Comment on: Antimicrobial stewardship: the role of scientists?

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Sir,

Bowater’s (2015) paper1 calls on scientists to take a more active role in antibiotic control. Although we agree with most of the issues addressed, we think that antibiotic resistance should be evaluated from an evolutionary and quantitative perspective.

On the quantitative side, the author suggests that the use of antibiotic resistance markers to select genetically modified microorganisms in research laboratories may contribute to the spread of antibiotic-resistant bacteria. According to this view the problem is 2-fold: (i) discharge of antibiotics; and (ii) release of microorganisms carrying antibiotic resistance genes into the environment. We believe that both of these concerns are unfounded.

The author’s assertion that the use of antibiotics as selection markers is widespread in research laboratories is correct. However, there are strict biosafety regulations that enforce, among other things, that genetically modified bacteria cannot be discarded alive. Common decontamination practices, such as chlorination or autoclaving, ensure that all disposed bacteria are killed.

The second concern is about the release of unaltered antibiotics in the waste or sewage. A simple calculation will show that the quantity of antibiotics discarded by research laboratories is irrelevant when compared with the high doses of antibiotics released by industrial plants or by patients undergoing antibiotic treatment. For instance, suppose that 1000 research laboratories each prepare the huge amount of 500 Petri dishes per day, each containing 100 mg/L ampicillin (i.e. 2.5 mg of ampicillin/plate) and another 100 flasks (50 mL each) containing the standard concentration of 15 mg/L tetracycline. Thus, 1000 research laboratories would consume in total only 1.25 kg of ampicillin and 75 g of tetracycline per day. It should be noticed that the vast majority of these antibiotics will be destroyed by decontamination procedures prior to discarding. In contrast, antibiotic contamination from industrial plants has a considerably stronger impact.2 Just to put it in perspective, in Hyderabad, a region with many pharmaceutical industries in India, the estimated release of ciprofloxacin found in the effluent of a water treatment plant was ~44 kg/day.3

Another important source of antibiotic release in the environment in heavily populated areas is human consumption, as antibiotics are normally not completely metabolized by the body. For instance, >90% of ciprofloxacin4 and 60%–70% of amoxicillin5 two of the most prescribed antibiotics, are excreted unaltered from the organism. Global consumption of antibiotics in 2010 reached the staggering amount of 73,620,748,816 standard units (a standard unit is defined as a single-dose unit, and thus it varies according to the medical prescription, e.g. a 500 mg pill is the standard unit of amoxicillin).6 Since most of it is not absorbed by the body, it is clear that a significant amount of antibiotics released into the environment comes from the patients’ waste. In addition, animal treatment and the use of antibiotics as growth factors in animal farming (fortunately a practice that is increasingly being curbed) add even more active antibiotics to the soil and water bodies.

Antibiotic resistance existed in nature long before the use of these substances as therapeutic weapons.7 Bacteria do not ‘become’ resistant to antibiotics in the sense that they spontaneously turn refractory to their action. Resistance is a population phenomenon and should be studied from this point of view. Antibiotic action on bacterial populations exerts selective pressures and changes the frequency of resistance genes. The main drawback of current antibiotic therapy is the ‘single-target’ approach. All the molecules used in medicine are directed to specific enzymes or systems in the bacterial cell. This approach leads to the selection of resistant strains. Development of new antibiotics, or halting the production of old ones, will not solve this problem. What we need is a new approach to the use of antibiotics (new or old) that takes into account knowledge about the resistome and its evolution.8 This should involve an awareness initiative aimed at the following stakeholders: doctors and patients; those responsible for policy regarding the use of antibiotics; and the pharmaceutical industry involved in the development, production and distribution of antibiotics.

In summary, the utilization of antibiotics and resistance genes in research laboratories has, if any, only a negligible impact on the worldwide spread of antibiotic resistance.

Transparency declarations
None to declare.

References
Antimicrobial stewardship: the role of scientists?—author’s response

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Sir,

Spira and Winter1 have taken time to discuss my Leading article, ‘Antimicrobial stewardship: the role of scientists?’2 They have kindly provided useful comment and analysis on the suggestion that scientists should take a more active role in antibiotic resistance and postulate that the quantity of antibiotics discarded by research laboratories is irrelevant when compared with the high doses of antibiotics used and released elsewhere. They propose a simple calculation based on an estimate of the number of laboratories and possible antibiotic use. My rejoinder is that this is an excellent starting point and that quantitative evidence should now be gathered to allow us to accept (or not) this hypothesis. In addition, the authors report that regulation is provided to ensure strict biosafety processes are followed to protect the laboratory worker and the wider environment. Nevertheless, evidence suggests that it is likely that environmental and laboratory contamination events occur. This is perhaps because 100% compliance with biosafety guidelines is not always apparent at all times, within all laboratories and with all laboratory workers. As De Lappe et al.3 conclude, the ‘scale of laboratory cross-contamination in bacteriology is most likely under recognized’. Evidence-based initiatives that raise awareness of the outcomes of antibiotic use among stakeholders, such as doctors and patients, those responsible for policy regarding the use of antibiotics and the pharmaceutical industry involved in the development, production and distribution of antibiotics, are a sensible approach to tackle the growing concern of antibiotic resistance. I argue that scientists should also be considered as key stakeholders in addressing this concern and we should scrutinize the perceptions and outcomes of antibiotic use within our practice. This would provide us with the evidence to either accept or reject Spira and Winter’s null hypothesis that ‘the utilization of antibiotics and resistance genes in research laboratories has, if any, only a negligible impact on the worldwide spread of antibiotic resistance’.

Transparency declarations

L. B. is part of the Small World Initiative, developed by Yale University and currently running in more than 40 other Higher Educational Institutions and which has enrolled more than 1000 students across the USA. The programme trained trainers to provide an authentic research project for undergraduate students to address the worldwide health threat of antibiotic resistance. L. B. is currently working with the Society for General Microbiology (SGM) to bring this programme to undergraduate students in the UK. The SGM is taking the project further by including school pupils and the general public (Citizen Science).

References