Journal of Global Antimicrobial Resistance 7 (2016) 132–134

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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

Letter to the Editor

Global antibiotic resistance is mostly periodic

Sir,

Antibiotic resistance is an ancient bacterial survival mechanism that pre-dates modern medicine [1]. In local settings, such as hospitals, antibiotic resistance rises and falls in a cyclic pattern. Here we investigate whether antibiotic resistance is also governed by a cyclic pattern in global settings.

To this end, we counted the yearly occurrence of the word combination 'antibiotic' and 'resistance' in the scientific literature. For example, for ampicillin resistance in 1986, we counted the number of papers containing the word-pair 'ampicillin resistance' as indexed by PubMed in that year. We repeated this procedure for 300 generic antibiotics, and for all years between 1986 and 2015. Finally, we fit the data of antibiotic resistance to a periodic function.

Of the 300 generic antibiotics, ca. 150 were marketed after 1986 and as such were excluded from the study. Of the 150 remaining antibiotics, most presented <10 yearly citations and were considered statistically noisy and insignificant. Of the 12 antibiotics that did present recurrent yearly data, 11 displayed periodic resistance patterns (Fig. 1). These antibiotics included penicillin, erythromycin, cefacetrile, gentamicin, tetracycline, cefaloridine, chloramphenicol, ampicillin, kanamycin, cefoperazone and neomycin. Exceptionally, ciprofloxacin resistance did not show signs of periodicity and displayed an almost linear rise.

Periodic resistance was fit to a sine function as follows:

$$[\text{Antibiotic resistance}] = \alpha + \beta \cdot \sin(\text{Year} \cdot 2\pi\,[\text{Frequency}] + [\text{Phase}])$$

For each antibiotic, the frequency and phase were calculated using fast Fourier transform, and the curve was fitted using the least square deviation method. The frequency and phase are listed below each antibiotic. Based on these values, antibiotic resistance may be projected into the future, and peaks and troughs accurately predicted.

As a potential limitation to this study, it should be noted that due to several reasons, citations per year may not reflect the accurate prevalence of antibiotic resistance per year. Surprisingly, our theoretical data for antibiotic resistance correlate well ($R^2 > 0.8$) with experimental data published by the US Centers for Disease Control and Prevention (CDC) [2] (Fig. 1). While costly CDC data are incomplete, and until more experimental data become available, our inexpensive theoretical data could serve as a trend line for antibiotic resistance.

Periodic antibiotic resistance adheres to Darwin's principle of natural selection. At first, antibiotic resistance is an uncommon and sporadic trait. Then, following worldwide use of the antibiotic, survival of resistant bacteria is favoured, which in turn gives rise to the antibiotic resistance. Then, as resistance increases, the antibiotic becomes less used. Finally, as antibiotic use declines, natural selection diminishes and resistance decreases.

Strikingly, the periodic frequency of antibiotics acting through the same mechanism is quite similar (i.e. penicillin and ampicillin). On the other hand, the periodic frequency of antibiotics acting through different mechanism is considerably different. The relative periodic frequency is correlated with spectrum width and frequency of usage, and widely used broad-spectrum antibiotics (i.e. cefacetrile, tetracycline and chloramphenicol) have higher frequencies than less-used narrow-spectrum antibiotics (i.e. neomycin, gentamicin and penicillin). Finally, antibiotic resistance is sometimes governed by more than one principal frequency (i.e. cefoperazone).

As shown here, most antibiotic resistance is governed by a periodic function. This observation is clinically relevant and supports antibiotic cycling [3–5] favouring antibiotic use during the rise phase of resistance, and disfavouring use once the resistance peak is reached. Finally, these data show that most antibiotics are sustainable in the long run.

http://dx.doi.org/10.1016/j.jgar.2016.09.003

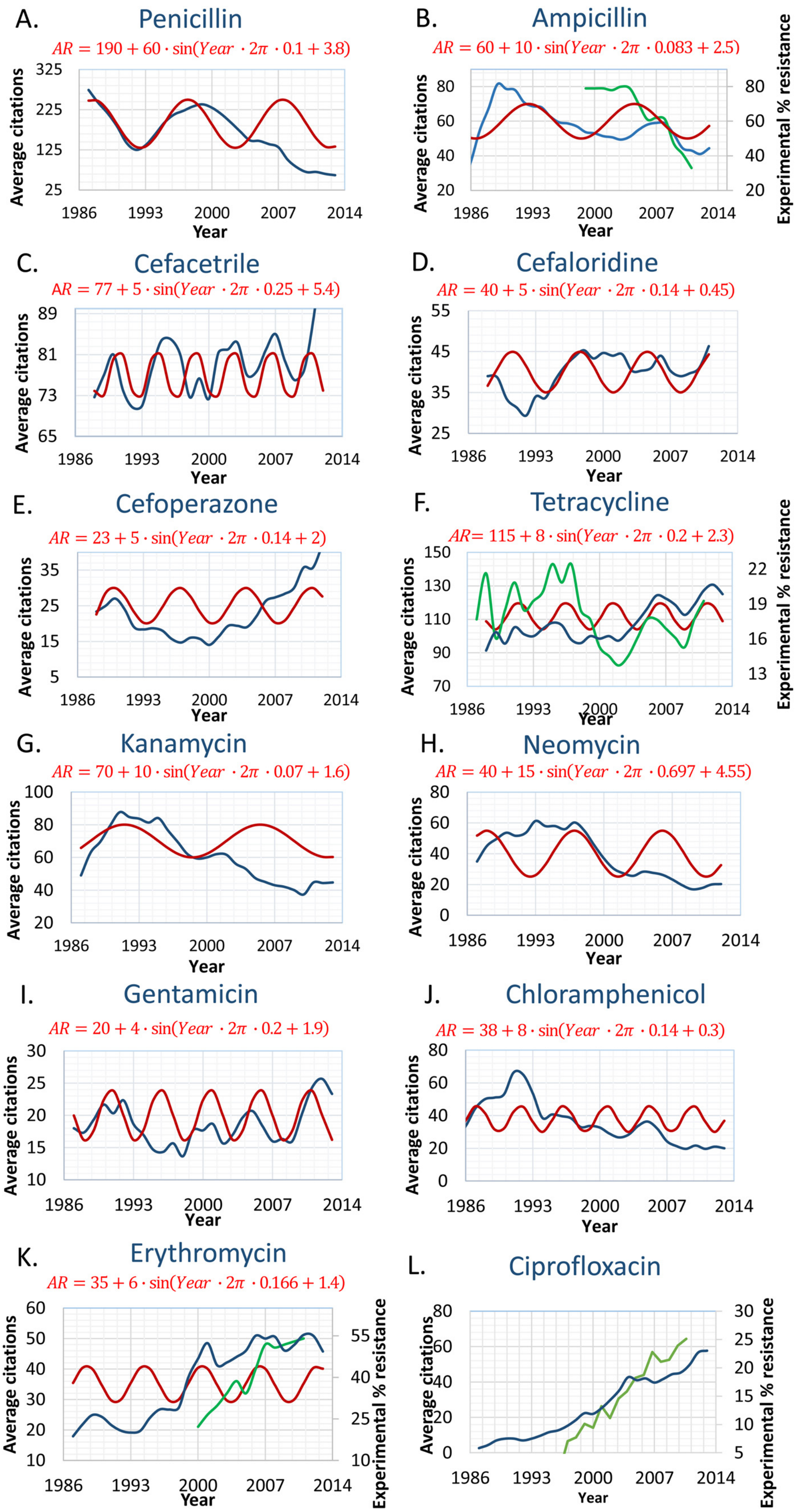

Fig. 1. Yearly antibiotic resistance. The theoretical antibiotic resistance as counted from PubMed citations is shown in blue, the fitted periodic function using Fourier transform and least square deviation is shown in red, and the experimental antibiotic resistance as reported by the US Centers for Disease Control and Prevention (CDC) is shown in green. Note resistance periodicity of most antibiotics.

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgements

We acknowledge grants received from the Leir Foundation and the Katz Foundation. We thank Prof. Ran Tur Kaspa for helpful comments.

References

[1] D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. Nature 2011;477:457–61.
[2] US Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: CDC; 2013 http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [accessed 30.09.16].
[3] Masterton RG. Antibiotic cycling: more than it might seem? J Antimicrob Chemother 2005;55:1–5.
[4] Sarraf-Yazdi S, Sharpe M, Bennett KM, Dotson TL, Anderson DJ, Vaslef SN. A 9-year retrospective review of antibiotic cycling in a surgical intensive care unit. J Surg Res 2012;176:e73–8.
[5] Roemhild R, Barbosa C, Beardmore RE, Jansen G, Schulenburg H. Temporal variation in antibiotic environments slows down resistance evolution in pathogenic *Pseudomonas aeruginosa*. Evol Appl 2015;8:945–55.

Rajaa Dabour
Tomer Meirson
Abraham O. Samson*
Faculty of Medicine in the Galilee, Bar-Ilan University, 8 Henrietta Szold St., Safed, Israel

* Corresponding author.
E-mail address: Avraham.Samson@gmail.com (A. Samson).

Received 19 June 2016

Available online 11 October 2016