The very first requirement of treatment is that it should do no harm*, so why are antibiotics still overprescribed?

**Adapted from Florence Nightingale, Notes on hospitals, 3rd edition, 1863. "The very first requirement (in a hospital) is that it should do (the sick) no harm"*

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Antibiotics should only be used when they are necessary and not otherwise. However, they are still overused and misused by health professionals, patients, farmers, and vets. As a consequence, multidrug resistant bacteria are now posing a major health problem [1].
Antibiotics are unique, in that their prescription to a patient may treat the infection successfully, but simultaneously promotes the emergence and spread of antibiotic-resistant bacteria. Unlike other treatment decisions, the decision to take antibiotics affects populations and their health directly: increased individual use of antibiotics results in less effective treatment for all. Estimates show that in the European Union 25,000 people die each year as a result of infection by multidrug resistant bacteria, at an estimated direct cost to healthcare systems of €1.5 billion per year [2]. Action must be taken to deal with the alarming threat to public health, in particular in the light of a lack of discovery and development of new classes of antibiotics [3].

One of the main confusions in understanding how antibiotic resistance spreads is the different levels at which the risk operates. The risk jumps between the occurrence of resistance in the bacterial population, to the individual, to the wider population. For the bacterial genome, resistance relates to the mutation rate or occurrence of a mutation that generates resistance. For the individual, resistance relates to the relative proportions (within the individual) of resistant and susceptible bacteria causing an infection. For a population, resistance relates to the relative risk of having an infection with a resistant pathogen. All these steps are enhanced by antibiotic use, starting at the level of the mutation which spreads by increased use and inter-personal contact, to the higher population level where, due to a cumulative ecological effect, overall antibiotic use results in a background population resistance. Resistance mechanisms in bacteria are associated with a fitness cost and resistance will (theoretically) reverse in the absence of the antibiotic. A higher fitness cost will result in less integrated/stable mutations which can result in a faster reversion if antibiotic use were reduced [4]. The higher the fitness

cost of the resistance for the bacterial community, the faster it will clear from the bacterial and thereby human population, but it will be unlikely to go down as far as 0%.

The mechanisms of resistance in bacteria and how resistance affects individual infections are well understood[5]. That this affects the whole of modern healthcare is clear from the increased number of difficult to treat infections [6]. It is however still unclear why resistance is so difficult to reverse in a population or how a reduction in antibiotic usage may affect this. For instance, no reduction in the occurrence of resistance could be observed 10 years after a major decrease in sulphonamide prescribing prescribing[7], while an immediate reduction could be observed for fluoroquinolone resistance of *E. coli* urine isolates[8]. Our lack of understanding of the mechanisms of the spread of resistance is also demonstrated by the implementation of interventions that aim to reduce prescribing rates by 10% without actually expecting a knock on effect on resistance, at least within the time frame of a research project[9].

Resistance epidemiology has the potential to improve our understanding by investigating the complex nature of antibiotic resistance at its different intricate levels. According to Magee, first posing its case, resistance epidemiology could provide a rational framework for effective interventions in resistance[5] by identifying factors that affect the incidence of resistant infections. Resistance epidemiology brings together various disciplines, including, but not limited to, microbiologists - to explain how resistance remains embedded in the genome and whether a threshold exists at which the fitness cost is too high to retain the resistant mutation - psychologists and social marketers, to understand how and when health care providers and patients will adopt behavioural changes - and sociologists, to explain how social deprivation is embedded in this behaviour [10]. The resistance epidemiologist will have the challenging task to quantify and explain how each factor affects the outcome of prescribing in the first place and resistance as its endpoint. Additional use of statistical modeling will allow quantification of the cumulative population impact from the individual risks.

There is no doubt that the only way to curb antibiotic resistance is by reducing the availability of antibiotics. Antibiotic overprescribing, over the counter prescriptions and usage as animal growth supplement have to be addressed within such a framework. This means that implementation and enforcing effective guidelines is the first step in addressing the problem of antibiotic resistance. However, because rational targets for the extent of reduction in antibiotic usage have not been formulated, only careful actions are undertaken by (government) authorities and research groups. The hesitation in enforcing prescribing limitations stems from an interaction between a lack of engagement, due to a lack of understanding of the extent of the problem, and the still unproven direct link between prescribing and resistance, due to the timescale between occurrence and spread.

For the GP and other healthcare professionals the aim is to maximise the immediate effect of treatment for the individual. Most infections are treated empirically with antibiotics without microbiological confirmation of the pathogen or its susceptibility. In about two-thirds of community patients antibiotic treatment remains empirical during its entire course, in other words, antibiotic treatment was not

necessary or may have been inappropriate [11,12]. If the only effect of antibiotics was for the individual, empirical treatment seems obvious, however, for antibiotics the additional population effect of individual treatment has to be taken into account. Each use of antibiotics, appropriate or not, diminishes the availability of effective antibiotics by some amount. This harm is probabilistic; there is no guarantee it will yield resistant bacteria that will sicken or kill. This harm is also indirect and diffuse and therefore difficult to follow and prove. So future harm is not a predictable or foreseeable consequence of current consumption [13,14]. The person we may harm by taking antibiotics is not known and might not even exist (yet), which is why taking bold steps to limit prescribing seems extreme. However, as there are few new antibiotics likely to become available for many years, antibiotics are a limited resource which should be regulated [14]. This is particularly important considering that in the last 40 years only 3 new classes of antibiotics have been discovered, of which 2 are obsolete today[13].

GPs may be concerned that avoidance of antibiotics could lead to more infectious complications or hospital admissions, an argument often used when considering strategies for limiting prescribing, such as delayed prescribing[15]. Many physicians are reluctant to impose even small avoidable risks of harm on patients[14]. To understand this risk in comparison with the harm previously described, it has to be quantified. According to the Health Safety Executive (HSE), "tolerable risks are those that we are prepared to accept in order that we might accrue some benefit" [16] and they offer a lower limit of a 1/10,000 risk of death as a guideline for a tolerable risk.

For instance, for urinary tract infections (UTIs), there is a risk of developing acute polynephritis that requires hospital admission. This risk is estimated to be about 25 per 100,000 per year for females [17]. Only very few of these women (estimated 0.1%) may develop subsequent more serious complications, such as urosepsis [18]. Keep in mind that the risk of developing a UTI is increased after antibiotic use in general [19] and that wrong empirical prescribing also entails increased risk of fatality due to delayed prescription of the appropriate antibiotic [20].
A life is never an acceptable risk when considering treatment or non-treatment, but interpretation of the risks may be out of balance due to legal and media challenges. Furthermore, risk is not a static event and regular re-evaluation of patients during the course of an infection to look for improvement or deterioration is an important aspect of medical care in the light of prudent use of antibiotics [10].

For the individual, there is also a risk in using the antibiotic itself. The prevalence of multiple drug allergy syndrome based (self-reported) is estimated to be 3.3% [21]. The risk of a serious adverse drug event after taking an antibiotic, based on emergency department admissions, is estimated to be 1 in every 1000 patients who take an antibiotic[22]. Antibiotic-associated diarrhea affects 5-25% of patients [23]. Antibiotics can also change the normal flora balance in the vagina resulting in thrush (vulvovaginitis), which occurs in an estimated 28%-35% of women after taking a course of antibiotics[24]. With an overall estimated gain of antibiotics reported to be half a day reduction in symptoms for UTI patietns, 5-25% of patients will have adverse reaction [9].

To allow future generations to experience health and to be able to treat infections, we have to implement the principle that actions have to be in line with the Public Harm Principle. The public harm principle is also implemented in the case of vaccination where a risk of the vaccination itself is accepted

in the population's interest of preventing many infections through obtaining herd immunity. For antibiotic resistance, this would mean a more balanced approach to risk and harm and thereby to stop the clock, or even turn it back, with regard to antibiotic resistance. Such actions require a multicompartmental approach with buy-in from ALL stakeholders. A first step may consist of specific and enforced guidelines about antibiotic use and re-evaluation of the practice of empiric prescribing, in particular with broad spectrum antibiotics. A list of infections can be devised for which antibiotics are warranted, and for which watchful waiting should be implemented. Such a list will give clarity and can be (legally) defended in the context of antibiotics as a limited resource and the principle of doing no harm. Pricing antibiotics on the basis of their social and therapeutic benefit and as a limited resource should also be considered and could incentivise the development of new agents, as well as support more prudent use [25].

For interventions to decrease prescribing and eventually to curb resistance, the underlying mechanisms have to be better understood. A collective multidisciplinary and long term approach is necessary to address all the factors involved. Interventions have been suggested to benefit from social marketing, practice guidelines, peer review with feedback, structured data entry and clinical decision support systems [26]. In addition, as delayed or refused prescription does not seem to affect patients' satisfaction with treatment in a negative manner, this procedure should be encouraged to achieve more prudent use of antibiotics in patients [27]. Not implementing such interventions because of perceived risks to patients do not serve the long term health of our population.

All stakeholders, patients, healthcare professionals, researchers and policy makers, need to be involved in a multidisciplinary approach based on the idea that individual risks have to be accepted for the greater good of a population.

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