Impact Objectives

- Establish a working group of experts on antibiotic stewardship and research design to determine the best way to design, analyse and report antibiotic stewardship interventions
- Formulate recommendations for the optimal design of future research in the field of antibiotic stewardship

Improving antibiotic stewardship

***Professor Martin Llewelyn** and **Dr Valentijn Schweitzer** discuss antibiotic stewardship and explain why there is an urgent need to develop recommendations for better research in this field*

Professor Martin Llewelyn

Dr Valentijn Schweitzer

Could you start by defining 'antibiotic stewardship' and explain why is it important?

ML: Antibiotic resistance is one of the greatest challenges facing the world. Bacteria are increasingly resistant to the antibiotics we use to treat and prevent common infections. Overuse of antibiotics in medical treatment is one major driver of antibiotic resistance. The term 'antibiotic stewardship' refers to using antibiotics in ways which minimises their impact on antibiotic resistance without compromising individual patient treatment – making sure that we will continue to be able to use effective antibiotics in the future. As much as 30 per cent of human antibiotic use may be unnecessary and healthcare systems around the world are aiming to achieve substantial reductions in unnecessary antibiotic prescribing through better antibiotic stewardship.

Currently, up to 80 per cent of published antibiotic stewardship studies are flawed in ways that mean their results are not robust. What are the primary reasons for this?

ML: Previous studies have not impacted practice as much as they should for two main reasons. First, many have methodological limitations. Observational studies (where we just compare groups of patients who have been managed differently) dominate this field because experimental studies (where we directly intervene to change how patients are managed) are harder to undertake. Many forms of bias are inherent in these observational studies and frequently these are not addressed as well as they could be in study design. Second, most studies just do not consider outcomes relevant to the patients being treated, both in terms of their illness and of antibiotic resistance. Instead, they focus exclusively on 'process outcomes' (e.g. does my intervention reduce antibiotic use?). Few show that this happens without detriment to treatment outcome or that it actually results in less selection for resistance.

How is your group working to help researchers overcome these limitations?

ML: We have done two things. First, we have undertaken a very broad overview of published research in this field. Where previous analyses have asked what the research tells us, we have asked what types of studies have been done and in what ways have they failed to deliver impactful findings. Second, we have brought together an international panel of researchers, statisticians and clinicians in this field. Together, we have developed a theoretical framework, a sort of roadmap, to guide the researchers designing these studies in the decisions they need to make and provide guidelines for different design features that researchers should aim to include in their studies.

How will you ensure that these recommendations translate into the real-world improvement of antibiotic stewardship trials?

VS: During the process of formulating these recommendations, we made sure to involve key opinion leaders in the field of antimicrobial stewardship. If these opinion leaders review and approve our work, it will increase the uptake of the recommendations.

Another way that real-world improvement can be achieved is if journals start considering these recommendations before considering studies for publication. Recently, the journal *Clinical Microbiology and Infection* published an editorial with the minimal quality requirements for stewardship studies. If more journals adopt this strategy, this may be an impulse for improvement and eventually the quality of the published literature on stewardship will improve. ●

A need for consensus

Overuse of antibiotics is a major problem worldwide. The ***Consensus on Antimicrobial Stewardship Evaluation (CASE) Working Group*** *aims to improve the quality of research on antibiotic stewardship and, in so doing, promote better practice*

Bacterial infections have assailed humans throughout history. In ancient times, application of mouldy bread was known to be an effective remedy for infected wounds. The antibiotic era began in 1928 when Alexander Fleming discovered the antibiotic activity of penicillin produced by the *penicillium* bread mould. During a 'golden era' of antibiotic discovery which followed World War Two, several novel, distinct 'classes' of antibiotic were discovered. Today, more than 100 different antibiotic agents are in use, but most fall into a handful of these chemically highly related 'classes': beta-lactams like penicillin, aminoglycosides, fluroquinolones, macrolides, sulphonamides, tetracyclines and glycopeptides. Antibiotics are among the most frequently prescribed medications in modern medicine and have saved millions of lives by inhibiting the growth of infectious disease-causing bacteria. Antibiotics underpin much modern medicine since treatments like cancer chemotherapy, immunotherapies and many forms of surgery are only possible because antibiotics are available.

However, bacteria have lived with humans for millennia and adapt quickly. When an antibiotic is used, strains and species of bacteria which are resistant to the effect of the antibiotic have a survival advantage.

The first Consensus on Antimicrobial Stewardship Evaluation (CASE) Working Group meeting in Utrecht, March 2017.

Emergence of antibiotic-resistant bacteria is now a critical issue in medicine. This rapid emergence of resistant bacteria has endangered the efficacy of antibiotics, posing a substantial threat to human health and placing a significant financial burden on healthcare systems.

Reducing medical use of antibiotics is one important way to reduce the selection pressure that drives resistance. Antibiotics can be overused in different ways, including prescribing an antibiotic when it is not necessary, prescribing more than one when one would be enough, prescribing broadly acting agents when more specific agents could be used, and continuing treatment longer than necessary.

IMPROVING ANTIBIOTIC STEWARDSHIP

In all these different ways, a significant proportion of antibiotics currently prescribed to patients are unnecessary. It is now clearly established that overuse of antibiotics is associated with increased risk of antibiotic resistance, both in populations and in individual patients. The challenge is how to use antibiotics more prudently but still make sure that patients get the effective antibiotic treatment they need. The term 'antibiotic stewardship' describes strategies to meet this challenge.

According to Professor Martin Llewelyn, the problem is that we do not have the evidence we need to tell us which antibiotic stewardship strategies we should be using. 'The situation arises out of very real issues with how to design research studies in the field of antimicrobial stewardship,' he explains. 'There has been an exponential increase in the number of published papers in this field of research, but the quality of these data – measured by the simple criterion of "Would it actually change anyone's practice?" – is very poor.'

Well-designed antimicrobial stewardship trials are essential to informing evidence-based practice. With this in mind, Llewelyn and colleagues from the University Medical Center Utrecht (Professor Marc Bonten, Dr Valentijn Schweitzer and Dr Henri van Werkhoven) and the University of Oxford (Professor Sarah Walker) launched the Consensus on Antimicrobial Stewardship Evaluation (CASE) Working Group. Their goal is to establish a consensus within the research world on how antimicrobial stewardship trials can be most effectively conducted. The group's work has followed three distinct stages: stage one involved the systematic evaluation of existing methodologies used in antimicrobial stewardship trials, stage two involved optimising project design to maximise impact, and stage three involved identifying key questions (for example: what is the potential for the intervention to compromise clinical outcomes?). The researchers' overarching aim is to contribute to understandings of how best to address antimicrobial resistance, improve research quality for future antimicrobial stewardship trials, and demonstrate to funders the importance of supporting these expensive yet profoundly vital studies.

The team is comprised of a highly multidisciplinary team of experts. According to Dr Valentijn Schweitzer, a coordinator in the group, this was essential. 'Even though the different disciplines (such as primary care, secondary care, critical and paediatrics) have a common goal in antimicrobial stewardship, there is not enough communication between the disciplines,' he explains. 'By using a multidisciplinary approach, we are able to learn from these experiences.' ▶

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RESEARCH RECOMMENDATIONS

From this research, some key findings have emerged. The team has proposed a novel theoretical framework for antimicrobial stewardship trials where four aspects of the intervention must be evaluated: its basis in theory and evidence, the intervention setting, the intervention features and the intervention aims. The team then proposes a series of key design questions that the researchers should answer in order to make the best study design decisions.

The final step is to set out a series of specific consensus recommendations for researchers. Already, several important insights have emerged. 'We recommend that future studies should always specify a clinical outcome to be measured to address concern that reducing antibiotic exposure might be detrimental to the patients being treated. This should sit alongside process outcomes to show that the stewardship intervention has reduced antibiotic use in the way the intervention intended,' Llewelyn reveals. 'We also set a benchmark for situations in which large, multicentre, controlled studies are not feasible but there is still a need for evidence to guide practice. Single centre observational studies have the potential to deliver valuable evidence – but only when they include properly conducted interrupted time series analysis.'

At present, the CASE Working Group is taking steps to actively disseminate its guidance, for example through conferences and publications. By exposing its findings to a wide range of scientists and stakeholders, the group hopes to make a significant economic and societal impact. With an international research team that consists of experts in the fields of clinical stewardship, adult medicine, paediatrics, statistics and implementation research, Llewelyn believes that their guidance to other researchers will be both thorough and authoritative.

SAVING LIVES

If current antibiotic practices continue unchanged, it is estimated that bacteria will continue to become more resistant so that, by 2050, antimicrobial resistance will be responsible for up to 10 million annual deaths. This rise in morbidity does not just come at tremendous human cost; it will also lead to a reduction in Gross Domestic Product (GDP) of up to 3.5 per cent, costing the world an estimated US $100 trillion. No one wants these dreadful statistics to become a reality. The only way to stop antimicrobial resistance from progressing is to adopt an effective, evidence-based antibiotic stewardship approach – a feat that requires international consensus on best antimicrobial stewardship research practices.

If the CASE Working Group's recommendations are followed, the team anticipates stronger antimicrobial stewardship studies with far fewer limitations. 'The potential impact is huge if our findings are translated into better antibiotic research,' Llewelyn states. 'The key thing for us is getting the best research done to produce the evidence clinicians need to use antibiotics precisely.' Convincing healthcare professionals to re-evaluate their views and prescription policies regarding antibiotics is an uphill battle. However, by coming together as a united front, researchers from all around the world can pave a way to stopping antimicrobial resistance growth and, in turn, save millions of patient lives. ●

Project Insights

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BIOS

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Dr Valentijn Schweitzer is a medical doctor and PhD candidate at the Epidemiology of Infectious Diseases Department of University Medical Centre Utrecht. His PhD tract focuses on antimicrobial stewardship and community-acquired pneumonia under the guidance of Professor Marc Bonten. Schweitzer is currently involved in a large multicentre trial on stewardship in community-acquired pneumonia patients. After completing his PhD, he will start residency training in clinical microbiology.

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