About THRESHOLDS

In a worrisome scenario where not enough new antibiotics are expected to be available in the near future, it is critical to investigate approaches that help us to optimize the use of currently available antibiotics. THRESHOLDS present a scientific proposal trying to explain the relationship between antibiotic use and resistance from a different perspective that might help us to better understand this phenomenon. This proposal is based on the findings of three research articles that have been published in the last couple of years [1-3].

Time Series Analysis (TSA) techniques were used to study the relationship between antibiotic use and resistance as early as in 2000. The rationale was that resistance, measured over time and from an ecological point of view, is a stochastic phenomenon that results from the dynamic interaction of several factors, which, in turn, are also stochastic (use of antibiotics, spontaneous modifications of bacterial flora, hygiene and infection control measures, etc.) [4]. The latter proposal was based on a linear conception of the relationship between the triggers factors and their outcome, resistance: that is to say, the more antibiotic use, the more resistance, regardless of the level or intensity of use.

Stuart Levy [5], in 1994, hypothesized that such a relationship might not be linear. He suggested that there might be a threshold of antibiotic use beyond which, resistance would be triggered. On the other hand, below that given threshold or level of antibiotic use resistance would remain at infraepidemic levels, as a sporadic phenomenon.

In the three papers above mentioned, we introduced a statistical methodology, from the field of Econometrics, suitable for the identification and estimation of nonlinear models. This is what is known as Multivariate Adaptive Regression Splines (MARS), based on the separation of the data into sections or "regions" in which the ratio of the explanatory variables to the dependent variable changes and allows the identification of the nodes in that change occurs. This statistical approach has allowed us to detect multiple situations in which, up to a certain threshold, no relationship is detected between the use of antibiotics but, beyond that threshold, the relationship is positive.

Likewise, if we were able to detect thresholds for all antibiotics used in a particular hospital, we could establish a policy of use aimed at not exceeding those thresholds, in the hope that resistance levels would remain at acceptable levels. For example, establishing quotas (max number of treatable patients) in order to remain under the threshold [3].

References:

1. Lawes T, Lopez-Lozano JM, Nebot CA, Macartney G, Subbarao-Sharma R, Wares KD, Sinclair C, Gould IM. Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of Clostridium difficile infections in a region of Scotland: a non-linear time-series analysis. The Lancet Infectious Diseases , Volume 17 , Issue 2 , 194 – 206
2. Lawes T, Lopez-Lozano JM, Nebot CA, Macartney G, Subbarao-Sharma R, Dare CR, Wares KD Gould IM. Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. The Lancet Infectious Diseases , Volume 15 , Issue 12 , 1438 – 1449
3. Lawes T, López-Lozano J-M, Nebot C, et al. Turning the tide or riding the waves? Impacts of antibiotic stewardship and infection control on MRSA strain dynamics in a Scottish region over 16 years: non-

linear time series analysis. BMJ Open. 2015;5(3):e006596. doi:10.1136/bmjopen-2014-006596.

4. López-Lozano JM, Monnet DL, Yagüe A et al. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. Int J Antimicrob Agents 2000;14:21–31

5. Levy SB. Balancing the drug-resistance equation. Trends Microbiol 1994;2:341–2

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Several posters on antibiotic thresholds were presented at ECCMID conference (http://thresholdsnetwork.org/image-post-format/)

About Us

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