Antibiotic use versus resistance has a non-linear relationship

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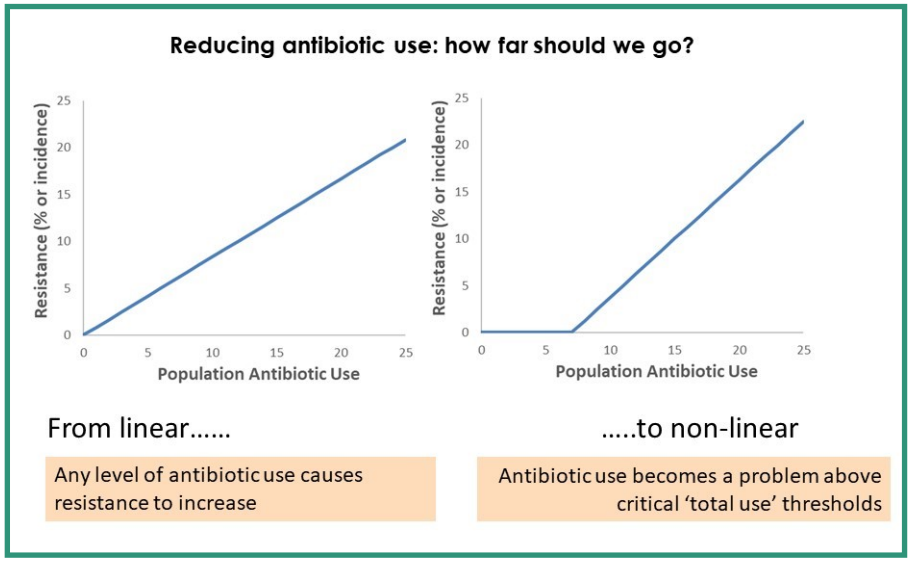
With current problems in antibiotic resistance and new antibiotic development it is important to understand how best we can optimise antibiotic use to delay the development of resistance

Time Series Analysis (TSA) techniques have been used to study the relationship between antibiotic use and resistance for 20 years now[1]. The theory was that resistance, measured over time and from an ecological perspective, is a stochastic phenomenon resulting from the dynamic interaction of several factors, (e.g. antibiotic use, changes in the microbiome, infection control measures). Previously, analysis was based on a linear concept of the relationship between the trigger, e.g. antibiotic use and the outcome, resistance: i.e., the more antibiotic use, the more resistance, regardless of the level or intensity of use.



Not withstanding this, an extremely important observation using linear ecological analysis, was the dynamic character of the relationship between antimicrobial use and antimicrobial resistance such that any specific antimicrobial use precedes specific resistance with unique lags. Ultimately though, for every resistance problem and its causative antibiotic use, there is a specific impact (how much resistance rises when antibiotic use increases).

Balancing the drug-resistance equation[2]

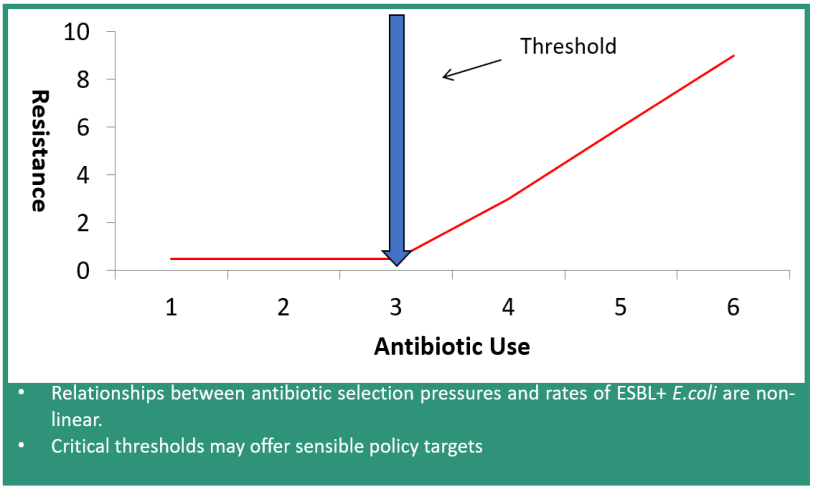
In a ground-breaking editorial published in 1994, Stuart Levy hypothesised that the relationship between intensity of antibiotic use and resistance might not be linear. Non-linear relationships are common in other biological systems but hadn't been considered in the context of antibiotic resistance up until then. Levy suggested that there might be a threshold of antibiotic use beyond which resistance would be triggered. Correspondingly, below that given threshold or level of antibiotic use, resistance would remain below epidemic levels, only as a sporadic phenomenon, because the cost to the microbe of carrying the resistance genes would outweigh any possible survival values.

Thresholds

In the last few years, on the basis of Levy's 1994 hypothesis, we introduced statistical methodology from the field of econometrics, suitable for the identification and estimation of non-linear models[3-6]. This methodology 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 which that change occurs. This statistical approach has allowed us to detect multiple antibiotic use / resistance combinations in which, up to a certain threshold, no relationship is detected between the use of antibiotics and resistance, but beyond that threshold the relationship is positive.

A threshold is an estimate of the maximum use of any antibiotic in a population that can be used over a specific period without generating resistance to that antibiotic. This can be converted into a maximum number of patients to be treated with that antibiotic in the population (e.g. a community or hospital, ward or unit). Each antibiotic has a threshold for each resistance although this is likely to be variable depending on the microbe, use of other antibiotics, and other factors still

to be researched such as the patient population, infection prevention and control (IPC) measures and the adaptability of the bacteria.



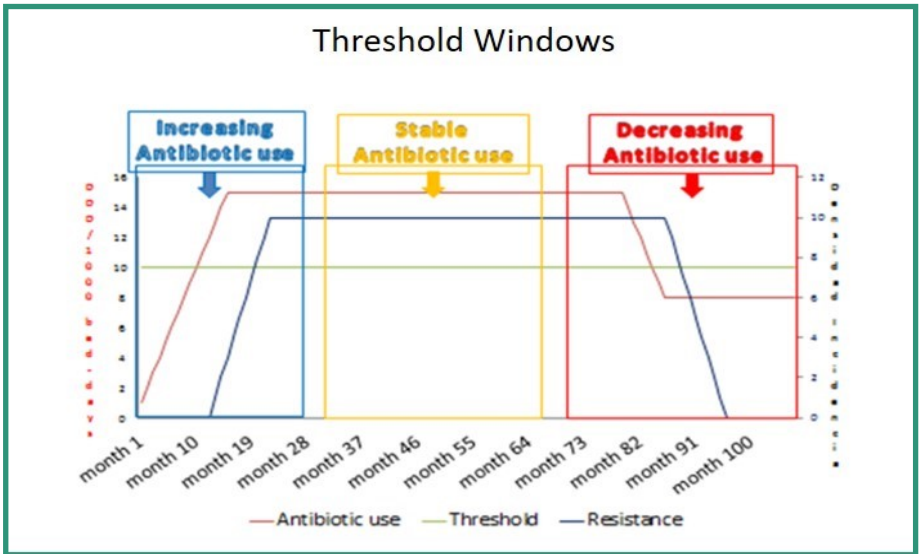
- Relationships between antibiotic selection pressures and rates of ESBL+ *E.coli* are non-linear.
- Critical thresholds may offer sensible policy targets

Thresholds too have been found for other factors, e.g. pertaining to MRSA, alcohol hand rub use, admission screening, number of positive admissions for MRSA, bed numbers and length of stay all displayed non-linear associations with MRSA prevalence. Ceiling effects too have been described, where above a certain level of use more resistance does not arise. Similarly, for MRSA, econometrically we have not found a threshold for 3rd generation cephalosporins, as even low levels of use increase MRSA prevalence.

A recent advance by our group has been provision of a confidence interval around each threshold estimation[3]. This is one of our econometric contributions; MARS does not provide this measure of uncertainty of the threshold estimation. This is relevant for establishing policies.

Further Questions

If we were able to detect thresholds for all antibiotics used in a particular hospital, unit or community, we could establish a policy of use aimed at not exceeding those thresholds for each antibiotic in the hope that problematic resistances would remain at acceptable levels. This would be similar to establishing quotas (max number of treatable patients) in order to remain under the threshold, something akin to carbon credits to reduce CO_2 production. Detection of thresholds requires long time series data sets, often of several years use and resistance and usually measured in monthly periods. Further research is needed on likely factors to influence specific thresholds, such as population vulnerability (maybe lower in geriatric inpatients), molecular epidemiology (e.g. MRSA strain), intensity of IPC measures (contributes in multivariate analyses) or the epidemic phase of an outbreak strain (compensatory mutations may occur to lighten the cost of resistance).



Time-series length and epidemic phase may affect ability to detect threshold

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