THE GLOBAL DEFINITION OF RESPONSIBLE ANTIBIOTIC USE: THE DRIVE-AB PROJECT

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Antibiotic use is a proven cause of antimicrobial resistance. Using antibiotics in a more appropriate and responsible way is of crucial importance if we want to avoid the risk of being unable to treat certain bacterial infections in the near future. The DRIVE-AB project represents a good example of a multidisciplinary project aimed at identifying new and sustainable strategies to tackle this problem. The definition of responsible use of antibiotics in humans constitutes the starting point of the project.

DRIVE-AB (http://drive-ab.eu/) is a three-year European project funded by the European Union (EU) Innovative Medicines Initiative and based on a public-private partnership between 14 public and nine private partners from academia and the pharmaceutical industry *(1)*. The project started in October 2014 and is ambitious as it aims to develop new economic models for the development of antimicrobials that will most likely de-link profits from sales, whilst still making it attractive for pharmaceutical companies to invest in the development of new antibiotics (in particular, antibiotics with novel mechanisms of action) by incentivizing research and development where it is needed most. In fact, despite the global burden of antibiotic resistance, few antibacterial drug discovery programmes are now maintained by pharmaceutical companies.

The implications of the project could be promising in a time in which antibiotic drug resistance has become a real threat that could potentially bring patients and doctors back to a pre-antibiotic era where the treatment of some infections due to multi-resistant Gram-negative bacteria will have no or very few effective options available *(2)*.

Policy-orientated initiatives to control resistance

The problem of drug resistance has seen a worldwide increase in awareness over the last few years and has become a priority for many organizations.

Some high-level actions that have already taken place include: a direct request in 2015 from US President Barack Obama for a national action plan that is supposed to tackle antibiotic resistance on multiple levels starting from controlling the use of antibiotics in animals to improving antibiotic prescribing by reducing the overprescribing of unnecessary antibiotics *(3)*.

Similar initiatives have been promoted recently by other countries, as in the case of India, a country with high bacterial resistance rates, where, in 2012, representatives of the different Indian medical societies gathered together in Chennai to establish a consensus roadmap (the so-called "Chennai Declaration") to address the problem over the next five years by setting realistic goals and objectives based on the Indian scenario *(4)*. This set of recommendations, addressing both infection control practices and antimicrobial stewardship measures, not only changed the way the issue of antibiotics resistance was perceived by the medical community and authorities, but could also be used as the basis for similar programmes in other low- and middle- income countries.

Successful initiatives to promote best practices and innovative solutions should always be achieved through an interdisciplinary process involving different stakeholders, taking the issue of resistance outside of expert conference rooms and putting the issue on the agenda of global institutions and policymakers. The DRIVE-AB project follows this trend, bringing academics and colleagues from the pharmaceutical industry to work together to find new solutions to the problem of resistance.

The task is not an easy one since the point of view of each participant will be most certainly different and influenced by their professional background and experience, their local context of action and the outcomes they will take into account in order to make their evaluations.

Promoting the responsible use of antibiotics

The responsible use of antibiotics aims at reducing the misuse of antimicrobial agents, as this has been clearly demonstrated to be a cause of the inevitable rise in resistance rates *(5)*. Unfortunately, many barriers stand in the way of the responsible use of antibiotics. In part, the problem is technical and some doctors tend to overprescribe antibiotics because of diagnostic uncertainty and the lack of rapid test results that can help, for

example, rapidly distinguish a real bacterial respiratory infection from a viral one that does not need antibiotic treatment. This kind of rapid test would also be very important for drug-resistant bacteria in order to decrease empiric therapy and target antibiotics from the beginning as the causative pathogen (6).

Another reason behind antibiotic misuse is lack of epidemiological data about antimicrobial resistance patterns at a local level in many countries. A notable exception to this rule is the ECDC-funded EARS-net which provides clinically and epidemiologically valuable data on antimicrobial resistance. Monitoring resistance rates can help physicians in their daily prescribing practice and the more detailed this information is, the more helpful it is for the prescriber (7).

Often, frequencies of bacterial infections cannot by themselves explain the large variation in consumption patterns seen even among geographically close settings and therefore, other cultural, social and institutional factors need to be taken into account (8). That is why many studies have focused not only on the clinical and microbiological aspects but have also incorporated the behavioural determinants involved either to describe patterns of consumption or to incorporate those determinants in interventional studies (9). This type of approach could prove effective not only in hospitals, but also in the outpatient setting where most of the antibiotics are used and where public awareness campaigns are most needed (10).

All the above-mentioned aspects that influence antibiotic prescribing could have a positive impact on how antibiotics are used. This issue is increasingly important since antibiotic use has increased by 36% worldwide between 2000 and 2010, especially in developing countries. Thomas Van Boeckel and his colleagues have described this increase well, reporting that 76% of the rise is due to the BRICS countries alone (Brazil, Russia, India, China and South Africa) (11). Some high-income countries have also shown an increase in antibiotic consumption over the same period, such as Australia and New Zealand. It is very likely that most of these increases are due to inappropriate use and increased access to antibiotics, more than to demographic changes. Inappropriate overconsumption of antibiotics, in addition to the effect on resistance, can also substantially increase healthcare costs because infections caused by multidrug-resistant pathogens are more severe and require the use of expensive second-line drugs that are not available or affordable in many settings, especially if expenditure is limited, for example, in developing countries.

Metrics for measuring responsible antibiotic use

Reliable antibiotic use data are a prerequisite for the comparative analysis of antibiotic consumption and the necessary basis for interventions aimed at optimizing prescribing practices. In this context, the DRIVE-AB project is developing a list of quality and quantity indicators to evaluate the responsible use of antibiotics, both in hospitals and in primary care-taking into account also factors such as existing differences between high- and middle-low-income countries. This process is based on a systematic literature review followed by a consensus procedure that involves the active participation of a wide range of stakeholders (including policy-makers).

Generic and specific indicators have already been described many times for specific settings and related to specific populations. Ideally, they need to be few and easy to use in practice, especially considering that personnel and funding to implement their use are limited even in high-income countries (12). Therefore, more refined metrics are needed.

The most commonly used approach to evaluate and regulate antibiotic prescribing practices is measuring the quantity of antibiotic consumption and many metrics have been developed for this purpose. Nevertheless, benchmarking based on these metrics has to be done carefully since it has been demonstrated that just combining different nominators and denominators can lead to substantially different results (13). This proves that a conclusive statement on which metrics should be used is not easy to make since each metric can be more appropriate than the other ones depending on what is the outcome of interest.

If, for example, we take into account only the clinical response to the treatment (in terms of success or failure) or the risk of developing resistance or how to limit costs for the institution, the answer will differ, meaning there was no universal answer to the question of whether an antibiotic was used appropriately or not because the appropriateness is determined by the context.

This kind of performance measurement has not only a value for prescribers, but also offers policymakers a major opportunity for securing heath system improvement and accountability. This is the reason why the World Health Organization in 1985 already included in its list of core drug use prescribing indicators, an indicator related to antibiotic use which is percentage of physician encounters with an antibiotic prescribed. This indicator is often used to monitor antibiotic use patterns in low- and middle-income countries.

Many classifications of antibiotic indicators exist in the literature. Table 1 summarizes some of the most frequently used structure indicators related to antibiotic consumption in the hospital setting. Most of them could be the target of an antimicrobial stewardship intervention whose feasibility and relevance will have to be adapted to the local context (14).

How DRIVE-AB will improve the monitoring and adherence to prudent antibiotic use

Definitions of responsible use and sets of indicators of antibiotic use are already available. However, the unique contribution of DRIVE-AB will be that the main recommendations will be

Table 1: . Indicators for measuring antibiotic stewardship in the hospital setting

Mandate	Presence of a multidisciplinary antibiotic stewardship team (composed at least of an infectiologist, a microbiologist and a pharmacist)	Time resources allocated to the antimicrobial stewardship team	All experts of the antimicrobial stewardship team should be involved in the development of local guidelines
Services	Consultant advice on antibiotics available on request on the same day	Regular ward rounds to discuss antibiotic management	Clinical audit of prescribers to assess compliance with local guidelines
Tools	Available guidelines (possibly based on local epidemiology)	Available and updated antibiotic formulary	Computerized antibiotic prescription and time-limited drug delivery
Diagnostics	Regular meetings between microbiologists and practitioners	Microbiological rapid tests (eg. *Clostridium difficile* toxin test within 18 hours)	
Antibiotic consumption surveillance	DDD/different denominators	Parenteral vs oral consumption	Broad spectrum vs narrow spectrum

based on consensus among the different stakeholder groups that deal with antibiotic use at different levels. This should give a new and more comprehensive framework of action that could prove useful in the future to address the problem of misuse of antibiotics and have implications on the costs and performance of healthcare. The next step will then be to find alternative incentives for the development of new antibiotics by pharmaceutical companies.

Unfortunately, this approach will not provide a definitive solution to the problem of drug resistance, since even if new treatments are developed, microbes will still be able to evolve and find new ways of becoming resistant. This continuous threat makes it necessary to raise continuous awareness about the importance of improving antibiotic use. ■

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