International Journal of Infectious Diseases 85 (2019) 67–69

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Population-level macrolide consumption is associated with clarithromycin resistance in *Helicobacter pylori*: An ecological analysis

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ARTICLE INFO

Article history:
Received 15 April 2019
Received in revised form 18 May 2019
Accepted 22 May 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
H. pylori
Macrolide
Antimicrobial resistance
Ecological study

ABSTRACT

Bystander selection has been shown to result in strong population-level correlations between the level of antimicrobial consumption in the general population and resistance to that antimicrobial or similar antimicrobials in a range of bacteria. The prevalence of clarithromycin resistance in *Helicobacter pylori* has been increasing rapidly resulting in increased difficulty to eradicate this infection. Using country- and WHO-world-region-level macrolide resistance data from a systematic review and macrolide consumption data from the MIDAS Quantum data base, we tested the hypothesis that the prevalence of clarithromycin resistance was correlated with macrolide consumption. At a country level, we found these variables to be positively correlated (Spearman's rho = 0.49; P = 0.007). Whilst positive, the correlation between macrolide consumption and primary resistance was not statistically significant at world region level (Spearman's rho = 0.95; P = 0.05).

Introduction

Increasing prevalence of resistance to macrolides in *Helicobacter pylori* (*H. pylori)* and the adverse effects this has on treatment success have led the World Health Organization to classify clarithromycin-resistant *H. pylori* as a high priority threat (Savoldi et al., 2018). In order to better understand the forces driving this antimicrobial resistance (AMR) we test the hypothesis that bystander selection plays a role. Bystander selection refers to the inadvertent selection of AMR in microbes not targeted by a specific antimicrobial therapy (Tedijanto et al., 2018). Macrolides for example, have been shown to result in a high prevalence of macrolide resistance in commensal nasopharyngeal streptococcal species (Malhotra-Kumar et al., 2007). This is independent of the indication for their use (Malhotra-Kumar et al., 2007). Bystander selection is particularly likely for bacteria like *H. pylori* that are highly prevalent and colonize humans for long periods during which time they may be exposed to antimicrobials taken for any indications (Tedijanto et al., 2018; Malhotra-Kumar et al., 2007; Kenyon, 2018). Bystander selection has been shown to result in strong population-level correlations between the level of antimicrobial consumption in the general population and resistance to that antimicrobial or similar antimicrobials in a range of bacteria (Kenyon, 2018; Bronzwaer et al., 2002; Goossens et al., 2005; Riedel et al., 2007; Kenyon et al., 2019; Seppala et al., 1997). A previous study limited to 18 European countries found that the prevalence of clarithromycin resistance in *H. pylori* was positively associated with national levels of macrolide consumption (Megraud et al., 2013). In the current study we assessed if the same association was present globally.

Methods

To test the bystander hypothesis globally, we used Spearman's correlation to assess the correlation between macrolide consumption and the prevalence of macrolide resistance at two ecological levels - country and WHO world regions. Our AMR data came from a systematic review that provided pooled country- and world region-level prevalence of clarithromycin resistance based on studies published between 2007 and 2017 (Savoldi et al., 2018). In this review, AMR was assessed both geno- and phenotypically and was defined as the overall prevalence of AMR. This included both primary resistance and secondary resistance. These were defined according to if the resistance was prior to the first eradication

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https://doi.org/10.1016/j.ijid.2019.05.028

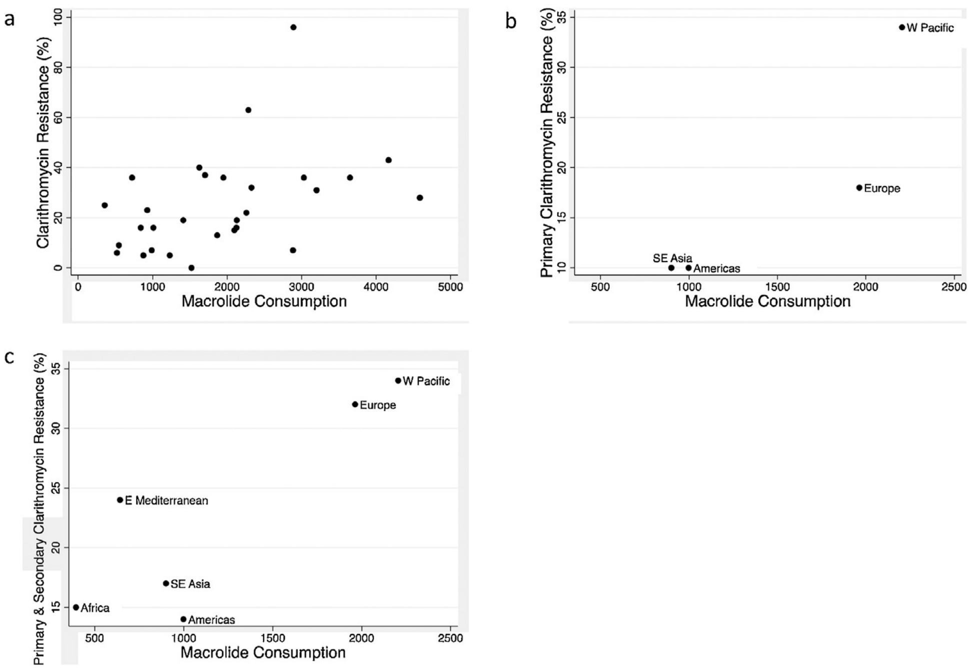

Figure 1. Scatter plots of macrolide consumption (in number of standard doses per 1000 population per year) versus pooled clarithromycin resistance (expressed as a percentage) in countries (a) and WHO world regions for primary resistance (b) and combined primary and secondary resistance (c).

treatment (primary resistance) or followed a previous eradication therapy (secondary resistance). At a country level, only combined primary and secondary resistance was reported whereas at a world region level this data was reported as combined and disaggregated (primary/secondary) resistance (except for Africa where the disaggregated data was not reported).

National and WHO world region macrolide consumption were obtained from MIDAS Quantum data base of the marketing research company IQVIA (IQVIA, Danbury, CT, USA). IQVIA uses national sample surveys that are performed by pharmaceutical sales distribution channels to estimate antimicrobial consumption from the volume of antibiotics sold in retail and hospital pharmacies (Klein et al., 2019). The sales estimates from this sample are projected with use of an algorithm developed by IQVIA to approximate total volumes for sales and consumption. Antimicrobial consumption estimates are reported as the number of standard doses (a dose is classified as a pill, capsule, or ampoule) per 1000 population per year (Klein et al., 2019). We used data for the year 2012 (the midpoint of the 2007–2017 time period used to provide AMR data. The median value of all countries in a world region were used as summary measures of antimicrobial consumption and resistance prevalence at world regional level. All statistical analyses were performed in Stata 14.0.

Results

Country level

Data was available for macrolide consumption and resistance was available in 31 and 52 countries, respectively. There were large differences in the prevalence of macrolide resistance (median 20.5%, interquartile range [IQR] 8–36%) and macrolide consumption (median 1664, IQR 998–2254). The prevalence of clarithromycin resistance was positively correlated with macrolide consumption in the 29 countries with data available for both variables (Rho = 0.49; P = 0.007; Figure 1a).

World region

The two world regions with the highest levels of macrolide consumption (Europe and Western Pacific) had the highest prevalence of clarithromycin resistance (Figure 1b and c). Whilst positive, the correlation between macrolide consumption and resistance was not statistically significant for primary resistance or combined primary and secondary resistance (Rho = 0.95; P = 0.05 and Rho = 0.60; P = 0.20, respectively).

Discussion

Our finding of a positive association between macrolide consumption and resistance in *H. Pylori* adds to the list of bug-drug combinations where bystander selection appears to play a role in the genesis of AMR. The analysis is ecological and thus susceptible to the ecological inference fallacy. It also uses AMR data from an 11-year period and compares this to a single time point of antimicrobial consumption. Our country-level analyses could only be performed on combined primary/secondary resistance figures which may have introduced a misclassification bias. Furthermore, there were only 29 countries with data on both consumption and AMR. Whilst these results should be re-analysed in larger datasets and further interrogated in modelling studies, the results are compatible with those showing the importance of bystander selection in other bacteria. The results are also biologically plausible as macrolide exposure has been shown in vivo and in vitro to lead to macrolide resistance inducing mutations in *H. pylori* and that these mutations persist long term (Hulten et al., 1997). Given the increasing difficulty to treat *H. pylori*, the study therefore serves as further evidence of the need for macrolide stewardship so as to limit the use of macrolides in the general population to clearly defined indications.

Data availability

The data we used is available from Salvoldi et al's AMR review paper (Savoldi et al., 2018) and MIDAS Quantum data (https://www.iqvia.com).

Funding

No specific funding was received for this work.

Transparency declarations

None to declare. The authors declare that they have no conflicts of interest.

Acknowledgements

Nil.

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