Combating the complex global challenge of antimicrobial resistance: what can Antimicrobial Stewardship contribute?

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Antimicrobial resistance is a major health issue and a worldwide problem. The *O'Neill report* published in 2016 analyses different aspects and provides an extrapolation of the consequences.[1] An increasing number of stakeholders are recognizing the fact that such a large and complex problem requires multiple approaches tackling it from different angles and perspectives – the *One Health approach*.[2] It is not just a problem in hospitals for medical professionals to solve. Antibiotic resistance is much more complex. It is also about over-use of antibiotics in livestock, about general over use in general practice, about unregulated access, about long-term care facilities, about frequent and easy travelling across the globe, about the pharmaceutical industry and financial incentives, both in general economy as well as in health care insurance. So many factors have a wide economic impact across all different sectors.[3] This has drawn political attention and action so as to stimulate all parties to work together towards a sustainable future from a One Health perspective.

Patients' safety against healthcare associated infections (HAI) is a key indicator of the quality of healthcare. This has been underlined recently by the first report on communicable diseases of the European Centres for Disease Prevention and Control stating that HAI without or with antimicrobial resistance [*e.g.* Methicillin-resistant *Staphylococcus aureus* [MRSA], and carbapenem-resistant *Enterobacteriaceae* (CRE)] are the most important infectious disease threat in the European Union, ranking higher than HIV, pneumococcal infections and influenza.[4] This is furthermore underlined by the recent publication of the WHO list of Top-12 organisms wherein the most critical microorganisms all are most frequent causes of healthcare-associated and less frequently community-associated infections [*e.g.* carbapenem-resistant *Acinetobacter baumanii* (CRAB)]. Within a given healthcare system, the spread of antimicrobial resistant microorganisms (AMR) is largely determined by the flux of patients through referral networks.[5] With those patients AMR are transferred, as well. It is thus crucial to take these referral networks into account when organizing measures for Antimicrobial Stewardship and prevention of AMR. This concept has led to the most recent Dutch approach of creating ten regional health care regions.[6] This concept has been also adopted on a supranational level, *e.g.* in the EU. The importance of antimicrobial resistance as a factor which increases mortality and morbidity of communicable disease for patients in European member states has been expressed by the Council Resolution (1999/C195/01) on antimicrobial resistance claiming a strategy against the threat of antimicrobial resistance. Different healthcare systems, such as the Dutch and the German are strongly divided by two totally different prevalences of healthcare-associated infections (HAI). This is difference is especially caused by AMR, such as MRSA, Vancomycin-resistant *Enterococcus faecium* or carbapenem-resistant *Pseudomonas aeruginonsa*. The EUREGIO networks *MRSA-net* and *EurSafety Health-net* (www.eursafety.eu) have shown that infections with MRSA occur up to 32 times more frequently in Germany than in the Netherlands.[7] On the other side it made clear that in the Netherlands there are up to 3 times fewer hospital-beds per 1000 inhabitants and up to 4 times fewer doctors in outpatient service, making access to health care and possibly to most antibiotics also difficult. Higher rates of death due to pneumonia in the Netherlands might be an indicator for lower accessibility to healthcare services, leading to a late diagnosis. A proper (tentative) diagnosis in turn is needed for a prudent use of antibiotic treatment, as has been also underlined by the Council recommendation (2002/77/EC).

Whilst we recognise that the link between use in livestock and agriculture on the one side and resistance in humans is still not completely understood, antimicrobial use in the livestock and agricultural sectors is several times more than is used for humans.[8] Estimates range from roughly 63,000 tons globally in 2010, rising to roughly 105,000 tons in 2030[9] to several hundred thousand tons.[10]

This issue of *Infectious Disease Reports* addresses the challenge of antimicrobial resistance from different perspectives and provides examples of different solutions that people are actively pursuing with a focus on the health care sector and sustainable use of antimicrobials. This issue focuses on the clinical (inpatient) setting where the impact of resistant infections is current greatest leading to use of last resort antimicrobials. It is this setting that also most urgently identifies the need for a balanced approach to antimicrobial resistance- supporting innovation through developing new antibiotics and preservation of existing antimicrobials- antimicrobial stewardship. Antimicrobial stewardship programmes (ASP) immersed in a model that integrates appropriate and timely diagnostics and an optimal infection prevention and control programme perhaps is an effective model for optimising the clinical response to drug resistant infection in this setting.[11] Adaption of such a model is clearly important and dependent on local resources, geography, cultures and healthcare systems.

ASPs usually comprise bundles of interventions designed to increase prudent use of antimicrobials by a range of restrictive and persuasive methods including guidelines, pre-authorisation, review, audit and feedback, supported by education and incentives.[12] Core stewardship interventions are local guidelines and education. The importance of educating the multi-professional healthcare team in delivering antibiotics effectively and safely is critical. Rocha-

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Pereira *et al*. provide an overview of a range of traditional and novel educational methods currently employed to support stewardship.[13] In order to provide the correct and treatment, identifying the organism through better use of existing and novel diagnostics is vital. Indeed, establishing a correct diagnosis is one quality indicator for optimal treatment. Maurer *et al*. show an overview of new techniques that are being developed right now and discuss the impact of those diagnostic modalities on ASPs.[14] Furthermore, the systematic review of Kallen and Prins looked at quality indicators described in the literature and provide an overview.[15] Such indicators are important when establishing an ASP and as a means of evaluating its impact over time. If all is in place and an institution is able to provide optimal antimicrobial therapy, the effects will differ for each patient. One striking example of the impact of this treatment is in the case of bloodstream infections (BSIs). Without proper and timely action, a BSI can be fatal for the patient. Therefore, there has been a strong focus on providing the correct treatment with antimicrobials for patients with BSIs. Coulter *et al*. provide an overview of the literature published on this topic.[16] Besides the rather evident clinical impact of optimal antimicrobial use, there is also a strong economic impact. It is important to consider this when implementing an ASP in an institution. As this special issue of IDR shows, a Stewardship for infections consists of many aspects and many different people involved during the whole process of infection management. Technical support is thus an important aspect. A wide range of eHealth tools exists to support healthcare professionals in their tasks. Beerlage-De Jong *et al.* review these tools and their impact during the implementation of an ASP.[17] A systemic perspective is highly important for a useful financial evaluation of any intervention. Dik *et al*. show aspects of a sustainable financial implementation of an ASP.[18] Over the years, there are numerous publications of studies regarding the financial impact of ASPs. Oberjé *et al.* provide some best practices from different European studies, showing that there are already interesting publications that describe a positive financial impact.[19] Finally, coming back to the One Health approach, the economic impact can be seen at an even bigger scale, including also *e.g.* the costs of the development of new antimicrobials. This is an issue that still is not solved completely. Theuretzbacher *et al.* provide more insight into this important topic.[20] Showing that this problem is too big to approach from just the hospital or clinical perspective.

To optimally address the global challenge of increasing antimicrobial resistance major, coordinated efforts are required. They need to involve all stakeholders, *i.e*. patients, healthcare providers (both for inpatients and outpatients), scientists, healthcare insurances, pharmaceutical industry, agriculture/livestock, sewage and garbage facilities, regulatory institutions, and politics. All stakeholders need to collaborate in order to halt antimicrobial resistance development and spread. This issue aims at providing insights and viewpoints regarding this goal.

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