Title: ESTIMATING THE MAXIMUM BENEFIT OF ANTIBIOTIC USE IN AN ANTIBIOTIC STEWARDSHIP PROGRAM IN GENERAL SURGERY USING AN INTERRUPTED TIME-SERIES ANALYSIS

Authors: Secchettin Erica [1], De Pastena Matteo [2], Paiella Salvatore[2], Carrara Elena[3], Anna Maria Azzini[3], Evelina Tacconelli[3], Damiano Caputo[4,5], Roberto Coppola[4,5], Claudio Bassi[2],Roberto Salvia[2], Claudio Bassi[2]

Affiliations:
1 Department of Surgery, Dentistry, Paediatrics and Gynaecology
2 General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona, Verona, Italy
3 Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, Verona, Italy.
4 General Surgery, Università Campus Bio-Medico di Roma, 00128 Rome, Italy.
5 Operative Research Unit of General Surgery Unit Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy.

Introduction:
Antimicrobial resistance (AMR) is a growing public healthcare problem worldwide. In addition to its clinical implications, AMR imposes an economic burden. The WHO fights the matter on two sides: preventing the spread of resistant micro-organisms by infective control programs and reducing inadequate prescription and use of antibiotics (AWaRe classification), consequently saving the cost of drugs[1, 2]. Antimicrobial stewardship programs (ASPs) effectively reduce the spread of AMR and improve antibiotic prescription[2, 3]. Interrupted time series (ITS) analysis is arguably the strongest test to evaluate a change in the outcome rate given a period split into two (before and after) according to implementing a policy/program designed to change the outcome[4]. We applied ITS to a prospective APS in two high-volume surgery centers to evaluate its effectiveness in improving antibiotics consumption and saving costs.

Objective: The aim is to evaluate whether introducing a bundle of APS interventions has affected antibiotic consumption and cost savings.

Methods:
The ASP was conducted in the Pancreatic Surgery Unit of the University of Verona and the Campus Bio-Medico University Hospital of Rome between 2015 and 2022, and the two periods compared included 2015-2018 (before) and 2015-2018 (after). The prospective ASP includes tailored antibiotic prophylaxis based on the results of a surveillance rectal swab conducted preoperatively to identify multidrug-resistant microbes.
The total amount of antibiotics' grams per class was converted into Defined-Daily-Doses following the 2023 ATC/DDD index issued by the World Health Organization. Patient days were used to normalize ward-level antibiotic consumption data and were collected from the hospital administrative data. The trend of "Access" and "Watch" antibiotics (per WHO-AWaRe classification) consumption and cost savings were evaluated. The model was fit using an ordinary least squares regression analysis (Newey-West), and autocorrelation in the error distribution was tested using the Cumby and Huizinga general test for autocorrelation. The change in the slope and level, before and after the ITS, was assessed using ordinary least squares regression analysis. Differences in antibiotic costs were measured through a before-after comparison of pre- and post-intervention costs. All analyses were conducted using STATA Software (© 2015 StataCorp LLC, Texas)[5].

Results:
The mean number of patients monthly hospitalized in the two centers was 70, with a median length of stay of 9 days [IQR 7- 19]. The ITS analysis showed a significant decrease in overall antibiotic consumption from the pre- to the post-intervention. When analyzing antibiotic groups according to the WHO AWaRe classification, the "Watch" antibiotics demonstrated a decrease in the post-ASP period (-2.61 (3.91), p=<0.001) (Figure 1), denoting a shift in prescription habits. Overall antibiotic costs were also reduced with an overall saving of 247.460,00 euros.

Conclusions:
The bundle of interventions included in the ASP produced a more judicious use of "Watch" antibiotics, as per WHO recommendations, and cost savings. Besides the clinical benefits, ASP may be instrumental to positive investment returns in long-term care.

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Figure 1. ITS analysis about the Watch antibiotics consumption.