (21.5)	1 (5.0)	24 (18.0)	14 (43.8)	32 (54.2)
Infected or colonized	76 (21.3)	14 (41.2)	12 (15.2)	4 (20.0)	21 (15.8)	7 (21.9)	18 (30.5)
Type of controls/noncases							
Uninfected	27 (7.6)	3 (8.8)	8 (10.1)	1 (5.0)	8 (6.0)	3 (9.4)	4 (6.9)
Not colonized with MDRO	88 (24.6)	2 (5.9)	17 (21.5)	1 (5.0)	25 (18.0)	13 (40.6)	30 (50.9)
Infected with DS pathogen	158 (44.3)	12 (35.3)	36 (45.6)	15 (75.0)	82 (61.7)	7 (21.9)	6 (10.2)
Infected or colonized with DS pathogen	34 (9.5)	9 (26.5)	5 (6.3)	2 (10.0)	10 (7.5)	1 (3.1)	7 (11.9)
Other	23 (6.4)	2 (5.9)	7 (8.9)	0 (0.0)	2 (1.5)	3 (9.4)	9 (15.3)
Not reported or unclear	27 (7.6)	6 (17.6)	6 (7.6)	1 (5.0)	6 (4.5)	5 (15.6)	3 (5.1)
Timing of antibiotic exposure[b]							
Prior 14 days	31 (8.7)	7 (20.6)	5 (6.3)	5 (25.0)	8 (6.0)	3 (9.4)	3 (7.6)
Prior 30 days	68 (19.0)	9 (26.5)	16 (20.3)	3 (15.0)	32 (24.1)	2 (6.3)	6 (10.2)
Prior 2 months	13 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	9 (6.8)	1 (3.1)	3 (7.6)
Prior 3 months	69 (19.3)	0 (0.0)	19 (24.1)	5 (25.0)	34 (25.6)	2 (6.3)	9 (15.3))
Prior 6 months	23 (6.4)	1 (2.9)	8 (10.1)	0 (0.0)	9 (6.8)	3 (9.4)	2 (3.4)
Prior 12 months	13 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (7.5)	2 (6.3)	1 (1.7)
During hospital stay (no further details)	30 (8.4)	3 (8.8)	9 (11.4)	5 (25.0)	8 (6.0)	3 (9.4)	2 (3.4)
Other	10 (2.8)	0 (0.0)	3 (3.8)	0 (0.0)	1 (0.1)	4 (12.5)	2 (3.4)
Not reported or unclear	100 (28.0)	14 (41.2)	19 (24.1)	2 (10.0)	22 (16.5)	12 (37.5)	31 (52.5)

The distribution of studies across categories of key characteristics is reported. Eight of the 349 unique studies that met the inclusion criteria reported on two different pathogens, thus bringing the total number of studies contributing to the analysis to 357.
CRAB, Carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; DS, drug-susceptible; ESBL-EB, extended-spectrum beta-lactamase-producing *Enterobacterales*; ICU, intensive care unit; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus spp*.
[a] Country income levels were categorized in accordance with the World Bank classification; the year of study start was considered for the purpose of this assessment.
[b] Relative to outcome onset. If antibiotic exposure was assessed at multiple points in time (e.g. in the prior 3 months and during hospital stay), only the most inclusive and/or furthest away from the time of outcome occurrence was considered.

quinolones was most strongly associated with MRSA across all AWaRe categories (28 studies; OR = 2.2 [95% CI: 1.8–2.7]), followed by 3GC (11 studies; OR = 2.1 [95% CI: 1.8–2.5]). Prior exposure to glycopeptides had the strongest association with VRE (57 studies; OR = 2.7 [95% CI: 2.2–3.2]), followed by carbapenems (32 studies; OR = 2.6 [95% CI: 2.1–3.3]).

Most estimates from our primary analyses were reasonably robust to several MDRO-specific sensitivity analyses, and associations were similar across a range of subgroup analyses (Tables S9–S14 and Figs. S41–S49), with few exceptions. Among 23 studies reporting on Access-group penicillins and ESBL-EB (OR = 1.6; 95% CI: 1.3–2.1), those involving children likely pulled the estimate away from the null: when we restricted to studies of adult patients only, the magnitude of the association decreased to 1.3 (95% CI: 1.1–1.5). A similar association was estimated for Access-group penicillins across 12 studies on VRE (OR = 1.5 [95% CI: 1.1–2.2]), but this varied widely across subgroup analyses (Table S9, Table S10, Table S14, Fig. S47).

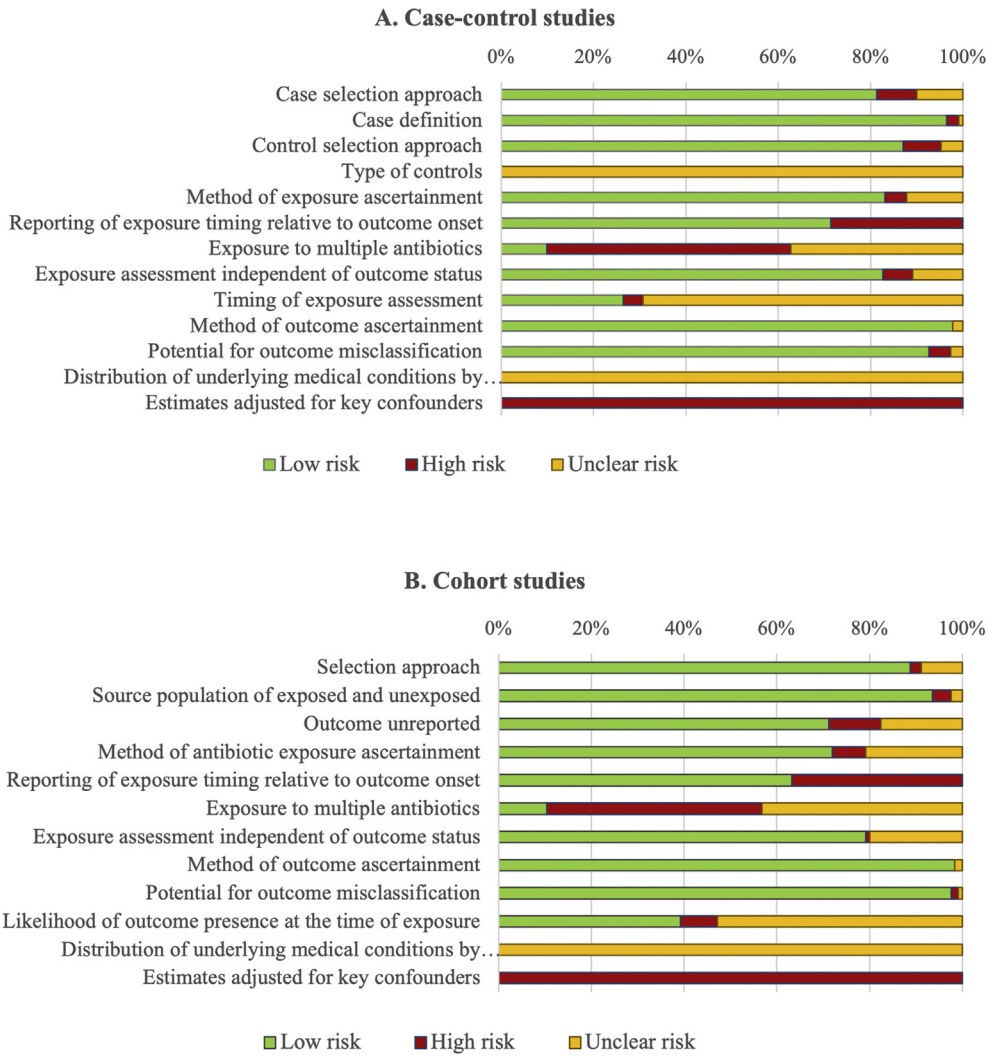


Fig. 2. Summary of risk of bias assessment for case-control studies (A) and cohort studies (B). The graphs show overall results combining studies on any critical or high priority pathogen among carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant or extended spectrum beta-lactamase-producing Enterobacterales, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* spp.

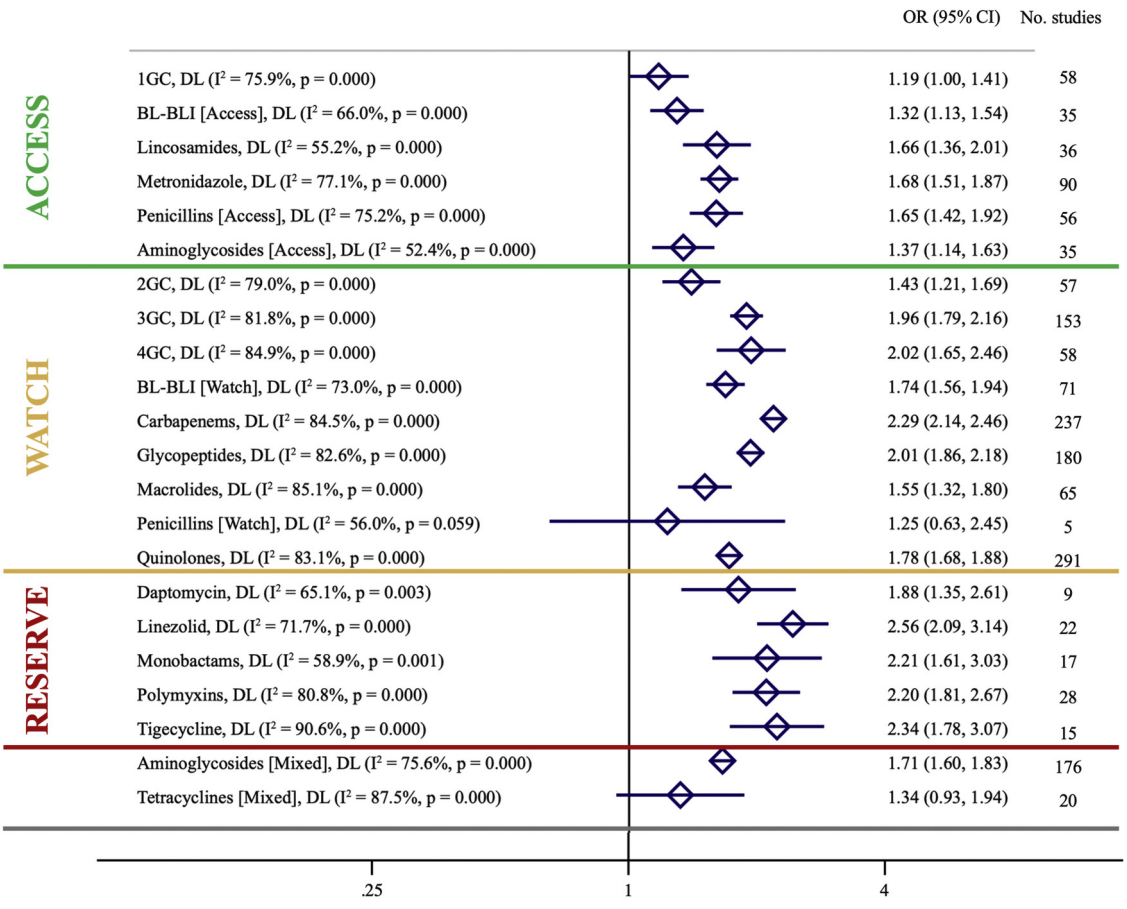
After restricting to studies focused on community-acquired ESBL-EB (Table S11), several Watch antibiotics were significantly associated with the outcome, with higher ORs for 3GC (6 studies; OR = 3.1; 95% CI: 2.2–4.4) and quinolones (25 studies; OR = 2.0; 95% CI: 1.8–2.3), whereas quinolones had the strongest association (5 studies; OR = 4.4; 95% CI: 2.3–8.2) with community-acquired MRSA. Among studies of hospital-acquired infection/colonization, carbapenems had the strongest association with CRAB (14 studies; OR = 2.0; 95% CI: 1.6–2.7) and CRE (24 studies; OR = 2.4; 95% CI: 2.1–2.6), whereas 3GC had the strongest association with ESBL-EB (9 studies; OR = 2.9; 95% CI: 2.4–3.5) (Table S12). We did not find any significant changes in estimates when restricting to studies where the case group included only patients with clinically relevant infections (Table S13).

Discussion

Our systematic review and meta-analysis found that prior use of any antibiotic examined is associated with increased likelihood of isolation of one or more MDROs. We estimated stronger associations for antibiotics belonging to Watch and Reserve groups than for Access group antibiotics, although no head-to-head comparisons were undertaken. Our findings are consistent with the hypothesis that important differences exist among antibiotics in terms of likelihood of contributing to resistance.

We observed a higher likelihood of isolation of any MDRO after exposure to a few Access-group antibiotics (metronidazole, lincosamides, and penicillins) relative to some Watch agents (2GC, macrolides). Although metronidazole exposure was significantly associated with isolation of ESBL-EB and VRE, these estimates might be inflated, as metronidazole is often given in combination with beta-lactams, quinolones, or aminoglycosides [20,21]. Similarly, we estimated a significant association between prior exposure to lincosamides (predominantly clindamycin) and isolation of ESBL-EB and VRE. Although lincosamides are often given as monotherapy, they may be combined with other antibiotics to provide anaerobic coverage [22].

We estimated that prior use of Access-group penicillins was more strongly associated with colonization/infection with any MDRO than 1GC, 2GC, and macrolides. However, on examining individual MDROs, exposure to this antibiotic class was consistently associated only with MRSA colonization/infection. Estimated associations between Access-group penicillins and isolation of either ESBL-EB or VRE must be taken with great caution owing to the



1GC, First generation cephalosporins; 2GC, Second generation cephalosporins; 3GC, Third generation cephalosporins; 4GC, Fourth generation cephalosporins; BL-BLI, Beta-lactam + beta-lactamase inhibitor; CI, Confidence interval; DL, DerSimonian-Laird; OR, Odds ratio; TMP-SMX, Trimethoprim-Sulfamethoxazole.

Fig. 3. Associations between exposure to select antibiotic classes (by AWaRe category) and colonization and/or infection with a drug-resistant pathogen. Pooled odds ratios (ORs), 95% confidence intervals (CIs), and I-squared (I^2) statistics were estimated through random-effects meta-analysis of studies that focused on a critical or high priority pathogen among carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant or extended spectrum beta-lactamase-producing Enterobacterales, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* spp. Lack of association corresponds to an odds ratio of 1. Pooled estimates were only calculated and reported if at least five studies were available.

impact of neonatal/pediatric studies where penicillins were likely combined with aminoglycosides as recommended by the WHO, particularly for sepsis treatment [23]. When we restricted the analysis to studies of adults, overall ORs decreased substantially or even became nonsignificant for VRE.

Although 2GC and macrolides were less strongly associated with isolation of any MDROs relative to some Access-group antibiotics/antibiotic classes, we found substantial heterogeneity across pathogens. These agents were more strongly associated with colonization/infection with ESBL-EB and MRSA, and macrolides (but not 2GC) were also significantly associated with VRE.

Our findings suggest that Access-group aminoglycosides may pose a lower risk for any MDRO selection, with consistent results across pathogens. However, when we examined prior exposure to aminoglycosides without differentiation by AWaRe category, we found significant associations across MDROs, suggesting caution in the interpretation of estimates.

Access-group antibiotics (1GC, BL-BLIs, specific aminoglycosides, TMP-SMX, and certain penicillins) are generally less likely to be strongly associated with any MDRO as opposed to antibiotics from Watch and Reserve groups. Hence, these findings corroborate the current classification of most antibiotics into existing AWaRe categories, with the possible exception of metronidazole and lincosamides, and consideration could be given to their future categorisation. Given the inconclusive findings with respect to amikacin and gentamicin (both Access), there is no evidence to support a recategorization of these agents within the AWaRe framework.

Our findings suggest that a more restricted utilization of Watch-group agents might be greatly beneficial. Carbapenem use was found to be strongly associated with hospital-acquired CRAB and CRE. Similar associations between 3GC use and both hospital- and community-acquired ESBL-EB were noted. Quinolones, which are widely used in clinical practice at all levels of care, were also significantly associated with community-acquired colonization or infection with MRSA and ESBL-EB. Finally, all antibiotics irrespective of AWaRe category were associated with MDRO selection, indicating the need to enhance focus on symptomatic care for minor infections with no routine antibiotic treatment. These observations are consistent with the new WHO Essential Medicines List AWaRE Antibiotic book recommendations where nine of the ten most common infections in outpatient settings can be either treated with no or Access antibiotics [24].

Our study has important limitations. Estimates are all crude as no adjustments could be made for key individual-level confounders. In addition to antibiotic exposure, several factors are

Table 2
Associations between exposure to different antibiotic classes and colonization or infection with a Gram-negative critical priority pathogen

Antibiotic	Colonization or infection with a critical priority pathogen											
	CRAB			CRE			CRPA			ESBL-EB		
	N	Or (95% CI)	I^2	N	Or (95% CI)	I^2	N	Or (95% CI)	I^2	N	Or (95% CI)	I^2
Access-group												
First generation cephalosporins	7	0.5 (0.3–1.0)	76.4	4	Not estimated	NA	2	Not estimated	NA	25	1.3 (1.1–1.5)	45.4
Aminoglycosides	6	1.1 (0.6–1.7)	40.8	3	Not estimated	NA	4	Not estimated	NA	7	2.0 (1.0–3.9)	73.3
BL-BLI [Access]	8	1.1 (0.8–1.5)	53.6	7	1.7 (1.1–2.7)	21.1	2	Not estimated	NA	15	1.4 (1.0–1.9)	76.7
Lincosamides	2	Not estimated	NA	5	2.4 (1.2–4.6)	17.7	1	Not estimated	NA	9	1.8 (1.3–2.6)	44.3
Metronidazole	5	1.2 (1.1–1.4)	0.0	26	1.4 (1.1–1.7)	78.9	3	Not estimated	NA	21	2.1 (1.8–2.5)	66.0
Penicillins [Access]	5	2.1 (0.8–5.7)	82.4	4	Not estimated	NA	2	Not estimated	NA	23	1.6 (1.3–2.1)	82.7
TMP-SMX	2	Not estimated	NA	7	1.6 (1.0–2.7)	45.0	3	Not estimated	NA	43	1.5 (1.4–1.8)	71.0
Watch-group												
Second-generation cephalosporins	8	1.0 (0.6–1.6)	79.6	10	0.9 (0.7–1.2)	8.4	1	Not estimated	NA	26	1.8 (1.4–2.3)	78.9
Third-generation cephalosporins	18	1.3 (1.1–1.5)	71.5	24	1.4 (1.0–2.0)	78.5	6	1.2 (0.8–1.6)	77.5	63	2.5 (2.2–2.9)	75.9
Fourth-generation cephalosporins	9	2.0 (1.1–3.5)	89.6	11	1.9 (1.0–3.4)	79.6	6	1.7 (1.5–2.0)	0.0	17	2.4 (1.6–3.8)	90.1
BL-BLI [Watch]	11	1.3 (1.1–1.5)	39.6	18	1.5 (1.3–1.8)	23.9	6	1.4 (1.1–1.8)	43.8	16	1.9 (1.4–2.5)	85.8
Carbapenems	34	2.2 (1.8–2.6)	89.6	74	2.5 (2.2–2.7)	73.7	19	3.2 (2.5–4.2)	91.8	65	1.8 (1.6–2.1)	73.5
Glycopeptides	19	1.5 (1.2–1.9)	84.7	44	1.9 (1.7–2.2)	74.9	7	1.7 (1.2–2.4)	78.0	37	1.9 (1.7–2.2)	75.8
Macrolides	2	Not estimated	NA	12	1.6 (1.3–2.0)	59.9	0	NA	NA	24	1.5 (1.3–1.8)	53.3
Quinolones	27	1.4 (1.2–1.6)	81.7	67	1.5 (1.4–1.7)	73.9	17	1.9 (1.6–2.3)	71.1	109	1.9 (1.7–2.0)	75.4
Reserve-group												
Daptomycin	0	NA	NA	5	1.8 (1.2–2.9)	75.1	0	NA	NA	4	Not estimated	NA
Linezolid	1	Not estimated	NA	11	2.1 (1.8–2.4)	19.9	1	Not estimated	NA	3	Not estimated	NA
Monobactams	0	NA	NA	4	Not estimated	NA	0	NA	NA	8	2.9 (1.7–5.0)	75.4
Polymyxins	4	Not estimated	NA	14	2.4 (2.0–2.9)	60.1	2	Not estimated	NA	4	Not estimated	NA
Tigecycline	2	Not estimated	NA	8	2.4 (1.8–3.3)	81.7	2	Not estimated	NA	0	NA	NA
Mix of Access and Watch (with Access-group agents largely predominant)												
Aminoglycosides (not differentiated)	23	1.3 (1.1–1.4)	51.6	45	1.6 (1.4–1.9)	76.5	8	1.7 (1.3–2.2)	40.1	66	2.0 (1.8–2.2)	72.7
Tetracyclines (not differentiated)	1	Not estimated	NA	5	1.3 (0.9–1.7)	0.0	0	NA	NA	9	1.7 (0.9–3.0)	92.9

Studies reporting on carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), or extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* (EB) were considered. Pooled odds ratios (ORs), 95% confidence intervals (CIs) and I-squared (I^2) were estimated through random-effects meta-analysis of case-control and cohort studies. Pooled estimates were only calculated and reported if at least five studies were available.

ATC, Anatomic, Therapeutic, Chemical (classification system); BL-BLI, beta-lactam–beta-lactamase inhibitor; CI, confidence interval; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant*Enterobacterales*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-EB, extended-spectrum beta-lactamase-producing *Enterobacterales*; NA, not applicable; OR, odds ratio; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 3
Association between exposure to different antibiotic classes and colonization or infection with either methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant Enterococcus spp

Antibiotic	Colonization or infection with a high priority pathogen					
	MRSA			VRE		
	N	Or (95% CI)	I^2	N	Or (95% CI)	I^2
Access-group						
First generation cephalosporins	10	1.2 (0.9 –1.5)	63.0	10	1.7 (0.6–4.5)	92.1
Aminoglycosides	5	1.4 (1.1–1.7)	0.0	10	1.5 (1.1–2.1)	33.4
BL-BLI [Access]	5	1.2 (0.8–1.7)	25.7	6	1.4 (0.8–2.2)	66.9
Lincosamides	7	1.6 (0.9–2.7)	77.8	12	1.8 (1.2–2.5)	42.9
Metronidazole	7	1.4 (1.0–1.9)	73.2	28	2.0 (1.5–2.7)	75.5
Penicillins [Access]	10	1.9 (1.6–2.2)	11.0	12	1.5 (1.1–2.2)	61.5
TMP-SMX	8	1.3 (0.8–2.0)	81.7	9	1.0 (0.8–1.3)	0.0
Watch-group						
Second generation cephalosporins	5	1.9 (1.7–2.2)	0.0	7	1.1 (0.4–3.1)	88.2
Third generation cephalosporins	11	2.1 (1.8–2.5)	44.7	31	2.2 (1.8–2.8)	73.5
Fourth generation cephalosporins	6	1.9 (1.5–2.3)	0.0	9	1.9 (1.3–2.7)	50.9
BL-BLI [Watch]	4	Not estimated	NA	16	2.4 (1.8–3.3)	56.4
Carbapenems	13	2.1 (1.5–2.8)	85.3	32	2.6 (2.1–3.3)	70.8
Glycopeptides	16	1.7 (1.4–2.2)	84.2	57	2.7 (2.2–3.2)	79.7
Macrolides	17	1.8 (1.2–2.6)	94.7	10	1.6 (1.1–2.4)	60.3
Quinolones	28	2.2 (1.8–2.7)	92.2	43	2.0 (1.7–2.4)	81.4
Reserve-group						
Linezolid	0	NA	NA	6	3.5 (2.0–6.1)	11.2
Monobactams	0	NA	NA	5	1.2 (0.7–2.3)	0.0
Mix of Access and Watch (with Access-group agents largely predominant)						
Aminoglycosides (not differentiated)	12	1.6 (1.2–2.0)	84.8	22	2.0 (1.6–2.5)	75.6

Pooled odds ratios (ORs), 95% confidence intervals (CIs), and I-squared (I^2) statistics were estimated through random-effects meta-analysis of case-control and cohort studies. Pooled estimates were only calculated and reported if at least five studies were available.

BL-BLI, Beta-lactam–beta-lactamase inhibitor; CI, confidence interval; Gen, gentamicin; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; OR, odds ratio; TMP-SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant *Enterococcus* spp.

associated with MDRO colonization/infection such as colonization pressure [25,26], adherence to infection prevention activities [27], horizontal gene transfer of plasmids [28], or combinations of these factors [29], none of which could be accounted for in our analyses. A proportion of patients across studies was likely exposed to more than one antibiotic during the observation period, thus potentially affecting the estimates in either direction [21]. The timing, duration, dose, and route of antibiotic exposure relative to the detection of the outcome was prone to significant variability. It is therefore difficult to comment on the nature of the relationship between exposure and outcome, and confounding by indication remains a concern despite the large effect sizes we found. All included studies were observational and were not primarily designed to compare risks of MDRO isolation across AWaRe categories. A moderate to high heterogeneity between studies was also observed. Nonetheless, most estimates were consistent across sensitivity analyses. Lastly, publication bias is a concern: we found several studies that only reported data on select antibiotics that were deemed to be of particular interest, such as quinolones and 3GC.

Our findings provide a strong rationale for enhancing the use of AWaRe as a tool to improve the quality of antibiotic prescribing globally. This is particularly relevant as the consumption of Watch antibiotics increased by 165% in low- and middle-income countries between 2000 and 2015 [30]. Optimizing antibiotic use is key not only to manage the selection and spread of antibiotic resistance but also to reduce the risk of potential toxicities and improve clinical outcomes [31,32]. Access antibiotics should be considered as first-line treatment option whenever possible, in order to limit the utilization of Watch and Reserve antibiotics to situations where they are clearly indicated.

Transparency declaration

We declare no competing interests. This review was funded by grants provided by the Governments of the United Kingdom, using UK aid funding through the Fleming Fund, and by the Ministry of Health of Germany, which had no role in data collection, analysis, or interpretation of data. The WHO Department of Health Product Policy and Standards was the recipient of these grants and coordinated the development of this systematic review through contract to Washington University in St. Louis, MO, USA. Contract PO#202553141. The corresponding author had access to all data and had final responsibility for the decision to submit for publication. Raw data from studies included in this review are partly available in supplementary data files. Additional data, such as the list of studies excluded after full-text screening, can be made available upon request.

Author contributions

G.S., S.S., and S.G. developed the review protocol with critical input from C.P., S.H., D.M., M.S., L.M., and B.H. L.H.Y. designed the search strategy in consultation with G.S., S.S., and S.G.. Title/abstract screening was conducted by two independent reviewers among G.S., S.S., S.K., N.B., I.G., M.A.C., E.T., S.Y., and S.G.. Full-text review of studies selected by title and abstract was conducted by G.S., S.S., S.K., N.B., I.G., M.A.C., E.T., and S.G. G.S. and S.G. made final decisions with respect to study inclusion or exclusion. G.S., S.S., N.B., I.G., and S.G. performed data extraction and risk of bias assessment of included studies. G.S. carried out all analyses. G.S. and S.G. prepared the first draft of the manuscript that was revised by all authors until finalization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.03.014.

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