Antimicrobial Resistance & Infection Control

REVIEW

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Usefulness of dynamic regression time series models for studying the relationship between antimicrobial consumption and bacterial antimicrobial resistance in hospitals: a systematic review

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Abstract

Backgroung Antimicrobial resistance (AMR) is on the rise worldwide. Tools such as dynamic regression (DR) models can correlate antimicrobial consumption (AMC) with AMR and predict future trends to help implement antimicrobial stewardship programs (ASPs).

Main body We carried out a systematic review of the literature up to 2023/05/31, searching in PubMed, ScienceDirect and Web of Science. We screened 641 articles and finally included 28 studies using a DR model to study the correlation between AMC and AMR at a hospital scale, published in English or French. Country, bacterial species, type of sampling, antimicrobials, study duration and correlations between AMC and AMR were collected. The use of β-lactams was correlated with cephalosporin resistance, especially in *Pseudomonas aeruginosa* and Enterobacterales. Carbapenem consumption was correlated with carbapenem resistance, particularly in *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii.* Fluoroquinolone use was correlated with fluoroquinolone resistance in Gram-negative bacilli and methicillin resistance in *Staphylococcus aureus*. Multivariate DR models highlited that AMC explained from 19 to 96% of AMR variation, with a lag time between AMC and AMR variation of 2 to 4 months. Few studies have investigated the predictive capacity of DR models, which appear to be limited.

Conclusion Despite their statistical robustness, DR models are not widely used. They confirmed the important role of fluoroquinolones, cephalosporins and carbapenems in the emergence of AMR. However, further studies are needed to assess their predictive capacity and usefulness for ASPs.

Keywords Antimicrobial, Dynamic regression, Healthcare-associated infections, Resistance, Time series analysis

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Background

Antimicrobial resistance (AMR) is increasing worldwide [1, 2] and by 2050, 10 million deaths per year could be related to infections caused by multidrug-resistant (MDR) bacteria, surpassing cancers [3]. Given the close link between antimicrobial consumption (AMC) and AMR, the World Health Organization (WHO) has encouraged antimicrobial stewardship programs (ASPs) and AMR surveillance in response to this alarming situation [4–6].

Observational or quasi-experimental studies using time series models are recognized as the gold standard for estimating the correlation between AMC and AMR [7–9]. Among these models, dynamic regression (DR) models, originally used in economics to study stock market fluctuations, are probably one of the best options for studying correlations between AMC and AMR [10].

Combining the advantages of Box and Jenkins' autoregressive integrated moving average (ARIMA) [11] and Pankratz's linear transfer function (LTF) [12], DR models can take into account the time lag between antimicrobial use and the emergence of AMR, as well as the prior prevalence of AMR, to best estimate the correlation between AMR and AMC. In addition, multivariate DR models can assess the effect of the use of different antimicrobials on AMR, and the burden of their use in relation to other mechanisms involved in the emergence of AMR [13].

Finally, DR models could be used to evaluate existing ASPs and to develop new ones, targeting the consumption of antibiotics that are more closely linked to the emergence of AMR [14]. However, their predictive capacity is the subject of debate and could limit their use to retrospective analyses only [15]. Indeed, external validation of DR models has been performed in few studies [15], in which they seems to be much better at describing the link between prior AMC and AMR, rather than predicting the emergence of resistance on the basis of presumed AMC.

In the last decade, numerous studies have been published, and it is not easy for readers to have an overview of these results, which can nevertheless influence our practice and the choice of antimicrobial therapy, particularly in hospital setting.

This systematic review aims to summarize the correlations between AMC and AMR reported in studies using DR models, and to explore the predictive ability of these models for use in the assessment and construction of ASPs.

Main text

Methods

Search strategy

The methodology of this literature review followed the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [16]. The study was registered on PROSPERO (CRD42022324469), the international prospective register of systematic reviews. Articles included in this systematic review were obtained from three databases of peer-reviewed literature: PubMed (NLM database), ScienceDirect and Web of Science. PubMed and Web of Science databases were searched using the following terms: ("antibiotic resistance" OR "antimicrobial resistance") AND ("antibiotic consumption" OR "antimicrobial consumption" OR "antibiotic use" OR "antimicrobial use" OR "stewardship program" OR "intervention") AND ("time series analysis" OR "times-series" OR "dynamic regression" OR "autoregressive integrated moving average" OR "ARIMA" OR "linear transfer function" OR "LTF"). ScienceDirect database was searched using the following terms: ("antibiotic" OR "antimicrobial) AND ("resistance") AND ("consumption" OR "utilization" OR "use") AND ("dynamic regression" OR "autoregressive integrated moving average" OR "ARIMA"). Database was searched from 2000 to 2023 ("2000/01/01" (date—publication): "2023/05/31" (date—publication)). Finally, we searched in the reference lists of selected articles to find additional studies.

Inclusion/exclusion criteria

All studies that used DR (or analogous) models and examined the in-hospital correlation between AMC and AMR rates or incidences, regardless of bacterial species, were eligible for inclusion. DR models are identified with different terminology [17], thus a statistician familiar with DR models (F.S.) checked all the models. DR models can be either univariate studying each antimicrobial separately, or multivariate studying several antimicrobials simultaneously. Community-based studies or those assessing both the hospital and community setting were not eligible for inclusion. Studies using other time series models (such as interrupted time series) were not included. Articles were limited to the English or French language. Reviews and animal studies were excluded. Meta-analyses with heterogeneous studies (different bacteria, different antimicrobials), were also ruled out.

Study selection

Two independent reviewers (P.L.-L. and A.S.) blindly screened potentially eligible abstracts. Then, full-text articles were assessed by two reviewers (P.L.-L. and F.S.). Whenever a discrepancy between reviewers arose after full-text reading, study's eligibility was discussed with another reviewer (A.S.) until a consensus was achieved.

Data collection

Author names, year of publication, study period and duration, study location, microorganisms, sample types,

antimicrobial treatments and study duration were collected from each report. When calculated, the coefficient of determination (R^2), which represented the percentage of variations in AMR explained by the DR as a function of AMC, was recorded. The authors of studies were contacted in case of missing or incomplete data. We did not carry out a meta-analysis due to the heterogeneity of the studies examined (different bacteria and different antibiotics analyzed), which would have led to inconclusive results.

Quality of studies

Conventional tools for assessing the risk of bias in non-randomized studies (EPOC, ROBINS, ORION reports…) were not suitable to assess the quality of quasi-experimental epidemiological time-series studies. Thus, after consultation with our team of methodologists and research of relevant existing tools, we created a specific checklist (Table S1) adapted from those of the Quebec university Hospital [18], the Newcastle-Ottawa Scale [19] and the STROBE checklist [20]. The quality of the studies was independently assessed by two reviewers (P.L.-L. and F.S.). Discrepancies were resolved by discussion with another reviewer (A.S.) to reach a consensus.

Results

Search results

The database search yielded 641 articles and seven additional records were identified from reference lists. Of these, 566 were excluded after abstract screening and 37 were excluded after full-text review. A further 17 articles were excluded after analysis for statistical issues (including 11 studies using ARIMA model and cross-correlation analysis without DR, and one study in which DR use was not confirmed despite attempts to contact the authors). Finally, 28 studies [8, 13–15, 21–44] met the inclusion criteria (Table 1; Fig. 1).

Studies characteristics

The characteristics of the studies are summarized in Table 1.

The 28 included articles [8, 13–15, 21–44] were published from 2000 to 2023. The studies were mainly conducted in hospitals in the United Kingdom (5/28) [21, 23, 25, 34, 35], France (5/28) [13, 15, 22, 26, 42], Germany (4/28) [14, 28, 29, 33], China (3/28) [38, 43, 44] and Greece (3/28) [30, 31, 39]. Most articles studied the correlation between AMC and AMR month by month, with a median follow-up ranging from 15 to 174 months [24, 29].

Twenty-six studies [8, 14, 15, 21–38, 40–44] included all the bacteriological samples available, while one [13] focused on urine analyses and one [39] on blood cultures. When different samples from the same patient were positive for the same microorganism, samples were deduplicated in most studies (23/28) [8, 13–15, 21–23, 26–32, 34, 36–38, 40–44]. Studies most frequently focused on *Staphylococcus aureus* (9/28) [21–23, 29, 32, 34, 35, 41, 44], *Pseudomonas aeruginosa* (7/28) [8, 14, 24, 26, 27, 33, 40], *Klebsiella* sp. (7/28) [8, 25, 28, 38–40, 43] and *Escherichia coli* (6/28) [8, 15, 27, 28, 40] and on the resistance to cephalosporin, methicillin, carbapenem and fluoroquinolone. Only three studies focused on the emergence of MDR bacteria [14, 24, 26]. Only seven of the 28 studies focusing on hospital-acquired infections or colonization were restricted to samples taken after 48 h of hospital stay according to the definition of nosocomial infections [15, 21–23, 28, 29, 42].

Comprehensive monitoring of AMC was carried out in 12 of the 28 included studies [21–23, 28, 29, 32, 34, 35, 37, 41, 42, 44], while some studies specifically analyzed the effect of antimicrobial classes on the emergence of AMR: carbapenems (12/28) [8, 14, 15, 24, 26, 30, 31, 33, 36, 38, 40, 43], cephalosporins (12/28) [15, 26, 27, 30, 31, 33, 38, 40], fluoroquinolones (10/28) [13–15, 24, 26, 30, 31, 33, 36, 43] and piperacillin-tazobactam (8/28) [14, 15, 24, 30, 31, 33, 36, 43]. All studies reported at least one statistically significant correlation between antimicrobial use and AMR (Table 1).

Correlation between antimicrobial consumption and resistance

The use of β-lactams was frequently reported to be correlated with the emergence of cephalosporin resistance. With a 0 to 5 months lag time, these correlations were reported for Enterobacterales and *P. aeruginosa* in seven and four studies, respectively and were mainly caused by extended-spectrum β-lactamases (ESBLs) and/or AmpC β-lactamases [8, 15, 24, 27, 28, 33, 36, 40, 42]. Overall, multivariate DR models including β-lactams and fluoroquinolones consumption explained 15–86% of variation in cephalosporin resistance [8, 15, 28, 36].

Three studies [15, 28, 42] reported specifically a correlation between fluoroquinolone consumption and cephalosporin resistance. The use of fluoroquinolones was also correlated with emergence of resistance to fluoroquinolone in Gram-negative bacteria with 0 to 5 months of lag time in six publications [13, 15, 24, 30, 42, 43]. In this case, DR model explained 40–66% of fluoroquinolone resistance variation [13, 15, 30, 43]. Fluoroquinolones use was also reported to be correlated with the emergence of methicillin resistant *S. aureus* (MRSA) in seven papers with a lag time of 2 to 4 months [21–23, 29, 34, 35, 41]. MRSA emergence was correlated with the use of macrolides in six articles, with a lag time ranging from 1 to 5 months. Multivariate DR model, including fluoroquinolone, macrolide and cephalosporin consumption,

Table 1 Characteristics of the studies assessing the correlation between the antimicrobial consumption and bacterial antimicrobial resistance using dynamic regression models

Reference	Country	Duration	Bacteria species studied	Antimicrobial studied	Sample type	AMR / AMC correlated (lag)	R^2 of the model
Aldeyab 2008	UK	60 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples from patients in the unit for > 48 hours, with deduplication + nasopharyngeal screening samples	MRSA / Macrolides (4 months), Fluoroquinolones (1 month)[1], 3rd generation cephalosporins (2 months) and Amoxicillin – Clavulanic Acid (1 month)	78% [2]
Bertrand 2012	France	108 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples from patients in the unit for > 48h or positive in the previous 12 months with deduplication	MRSA / Macrolides (2 months), Fluoroquinolones (2 months), Aminoglycoside (1 month)	41%[2]
Conlon-birgham 2019	UK	72 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples from patients in the unit for > 48 hours, with deduplication of following 7 days samples + nasopharyngeal screening samples	MRSA / Macrolides (1 month), Fluoroquinolones (3 months) and Piperacillin-Tazobactam (1 month)	UC
Erdeljić 2011	Croatia	15 months	*Pseudomonas aeruginosa*	Piperacillin-Tazobactam, Ciprofloxacin and Carbapenems	All types of samples	Resistance to Ciprofloxacin / Ciprofloxacin (1month) Resistance to Meropenem / Meropenem (0 months) Resistance to Cefepime / Cefepime (2 months) *P.aeruginosa* MDR / Meropenem (0 months)	UC
Gharbi 2015	UK	72 months	*Klebsiella pneumoniae*	Meropenem	All types of samples + rectal screening sample	*K. pneumoniae* OXA-48 / Meropenem (1 year)	79%
Hocquet 2008	France	84 months	*Pseudomonas aeruginosa*	Aminoglycosides, Fluoroquinolones, Cephalosporins, Penicillins, Carbapenems	All types of samples with deduplication	*P. aeruginosa* displaying MexXY-OprM overproduction / aminoglycoside (0,3,4,6 months) fluoroquinolone (0,5 and 6 months) and antipseudomonal cephalosporin (2 months) *P. aeruginosa* displaying MexXY-OprM overproduction (negative correlation) / non-antipseudomonal cephalosporin (0,2 and months), penicillin (0,1,3 and 5 months) and carbapenem (0,2,5 and 6 months)	81%
Hsueh 2005	Taiwan	13 years	*Escherichia coli* *Pseudomonas aeruginosa*	Cefotaxime, ceftazidime	All types of samples with deduplication in the following 7 days	Cefotaxime resistant *E.coli* / cefotaxime (NS) Ceftazidime resistant *P.aeruginosa* / Ceftazidime (NS)	UC

Table 1 (continued)

Reference	Country	Duration	Bacteria species studied	Antimicrobial studied	Sample type	AMR / AMC correlated (lag)	R^2 of the model
Kaier 2009	Germany	34 months	*Escherichia coli, Enterobacter Cloacae, Klebsiella sp. Acinetobacter sp., Citrobacter sp.*	All classes of antimicrobials	All types of samples from patients in the unit for > 48 hours, with deduplication + rectal screening sample	ESBL / 3rd generation Cephalosporins (3 months), Fluoroquinolones (1 month)	75%[2]
Kaier 2009	Germany	58 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples from patients in the unit for > 48 hours, with deduplication	MRSA /2nd generation Cephalosporins (1 month), 3rd generation Cephalosporins (3–4 months), Fluoroquinolones (4 month), Lincosamides (2 months)	66%[2]
Kousovista 2021	Greece	48 months	*Acinetobacter baumannii*	Cephalosporins, Fluoroquinolones, Meropenem, Colistin and Piperacillin-Tazobactam	All types of samples with deduplication	Resistance to Meropenem / Meropenem (2 month), Resistance to Ciprofloxacin / Ciprofloxacin (1 month), Resistance to Cefepime / Cefepime (2 months)	63% 66% 62%
Kritsotakis 2008	Greece	84 months	*Enterococcus sp.*	Amoxicillin-Clavulanic acid, Piperacillin-Tazobactam, Cephalosporins, Fluoroquinolones, Carbapenems, Glycopeptides, Metronidazole, Clindamycin	All types of samples with deduplication + rectal screening sample	ERV / glycopeptides (1 month), 3rd generation Cephalosporins (1 month), Fluoroquinolones (2 months) ERV (negative correlation) / Amoxicillin- Clavulanic Acid (6 months)	56%
Laffont-Lozes 2023	France	72 months	*Escherichia coli*	Penicillins, Amoxicillin-Clavulanic Acid, Piperacillin-Tazobactam, Cephalosporins, Fluoroquinolones, Carbapenems, Aminoglycosides, Sulfonamides	All types of samples from patients in the unit for > 48h or positive in the previous 1 months with deduplication	Resistance to Fluoroquinolones / Fluoroquinolones (0 to 5 months), Piperacillin-Tazobactam (0 to 3 months) Amoxicillin-Clavulanic Acid resistance / Amoxicillin-Clavulanic Acid (0 to 1 months) Penicillins resistance / 3rd generation Cephalosporins (5 and 8 months), Amoxicillin-Clavulanic Acid (0 and 5 months), Carbapenem (0 month) Cephalosporins resistance / 4rd generation Cephalosporins (0 month), Piperacillin-Tazobactam (0 to 2 months), Fluoroquinolones (0 to 4 months)	54% 53% 36% 15%
Lee 2012	Taiwan	84 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples with deduplication	MRSA / penicillins, including b-lactamase inhibitors (1 month)	26%[2]
Lepper 2002	Germany	48 months	*Pseudomonas aeruginosa*	Imipenem, Cephalosporins, Aminoglycosides, Ciprofloxacin, Piperacillin-Tazobactam	All types of samples	Resistance to Ceftazidime / Imipenem (0 and 1 month) Resistance to Piperacillin-tazobactam / Imipenem (0 and 1 month), Resistance to imipenem / Imipenem (0 and 1 month)	UC
López-Lozano 2000	Spain	90 months	*Pseudomonas aeruginosa, Escherichia coli, Proteus sp., Klebsiella sp., Enterobacter sp.*	Ceftazidime and Imipenem	All types of samples with deduplication	Gram-negative bacilli Resistant to 3rd generation Cephalosporins / Ceftazidime (1 month) *Pseudomonas aeruginosa* resistant to Imipenem / Imipenem (1 month)	44% 63%

Table 1 (continued)

Reference	Country	Duration	Bacteria species studied	Antimicrobial studied	Sample type	AMR / AMC correlated (lag)	R^2 of the model
Mahamat 2005	France	84 months	*Escherichia coli*	Fluoroquinolones	Cytobacteriological urine examination with deduplication	Resistance to Ofloxacin / Ofloxacin (4 months), Ciprofloxacin (4 months) Resistance to Ciprofloxacin / Ciprofloxacin (4 months), Ofloxacin (4 months)	64% 40%
Mahamat 2007	UK	96 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples with deduplication	MRSA / Macrolides (5 months), Fluoroquinolones (2 months)	UC
Monnet 2004	UK	55 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples except for nasopharyngeal screening samples	MRSA / 3rd generation Cephalosporins (4–7 months), Macrolides (1–3 months), Fluoroquinolones (4–5 months)	90%
O'Riordan 2022	Ireland	16 quarters	Enterobacterales and *Enterococcus faecium*	ceftriaxone, ciprofloxacin, levofloxacin, ertapenem, meropenem, piperacillin-tazobactam, gentamicin, co-trimoxazole and aztreonam; vancomycin	All types of samples with deduplication	*E.coli* 3rd generation Cephalosporins resistant (negative correlation) / Piperacillin-tazobactam (0 and 1 quarter)	86%
Ortiz-Brizuela 2020	Mexico	66 months	Enterobacterales	All classes of antimicrobials	All types of samples with deduplication	Resistance to Carbapenem non-susceptible Enterobacterales / Piperacillin- Tazobactam (6 months) Resistance to carbapenemase-producing Enterobacteriaceae/ Piperacillin- Tazobactam (6 months) Resistance to OXA-232 carbapenemase-producing Enterobacteriaceae / Piperacillin- Tazobactam (6 months)	21% 19% 24%
Qu 2019	China	60 months	*Klebsiella pneumoniae*	Doxycycline, Cephalosporins, Carbapenems	All types of samples with deduplication	Resistance to Carbapenems / Cephalosporins (0 and 1 quarter), Meropenem (0 and 1 quarter), Doxycyclin (2 quarters)	46–94% (according to antibiotic studied)
Tansarli 2018	Greece	174 months	*Klebsiella pneumoniae*	Colistin	Blood culture	Resistance to Colistin / Colistin (1 quarter)	69%
Tóth 2019	Hungary	142 months	*Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Acinetobacter baumannii*	Cephalosporins, Carbapenems, Colistin	All types of samples, with deduplication during the following month	*E.coli*: Resistance to Cephalosporins / Cephalosporins (1 month and 4 months) *Klebsiella pneumoniae*: Resistance to Cephalosporins/Cephalosporins (4 months and 5 months) Resistance to Carbapenems/Carbapenems (6 months) *Pseudomonas aeruginosa*: Resistance to Cephalosporins/Cephalosporins (0 months) Resistance to Carbapenems/Carbapenems (0 months and 1 month) *Acinetobacter baumannii*: Resistance to Carbapenems/Carbapenems (4 months)	UC
Vernaz 2008	Switzerland	80 months	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples with deduplication	MRSA / Fluoroquinolones (1 month), Macrolides (1 and 4 month), Cephalosporins (3 to 5 month), Piperacillin-Tazobactam (3 month)	57%[2]

Table 1 (continued)

Reference	Country	Duration	Bacteria species studied	Antimicrobial studied	Sample type	AMR / AMC correlated (lag)	R^2 of the model
Vibet 2015	France	84 months	Enterobacterales	All classes of antimicrobials	All types of samples from patients in the unit for > 48 hours, with deduplication	ESBL / 3rd and 4th-generation cephalosporins (5 months), Fluoroquinolones (3 months), Lincosamides (1 months), other antibacterial agents (4 months), Tetracyclines (3 months) ESBL (negative correlation) / Nitrofurantoin (1month), Ticarcillin and piperacillin with or without enzyme inhibitor (4 month)	UC
Wang 2021	China	90 months	*Klebsiella pneumoniae*	Penicillins, Penicillins + β-lactamases inhibitor, Cephalosporins, Carbapenems, Aminoglycosides, Fluoroquinolones, Sulfonamides	All types of samples with deduplication	Resistance to Amikacin / Amikacin (0 months) Resistance to Ciprofloxacin / Ciprofloxacin (0 months)	45% 62%
Willmann 2013	Germany	120 months	*Pseudomonas aeruginosa*	Carbapenems, Cephalosporins, Aminoglycosides, Fluoroquinolones and Piperacillin-Tazobactam	All types of samples with deduplication	*Pseudomonas aeruginosa* resistant to one or two antimicrobials classes / Cephalosporins (0 months) *Pseudomonas aeruginosa* resistant to 3 or 4 antimicrobials classes / Meropenem (1 month)	UC
Zhang 2018	China	28 quarters	*Staphylococcus aureus*	All classes of antimicrobials	All types of samples with deduplication	MRSA / Monobactam (2 quarters), Imidazole (1 quarter), sulfonamides (1 quarter) MRSA (negative correlation) / Glycopeptides (0 quarter), Oxazolidinone (2 quarters) aminoglycosides (2 quarters)	UC

Correlation between MRSA emergence and macrolide use 4 months previously, correlation between MRSA emergence and fluoroquinolone use 1 month previously

[2] Multivariate model also including infection control practices such as consumption of hydroalcoholic solution and/or promotion of hand hygiene and/or screening for the carriage of multi-resistant bacteria

UK: United kingdom, MRSA: Methicillin-resistant Staphylococcus aureus, UC: Uncalculated, MDR: Multidrug resistant, NS: not studied, ESBL: Extended spectrum beta-lactamase, ERV: vancomycin-resistant Enterococcus

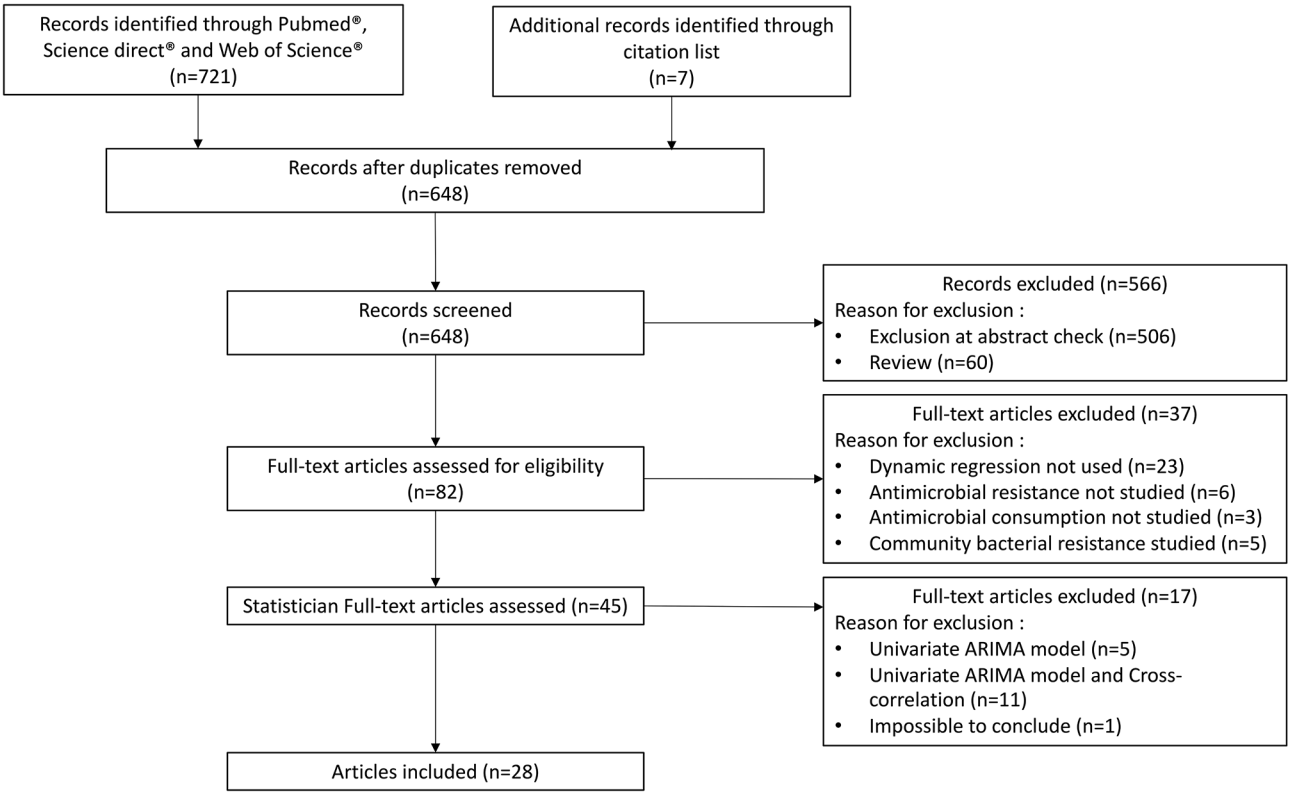

Fig. 1 Study selection flow chart

explained 41–96% of MRSA emergence [21, 22, 29, 34, 41].

Carbapenems use was correlated with the emergence of carbapenems resistance in *P. aeruginosa* in four studies [8, 24, 33, 40]. This correlation was also found in *Klebsiella pneumoniae* and *Acinetobacter baumanni*i in three and two papers, respectively [25, 30, 38, 40]. The lag time between emergence of carbapenems resistance and carbapenem consumption ranged between 0 and 12 months. DR models highlighted that 19 to 79% of carbapenem resistance rate variation was explained by carbapenem consumption [8, 25, 30, 38].

Model description

Twenty-one studies (21/28) [8, 13–15, 21–23, 25, 26, 30, 31, 33–36, 38–43] used DR as described by Pankratz [11, 12]. In the seven remaining studies, the statistical models used, namely, "dynamic lag times series" and "multivariate ARIMA lag structure regression model" were assessed as a DR model (7/28) [24, 27–29, 32, 37, 44]. One study did not perform lag time correlation [27], see Table 1.

Applications of DR model

Beyond correlating AMR and AMC, DR models have been reported to be useful to predict AMR emergence due to AMC [8, 14, 15, 27, 31, 34, 39]. They were considered effective tools for estimating the expected effect of a reduction in antimicrobial use on resistance [8, 14, 15, 22, 23, 28, 29, 34, 36, 41, 43]. Thus, they could be used to assess ASP efficiency and make new antimicrobial policies. However, their predictive capacity may be limited under certain conditions, notably when the incidence and prevalence of AMR is low [15].

Quality of studies

The quality of studies was mainly satisfactory, except for two studies [27, 44] (Figs. 2 and 3). Two studies [23, 27] reported unclear methods, mentioning only the ARIMA model while both the ARIMA and LTF models are needed to perform a DR model. However, in numerous papers, the term ARIMA was used instead of DR [35, 37, 41], and studies reporting a dynamic relationship between AMR and AMC, suggested a DR model was used. Finally, results were not clearly reported in one studies [25] and the discussion of limitations was moderately satisfactory in seven articles [21, 23, 27, 28, 34, 35, 40].

Discussion

In this review of 28 studies using DR models in hospital setting, we reported correlations between ß-lactams and fluoroquinolones use and cephalosporin resistance in Enterobacterales and *P. aeruginosa*, carbapenems use and

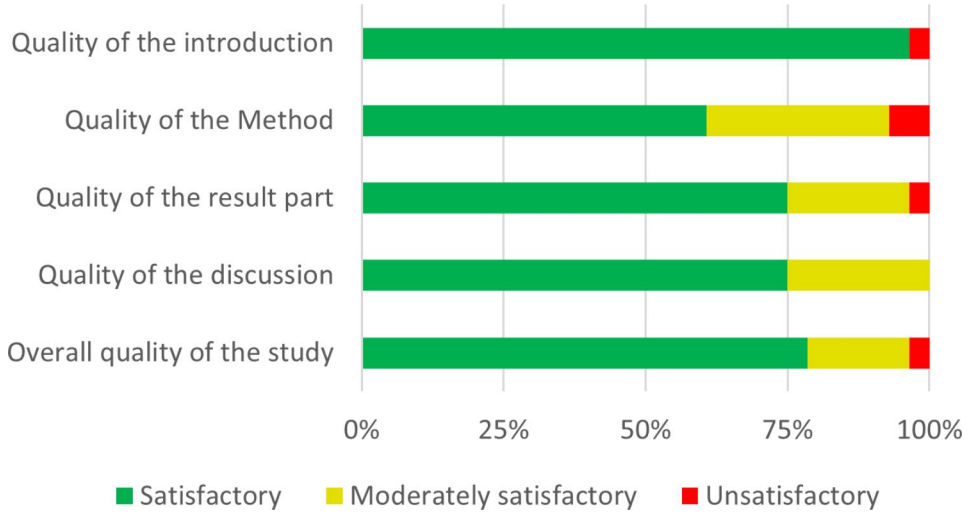

Fig. 2 Risk of bias assessment in the overall studies

carbapenem resistance in *P. aeruginosa, K. pneumoniae* and *A. baumannii*, and fluoroquinolones and macrolides use and methicillin resistance in *S. aureus*. A lag time of 2 to 4 months between AMC and the emergence of AMR was reported in most studies. In multivariate DR models, the burden of AMC on AMR fluctuation ranged from 15 to 96%. We also reported the potential usefulness of DR models in AMR prediction and, in accordance, their possible value in guiding ASP.

Many studies using linear or logistic regression models [45–47] or interrupted time series [48–51] have highlighted the selection pressure of antimicrobials. Indeed, antimicrobials with broad-spectrum activity, are frequently reported to be associated with AMR emergence, especially in the ESKAPE group (namely, *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter spp*) [49, 52–57]. These findings are in line with those reported using the DR models, which however have advantages over other studies [10, 58, 59]. Firstly, they are based on big data analyses providing a comprehensive view of selection pressure [7]. Secondly, the LFT allows temporal correlation, which increased the model's ability to early detect a correlation between antimicrobial use and AMR emergence as reported by Erdeljić et al. [24]. Thirdly, since AMR rates are not independent series, DR models avoid the bias of overestimating correlation, since they take into account the autocorrelation of the series studied [10, 53]. Finally, multivariate analysis of DR models could explain the burden of AMC in resistance fluctuation relative to the colonization pressure [10, 14].

Using DR models for assessing the correlation between AMC and AMR, the coefficients of determination represent the burden of a class of antibiotic on AMR [8]. It should be noted that coefficients of determination reported in our systematic review are disparate. This may be explained by the heterogeneity of the studies included, notably due to variations in practices such as hygiene protocols, variations in the bacterial species involved or stochastic variations [23, 24, 34, 53]. The crucial role of infection control procedures especially hand hygiene, and the strategic application of measures designed to curtail microbial transmission in influencing the landscape of AMR must be emphasized here, as they modify the complex relationship between AMC and AMR [60]. In addition, the genetic mechanisms underlying AMR (mutations and acquisition of resistance genes) lead to the development of cross-resistance - where AMC of one class results in resistance to other classes - contributing to the emergence of MDR strains [61]. Thus, the study of the correlation between AMC and AMR is complicated by the interplay of these genetic factors, which vary between antibiotic classes and bacterial species [62]. Moreover, DR models are based on large dataset analyses [7, 11], in which individual risk factors for AMR, such as age, immunosuppression, or chronic diseases, dose and duration of antimicrobial therapy, are not included. Nevertheless, it should be highlighted that antibiotic classes known for their ability to induce AMR, such as fluoroquinolones, exhibit both high correlation coefficients and narrow confidence intervals. This underscores their significant impact on the emergence of AMR [13, 15, 30, 43].

Finally, compared with other models, DR models have the advantage of being able to predict future fluctuations in AMR as a function of AMC. With the growing clinical importance of mathematical models to guide antimicrobials selection [63], DR models are seen as promising tools for the development of new ASPs. In fact, they can help select the most interesting antimicrobial agent to target, and then measure the effects of a given ASP on the incidence of AMR compared with the incidence initially

Fig. 3 Risk of bias per study

predicted [8, 14, 31]. As predictive tools, they could also be used to visualize the effect of a theoretical decrease in AMC on future AMR incidence [14]. However, external validations and cross validations between observations and predictions are mandatory, all the more so as the predictive capabilities of models can be undermined when the incidence of AMR is low [14, 15].

We must acknowledge some limitations in this review. First, studies were mainly geographically limited to European and Asian countries, limiting the generalization of the results to other geographical areas with different bacterial epidemiology. Second, studies included in this report have methodological limitations that could have induced bias in result interpretation. Particularly, several studies did not exclude duplicate samples (5 of 28) or patients previously known to be carriers of MDR bacteria [24, 25, 33, 35, 39]. Some studies were based on short follow-up times for DR modeling and unclear sampling timing [24, 27, 28, 30, 33, 36, 44], and three-quarters of included articles did not exclude samples taken within the first 48 h of hospitalization [8, 13, 14, 24, 25, 27, 30–41, 43, 44, 64]. Last, DR models focusing only on selection pressure and did not include the burden of colonization pressure. Nonetheless, these biases are common and inherent to all time series studies, which remain a reference model for studying AMR fluctuations at hospital scale.

Conclusion

To our knowledge, this report is the first systematic review of the use of DR models to assess the correlation between AMC and AMR at the hospital level. Although statistically recognized as a valid model for studying the correlation between AMC and AMR, DR models are little used in the literature. They have been used to highlight the correlation between cephalosporins use and cephalosporin resistance in *E. coli* and *P. aeruginosa*, carbapenems use and carbapenem resistance in *P. aeruginosa* and *A. baumannii* and fluoroquinolone use and fluoroquinolone resistance in Gram-negative bacteria and MRSA, after a lag-time of 2 to 4 months. Further studies are mandatory to analyze the link between AMR in other bacterial species and antimicrobials, and to assess the use of DR models for AMR forecasting and for ASPs building and evaluation.

List of abbreviations

AMC	Antimicrobial consumption
AMR	Antimicrobial resistance
ARIMA	Autoregressive integrated moving average
ASPs	Antimicrobials stewardship program
DR	Dynamic regression
ESBLs	Extended-spectrum β-lactamases
LTF	Linear transfer function
MDR	Multidrug resistance
MRSA	Methicillin resistant *S. aureus*
WHO	World health organization

Supplementary Information

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Supplementary Data: Table S1

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Authors' contributions

P.L-L and A.S. contributed to the study conception and design. Material preparation, data collection and analysis were performed by P. L-L., R.L., A.S. and F.S. P.L-L. wrote the original draft. R.L., G.L-B., C.D-R., J-P.L., A.S. and P.L. critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

The authors consent to share the collected data with others. Data will be available without undue reservation, immediately after the main publication and indefinitely.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

PLL has received support for attending meetings and/or travel from Shionogi. PL has received payment or honoraria for lectures, presentations, speakers' bureaus, or educational events from AstraZeneca, GSK, Janssen, MSD, Moderna, Pfizer, Sanofi Pasteur, and support for attending meetings and/or travel from AstraZeneca, Pfizer, and Sanofi Pasteur. AS has received consulting fees from Besins Healthcare and Karo Pharma, support for attending meetings and/or travel from Pfizer and MSD and participates free of charge on advisory boards of Biofilm Control and CTX Laboratory. RL has received consulting fees from MSD, payment or honoraria for lectures, presentations, speakers' bureaus, or educational events from BioM?rieux, MSD, Pfizer and Shionogi, and support for attending meetings and/or travel from BioM?rieux, Roche Diagnostics, MSD, Pfizer and Shionogi. All other authors declare that they have no conflict of interest.

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