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Review

Systematic review of the use of time series data in the study of antimicrobial consumption and *Pseudomonas aeruginosa* resistance

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ABSTRACT

Objectives: In the field of antimicrobial resistance, the number of studies using time series data (TSD) has increased recently. The purpose of this study was to systematically review all studies on antimicrobial consumption and *Pseudomonas aeruginosa* antimicrobial resistance in healthcare settings that have used TSD.

Methods: A systematic review of the literature up to June 2017 was conducted. All studies that have used TSD and have examined in-hospital antimicrobial consumption and *P. aeruginosa* resistance rates or incidence were eligible for inclusion; no other exclusion criteria were applied. Data on the structure, terminology used, methods and results for each article were recorded and analysed where possible.

Results: A total of 36 studies were retrieved from PubMed, of which 23 were in accordance with the inclusion criteria. Thirteen studies were quasi-experimental studies and ten were ecological observational studies. Twenty studies collected TSD for both parameters, and the statistical methodology time series analysis was applied in nine studies.

Discussion: Most of the studies were published in the last 8 years. The interrupted time series design was the most widespread. As expected, there was high heterogeneity with regard to study design, terminology and statistical methods applied.

Contents

1. Introduction

Systematic recording of observations at regular time intervals, i.e. time series data (TSD), has been a useful approach in the field of public health and especially in infectious diseases surveillance [1,2]. Recently, TSD have become a useful tool in studying antimicrobial consumption and resistance development [3,4].

TSD of antimicrobial consumption and antimicrobial resistance rates/proportions can be studied using time series analysis (TSA), a methodology aimed at adjusting a mathematical model to a series of observations taken over time, for the purpose of predicting future behaviour of the series, explaining its characteristics, identifying factors influencing the series and also to assess possible relationships between two or more time series [3]. In addition, relevant TSD can be used in interventional studies

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designed as interrupted time series (ITS). In ITS studies, a time series of a particular outcome of interest is used to establish an underlying trend, which is 'interrupted' by an intervention at a known point in time [5]. Comparison between the expected trend in the absence of the intervention and the observed trend provides an assessment of the impact of the intervention.

So far, there has been no published systematic review of the literature focusing on the use of TSD in antimicrobial stewardship studies and antimicrobial consumption/resistance development correlation studies, neither has there been proposed a common framework for these studies, although many articles have been published with the aim to reduce heterogeneity of epidemiological studies in general [6–8]. In this study, we make an overview of all relevant studies in order to report the different approaches and to present the outcomes that have been yielded so far. For reasons of economy, we focused only on studies involving *Pseudomonas aeruginosa*, since it is one of the most studied pathogens given that it is a main cause of nosocomial infections and has a potential for multidrug resistance [9].

The purpose of this study was to systematically review all in-hospital studies on antimicrobial consumption and *P. aeruginosa* resistance that have used TSD of at least one of the above parameters.

2. Methods

Relevant studies included in this review were identified from PubMed (date of search 26 June 2017). All studies that have used TSD and have examined in-hospital antimicrobial consumption and *P. aeruginosa* resistance rates or incidence were eligible for inclusion. No other exclusion criteria (e.g. language, type of article, date of publication, etc.) were applied. The database was searched using the following terms: 'time series' or 'time-series' and pseudomonas or aeruginosa or ps.aeruginosa and resistan* or susceptib* or sensitiv* (all fields). Articles were screened by both authors for eligibility and relevant articles were reviewed and classified according to the classification of medical research proposed by Röhrig et al. [10]. In every study, the following data were sought: duration of study; setting(s) where study was conducted; country; year of publication; selection of study isolates (e.g. exclusion of duplicates); existence of a control group; existence of TSD for antimicrobial consumption and for resistance rates/incidence; susceptibility criteria used; statistical measurement of antimicrobial consumption; statistical methods; and outcomes (positive correlation of antimicrobial consumption and resistance development).

3. Results

A total of 36 studies were retrieved from PubMed, of which 23 studies were in accordance with the inclusion criteria. The remaining articles were excluded because they were irrelevant or were outside the scope of this review (Fig. 1). Studies regarding both in-hospital and out-of-hospital use as well as studies conducted in settings that included children's and/or psychiatric clinics, were not excluded.

The identity of the studies as well as their classification is shown in Table 1 [11–33]. Thirteen studies were quasi-experimental studies and ten were ecological observational studies according to the classification of Röhrig et al. [10]. Twenty one studies collected TSD for both parameters (antimicrobial consumption and resistance) and the remainder collected TSD for antimicrobial consumption only. The statistical methodology of TSA was applied in only nine studies [24–27,29–33]. Table 2 presents the positive associations between antimicrobial use and *P. aeruginosa* resistance that were identified in nine studies.

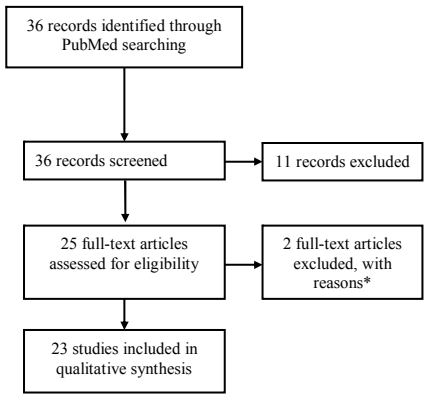

Fig. 1. Flow diagram of studies included in the systematic review. * No data on antimicrobial use.

With regard to the uniformity of reporting among the studies reviewed, almost all of the studies ($n = 20$) used daily defined doses (DDD) per number of patient-days as an expression of antimicrobial consumption [11–13,15–25,28–33], 2 used DDD per number of admissions [26,27] and 1 study used DDD per month [14]. For interpretation of antimicrobial resistance, 12 of the studies used Clinical and Laboratory Standards Institute (CLSI) criteria [13,14,18,19,22,26–29,31–33], 4 used other criteria [i.e. European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Comité de l'antibiogramme de la Société Française de Microbiologie (CA-SFM)] [16,20,24,25] and 7 studies did not report the criteria used [11,12,15,17,21,23,30]. Regarding resistance reporting, four studies reported both the proportion and the rate of resistant isolates [13,17,18,27], three more studies used only rates [20,25,30] and the remaining studies reported only proportions of resistant isolates [11,12,14–16,19,21–24,26,28,29,31–33]. Finally, all but four studies [20,23,26,30] reported a method to exclude duplicate isolates.

Regarding the 13 quasi-experimental studies, two more parameters were examined, namely the presence of a control group and their design. Nine studies were uncontrolled [11, 13–15,17–19,22,23], whereas eleven were designed as ITS studies [11,13–18,20–23].

4. Discussion

According to this research, TSD of *P. aeruginosa* resistance and in-hospital antimicrobial consumption have been used in observational ecological studies and quasi-experimental studies, mainly as ITS studies. The majority of the studies (78%; 18/23) were published in the last 8 years, whereas the first study was published no earlier than 2000 (Table 1). The statistical methodology of TSA was applied in only nine of the studies [24–27,29–33]. TSA corresponds to a group of statistical techniques aimed at adjusting a mathematical model to a series of observations taken over time. Of most importance is that, this method takes into account the possible relationship between consecutive observations. An ITS design was applied in 11 of the studies [11,13–18,20–23]. In ITS studies, data are collected at multiple time points before and after an intervention in order to detect whether or not the intervention had a significantly greater effect than any underlying secular trend [4,34]. Estimates for regression coefficients corresponding to two standardised effect sizes are obtained: a change in level (also called a 'step change'); and a change in trend before and after the intervention [4]. Most of the aforementioned ITS studies were part of an antimicrobial stewardship programme (ASP) that included various interventions. Of special interest are the studies that described a single intervention on the hospital formulary (mainly a