

# Fight antibiotic resistance – it's in your hands to improve antibiotic stewardship

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The public health threat emanating from the emergence and spread of multidrug-resistant bacteria is well known. Each year the World Health Organization (WHO) SAVE LIVES: Clean Your Hands campaign promotes a different theme; the call to action in this year's annual 'Global Hand Hygiene Day' on May 7<sup>th</sup>, 2017, is 'Fight antibiotic resistance – it's in your hands'.<sup>1</sup> Good hand hygiene is widely acknowledged as the single most important measure to prevent infections in hospital. However, it would be naive to believe that hand hygiene alone will solve the problems posed by multidrug-resistant Gram-negative bacteria (MDR-GNB). Several papers recently published in this Journal have identified that previous antibiotic exposure is an important independent risk factor for colonization or infection with MDR-GNB.<sup>2;3</sup> We already know that antibiotic stewardship has been a key component in the control of *Clostridium difficile* infection (CDI); Dingle et al. recently reported that restricting fluoroquinolone prescribing appears to have been the most important factor in the decline in CDI in England.<sup>4</sup> It is therefore timely that the WHO call to action on antibiotic resistance has coincided with publication of an updated Cochrane review on antibiotic stewardship.<sup>5</sup>

At first glance it is encouraging that the Cochrane review concluded that interventions are effective in improving antibiotic stewardship.<sup>5</sup> Key conclusions were that in 29 randomized studies, including 23,394 inpatients, 58% of hospital inpatients in the intervention groups received treatment in line with prescribing guidelines, compared with 43% of the patients in the standard practice groups. Likewise, they reported that interventions shortened the duration of antibiotic use from 11 to nine days per patient, and probably reduced hospital stay from an average of 13 to 12 days per patient. Importantly, they found no evidence that reducing antibiotic use led to an increase in harm to patients. The latter point is important, and should provide support to antimicrobial management teams who may have a hard task in convincing clinicians and hospital managers that judicious antibiotic use is a safe strategy. However, the impact of stewardship interventions on antibiotic use, even in these trials that were by definition performed by motivated teams with adequate resources, is somewhat underwhelming. After the interventions, more than 40% of patients were still receiving treatment outside prescribing guidelines, and although a reduction of two days in the duration of antibiotic use may sound encouraging, a mean duration of therapy of nine days post intervention still sounds too long.

Perhaps not surprisingly, therefore, there is limited evidence that the focus on antibiotic stewardship in recent years has had a significant impact on antibiotic prescribing globally. In Europe, ESAC-Net surveillance data for overall antibiotic consumption within the EU during 2010–2014 showed an increasing trend, whereas large inter-country variation in antibiotic consumption remained. In the present era of extensively or pan-drug-resistant carbapenemase-producing Gram-negative bacteria, it is notable that mean consumption of carbapenems in hospitals also increased; the increase was particularly pronounced in six rather diverse countries (Bulgaria, Denmark, Hungary, Ireland, the Netherlands, and Norway).<sup>6</sup> Some encouraging data have recently emerged in England, where the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) reported that in 2015 antibiotic use decreased substantially across the whole healthcare system for the first time; however, the smallest decrease was seen among hospital inpatients. Moreover, although the rate of increase in carbapenem use has slowed, between 2010 and 2015 carbapenem consumption in hospitals increased from 7.5 to 10.4 defined daily doses per 1000 admissions. This increase has been out of proportion to any rise in the number of infections caused by multidrug-resistant bacteria.<sup>7</sup>

Why is it that research into antibiotic stewardship does not yet seem to be translating into a measurable reduction in antibiotic use in hospitals? There are several possible reasons. First, findings of research studies many of which are performed in single centres may not be generalizable; the variation in antibiotic prescribing habits between countries may tell us that there is no 'one size fits all' approach to antibiotic stewardship. Sustainability of interventions is another important consideration. Studies have often been performed over a very short timeframe (usually a few months), and have not addressed the issue of maintaining a programme in the longer term against a background of rapid staff turnover (especially of junior doctors who are key antibiotic prescribers). There is also poor understanding of the behaviours around antibiotic prescribing.<sup>8</sup> We speculate that the divergence between the rises in carbapenem use and the number of infections that require an antibiotic of last resort indicate a risk aversion that is not rational. Another consideration that has been little studied is whether the move towards healthcare becoming a true 24/7 industry could have impeded antibiotic stewardship, because there is less continuity in staff care for patients; anecdotally the authors have observed this in intensive care units. Possibly laboratory tests are not being used as effectively as they could be to facilitate antibiotic stewardship. Whereas the current generation of rapid molecular tests for bacterial infections appears to have limited value in supporting antibiotic stewardship, it is not clear that we are using the tests that are already at our disposal – e.g. blood cultures, matrix-assisted laser desorption–ionization time-of-flight (MALDI-TOF) mass spectrometry, and biomarkers such as procalcitonin – as effectively as we might. Finally, consideration needs to be given to the finances of antibiotic stewardship. Most antibiotics are relatively inexpensive, meaning that investment in stewardship is unlikely to be paid back by reduced antibiotic prescribing costs alone. This point has also been made by Ryan et al., who reported that the savings in variable costs arising from effective infection prevention and control interventions are rather modest.<sup>9</sup>

We have just been awarded funding to undertake a pilot study using a mixed methodology approach to investigate antibiotic prescribing behaviours. We aim to identify the critical points in the antibiotic prescribing pathway (from the initial prescription through the reviews of therapy to the decision to discontinue therapy) for hospital inpatients where stewardship interventions are most likely to be successful. We will investigate the extent to which antibiotic prescribing decisions are driven by matters such as lack of knowledge, experience or empowerment of prescribers, organizational factors, lack of optimal access to or use of laboratory tests, or factors relating to the built environment. Our aim is to identify tangible points where stewardship interventions can be tested in subsequent randomized controlled trials.

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