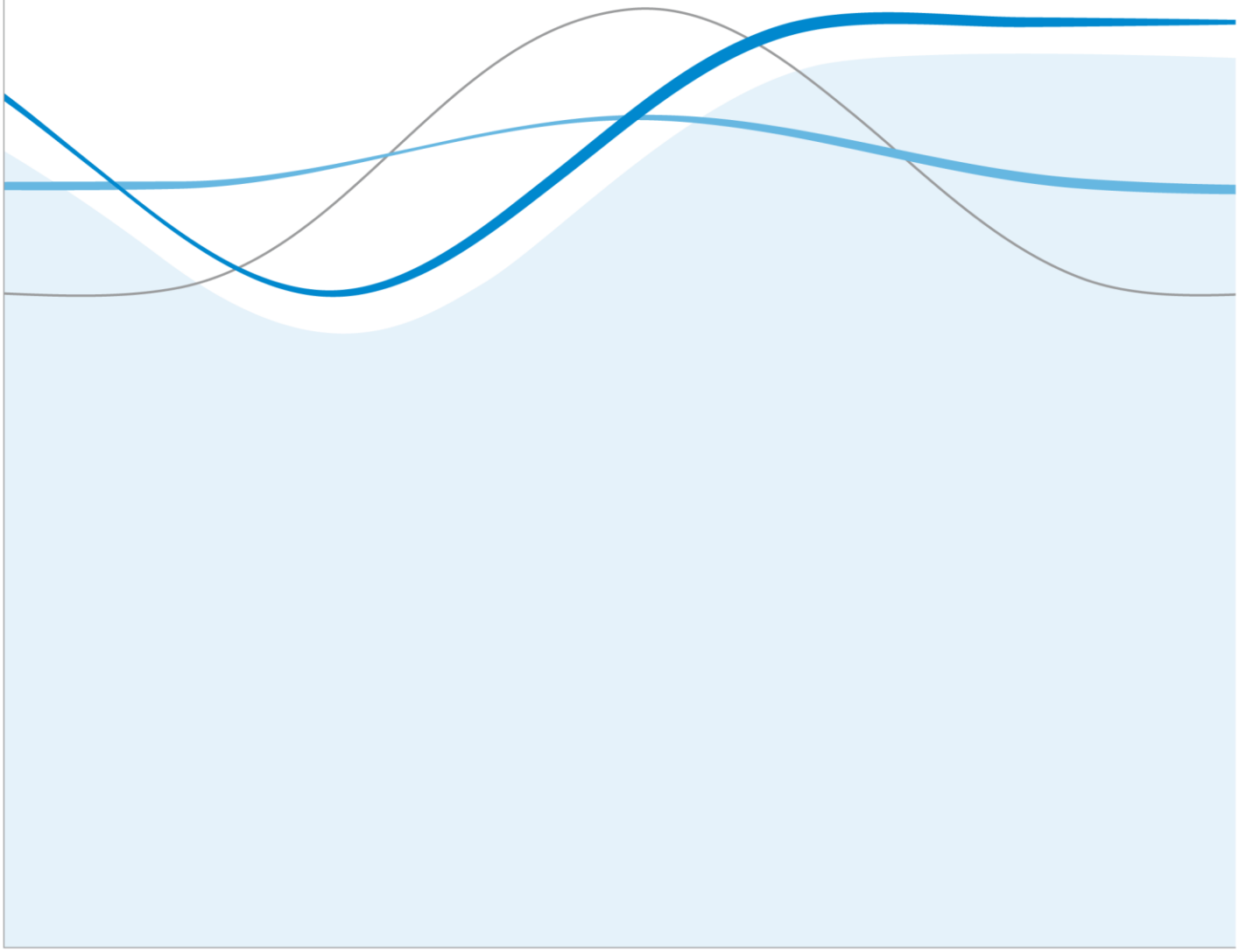
Office of Health Economics Consulting

HTAi Symposium Briefing

Antimicrobials Resistance: A Call for Multi-disciplinary Action. How Can HTA Help?

October 2017

Margherita Neri and Adrian Towse



Antimicrobials Resistance: A Call for Multi-disciplinary Action. How Can HTA Help?

A Summary of a Symposium held at HTAi Rome 2017

Margherita Neri[a] and Adrian Towse[a]

[a]Office of Health Economics

October 2017

Submitted by:
OHE Consulting Ltd
(a registered company number 09853113)
Southside, 7th Floor
105 Victoria Street
London SW1E 6QT
United Kingdom

For further information please contact
Paula Lorgelly
Deputy Director and Director of Consulting
Tel: +44(0)20 7747 1412
Or: +44(0)7789 435 855
plorgelly@ohe.org

About OHE Consulting Reports

Many of the studies OHE Consulting performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications.

Funding and Acknowledgements

This study was funded with an unconditional grant by Angelini Pharma SpA.

Table of Contents

EXECUTIVE SUMMARY

The term antimicrobial resistance (AMR) refers to the ability of microorganisms to change and start resisting antimicrobial drugs, which therefore become, over time, ineffective. Resistant microorganisms that are immune to antimicrobial treatments can colonise and spread infections to other individuals. The AMR problem poses a global threat in terms of our ability to treat infections, to perform medical treatments that are made safe by the use of antimicrobial drugs, and to avoid increasing costs to the healthcare system.

AMR is in part a natural phenomenon but its growth has been accelerated over time by different causes that now exert a cumulative effect. On the one hand bad practice favours the spread of infections, such as overuse of antibiotics in human and veterinary care, and poor prevention and hygiene practices. On the other hand, the scarcity of new treatments, both recently launched as well as in pharmaceutical industry development pipelines, reduces the chances of treating AMR effectively in the future.

The solution to bad practice nature should come from stewardship and prevention programmes. These should include practical actions such as:

- Cooperation and coordination across countries in identifying what works and in ensuring national plans are put in place and implemented;
- Improved awareness and education programmes for all stakeholder groups affected by AMR (professionals and patients), to avoid preventable infections;
- Strong monitoring systems to keep under surveillance the infection and the colonisation rates, as well as trends in antibiotics consumption.

The gains from programmes of this type are shown in the case of the 'Zero Tolerance' projects in Spain. In the hospital context, these projects have educated professionals on prevention practices and monitored the rates of infection and antibiotic consumption, thus succeeding at reducing the colonisation and infection rates of resistant pathogens. More generally, political involvement and support from international organisations will be crucial to ensure that strategies can work.

The slowdown in the R&D of antimicrobial drugs is explained by scientific challenges, regulatory and clinical factors, and economic factors. This is explained, respectively, by difficulties in the discovery of antibiotics, the difficulty of generating pre-launch data on clinical superiority and the limited returns from investment in antibiotics. In addition, current HTA/ payer methods fail to capture the full value of new antibiotics because they do not assess the impact on public health or on the growth of AMR. In order to ensure that novel antibiotics that can deliver such value are developed, and gain market access, the spectrum of elements considered by HTA bodies should extend beyond health gains, unmet need, cost offsets and productivity benefits. More specifically, it may be worth including additional dimensions of value such as: insurance value (treatment availability in case of catastrophic event), diversity value (using different antibiotics to preserve the efficacy of each drug), value of an available diagnostic (to speed up starting on the right therapy), innovation value (value of new mechanisms of action), enablement value (protecting the safety profile of surgical and other procedures that rely on the use of antibiotics) and spectrum value (narrow spectrum antibiotics are regarded as more effective). Improvements in HTA approaches will be more likely with collaboration between HTA bodies/ payers and with international organisations.

1. INTRODUCTION

Antimicrobial resistance (AMR) is a medical threat and challenge for the world because of the potential lack of medicines which could effectively contrast it in the future. As resistance to existing treatments grows, introducing new treatments within our healthcare systems will be increasingly important in order to tackle multi drug resistant (MDR) pathogens. The optimal assessment of antibiotics becomes a key challenge for payers and health technology assessment (HTA) bodies. They may have to modify their approaches to make sure the full benefits that antibiotics provide to patients and society are taken into account.

This briefing summarises an AMR symposium held on Monday June 19 at the HTAi 2017 annual meeting in Rome. The structure of the briefing is as follows:

- Section 2 summarizes the presentation by Dr Roman S. Kozlov on the role of antimicrobial stewardship programmes and the implementation of AMR surveillance;
- Section 3 sets out the evidence of the 'Zero Tolerance' programmes in Spain as presented by Dr Mercedes Palomar Martinez;
- Section 4 outlines the presentation by Dr Paola Testori on the fight against AMR from the Italian and European perspectives;
- Section 5 summarizes recommendations by Professor Adrian Towse on improving the HTA approach for antibiotics;
- Section 6 concludes with recommendations from Dr Krzysztof Landa and key remarks from the panellists.

2. ANTIMICROBIAL STEWARDSHIP PROGRAMMES AND AMR SURVEILLANCE IMPLEMENTATION

Roman S. Kozlov, Chief Specialist for Clinical Microbiology and AMR Programmes, Ministry of Health, Russia

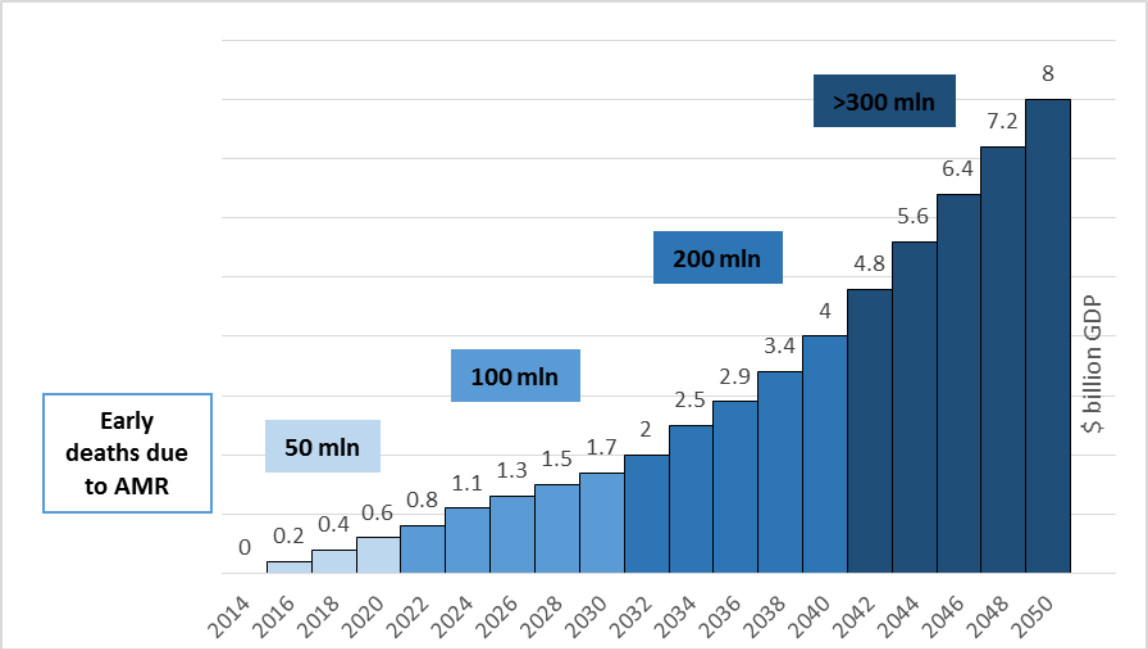
Dr Kozlov opened the symposium with an overview of the AMR issue and future challenges from a global perspective. He provided 'stewardship' guidelines, setting out the programmes and policies that should be implemented in the near future to tackle AMR effectively.

The impact of AMR

AMR is an issue of global reach concerning both the developed and the developing world. Assuming that AMR will continue to grow at the current rate, the global burden in terms of annual GDP loss is projected to reach $8 billion in 2050, with a cumulative loss of more than $100 trillion from now until 2050 (O'Neill, 2014). Converting these monetary figures to the number of premature deaths accumulated over the years until 2050 indicates a cumulative total of more than 300 million worldwide (Figure 1). At the continental level, the AMR threat shows different degrees of severity, with North America, Europe and Oceania at the lowest end of the mortality rate scale (5 per 10,000 population) and Africa at the highest (>10 per 10,000 population). However, even in the case of Europe, the total annual number of deaths due to AMR in 2050 is estimated to reach 390,000, as compared with 25,000 per annum now.

Several medical interventions that are supported, and made safe, by the use of antibiotics would become more risky to perform. Medical interventions like caesarean deliveries, joint replacements, cancer drugs and organ transplants, contribute collectively to around 4% of the world's GDP, which risks being undermined by the advance of AMR if we stopped doing them.

Figure 1. AMR impact on world's GDP and mortality



Source: Adapted from O'Neill (2014)

Dealing effectively with AMR requires us to consider health under a single umbrella term, encompassing public, human, veterinary, environmental, ecological, molecular and microbiological components.

Steps and initiatives to solve the problem

Solving the AMR problem requires strategies of a broad scale translated into initiatives in each national policy on antibiotics.

Among the actions of broader reach we find a mixture of scientific research (e.g. the development of new drugs or alternative treatments, or methods for AMR detection based on diagnostics using genetic imaging) and support from international organisations, private charities, and partnerships between the public and the private sector. A notable example is represented by the WHO plan on the fight against AMR, which was signed in 2014 by 194 countries worldwide. The recommendations that each country should follow include:

- The need to optimise the use of antibiotics in both the developing and the developed world, through improved sanitation programmes and control of hospital infections;
- The improvement of education and awareness of all stakeholder groups affected by AMR (health professionals, policy makers, public) on sustainable consumption and incentives to contain antibiotic use;
- Ensuring political commitment against AMR.

In order to ensure that countries accomplish these objectives, they will need 'AMR stewardship' programmes, namely "organizational or healthcare-system-wide approaches to promote and monitor judicious use of antimicrobials to preserve their future effectiveness" (NICE, February 2015). An optimal AMR stewardship programme needs at least five components:

1. Strategy and key developments. There are several examples in the literature providing strategic guidelines to AMR stewardship programmes (Shlaes et al., 1997; MacDougall and Polk, 2005; Dellit et al., 2007; Cruickshank, 2011; Ashiru-Oredope et al., 2012; MacKenzie et al., 2007). According to File Jr, Srinivasan and Bartlett (2014), for example, a stewardship strategy should follow the objectives of optimization of patient safety, improvement of clinical outcomes, reduction of resistance, combined drug intoxication and toxicity and control of costs.
2. Surveillance of antibiotic resistance and consumption, in an optimal combination of quantity and quality.
3. Metrics indicators for improvement and scrutiny, which enable a close assessment of the overall performance.
4. Training of healthcare professionals. Education programmes should be multi-professional and span across health communities, while benefiting from a variety of learning resources, particularly those available online that offer high impact at low cost (e.g. APIC, 2014; NHS Education for Scotland, 2015; Future Learn, 2017).
5. Translate the strategy into practical action in bedside care by means of data that can improve scrutiny and engagement.

Once the stewardship programmes have been defined, it is important that the political commitment is in place to provide support in multiple ways. In Russia for example, the Institute for Antimicrobial Chemotherapy of the Smolensk State Medical University, supported by the Ministry of Health of Russian Federation, has been leading research on AMR. Initiated in the 1990s, this work benefited from a number of governmental grants, and has achieved improved adherence to stewardship programs across all the regions of the country.

In conclusion, because AMR is a global threat, a unified effort must soon be taken towards the execution and evaluation of stewardship programmes. Political involvement has to play a crucial role in ensuring that all recommendations are followed. Local experiences, needs and culture should also be taken into account to ensure flexibility in implementation.

3. ZERO TOLERANCE PROGRAMMES IN SPAIN: FACTS, FIGURES AND OUTCOMES FROM THE ENVIN-HELICS DATABASE

Mercedes Palomar Martinez, Head of Intensive Care Unit, Hospital Arnau de Vilanova, Spain

Dr Palomar presented the main results of the Zero Tolerance programmes that aim to reduce the spread of Spanish hospitals' infections within intensive care units (ICUs).

Bacterimia Zero and Neumonia Zero

The first project to improve the behaviour of healthcare professionals and reduce the incidence of infections acquired in ICUs was implemented in a group of Michigan (US) hospitals in 2004 and targeted catheter-related bloodstream infections. With a significant reduction in the incidence of this infection rate within 3 months, patients were able to benefit almost immediately from the intervention (Pronovost et al., 2006).

A joint collaboration of the World Health Organization (WHO), the Spanish Ministry of Health, Social Policy and Equality (SMoH) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), aimed to replicate the initiative in Spain in 2009. The new programme, named Bacterimia Zero (BZ), was adapted to suit the organizational and cultural characteristics of the Spanish health care system, while the fundamental principles of engagement, education, execution and evaluation were preserved from the Michigan experience. The programme benefited from a solid organisational structure based on national and regional leadership, institutional support, and a consolidated surveillance network provided by the 'Estudio Nacional de Vigilancia de la Infección Nosocomial -Hospitals in Europe Link for Infection Control through Surveillance' (ENVIN-HELICS) database. The ENVIN-HELICS registry is a database created in 1994, which now aggregates annual data from more than 200 monitoring centres on ICU acquired infections (ICU-AI). As opposed to single interventions that are considered less effective in isolation, the programme introduced a bundle of evidence-based clinical practices, which had been missing from the culture of the Spanish ICUs until then. Immediate results from the BZ project showed that the incidence of ICUs infections decreased by 50% in all hospitals, regardless of their size and type (e.g. academic, non-academic) (Palomar et al., 2013).

Drawing from the positive experience of BZ, the Neumonia Zero (NZ) project used the same organisational structure and introduced a new bundle of clinical procedures and practices, in order to prevent ventilator-associated pneumonia (VAP) acquired in ICUs. The NZ also proved highly successful at reducing the rate of VAP ICUs acquired infections: from 10 to 6.9 VAP per 1000 days of MV (acronym to follow) (ENVIN-HELICS, 1999-2014). Available estimations on the impact of BZ and NZ suggest that the interventions have had a positive impact on reducing hospitalisation, mortality, and costs to the healthcare system. This evidence gave empirical support to the importance of implementing this type of programme across the whole country.

Zero Resistance

While initiatives like BZ and NZ were successful in decreasing certain targeted types of infection, infections rates related to MDR pathogens have been growing. Figure 2 shows the increasing number of patients being admitted in hospitals with resistant AMR after 2006.

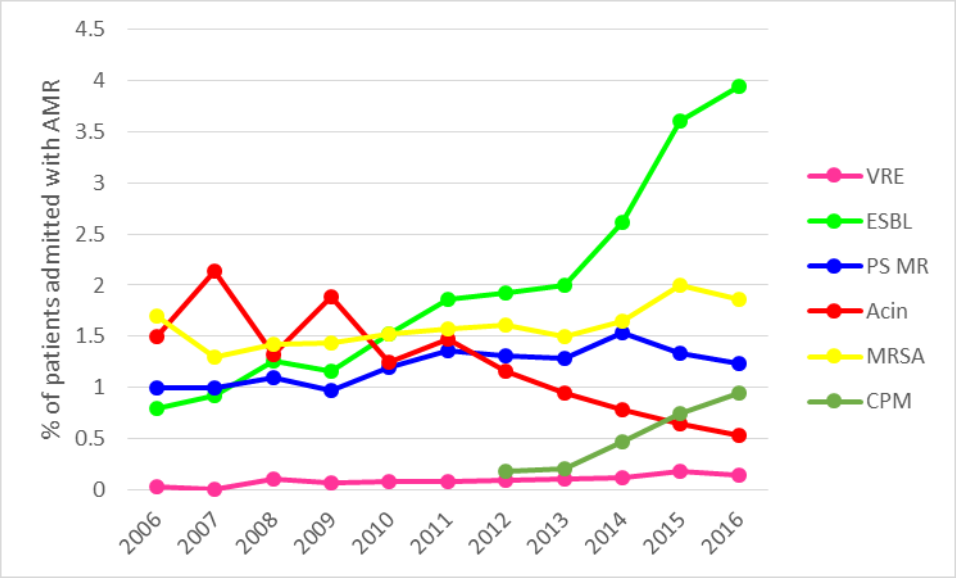
Having gained solid experience with BZ and NZ, the next step was to develop another 'bundle package' programme within the Zero Tolerance framework in ICUs, the Zero Resistance (ZR) intervention. The issues tackled by the ZR were: the level of prescription of antibiotics; the early detection of colonization of MDR pathogens, particularly on individuals at risk; implementation of prevention measures both daily and in the elimination of reservoirs of infections.

The 10 recommendations of the ZR are:

1) Presence, in each unit, of at least one intensivist, with experience in infection prevention, responsible for the use of antimicrobials;

2) Administer antimicrobials empirically against MDR pathogens only in case of severe sepsis or septic shocks, and, where a high risk of MDR pathogens is likely, based on patient risk factors and/ or the knowledge of local ecology. Early therapy in these patients increases survival;

Figure 2. Infection/ colonization rates of multidrug resistant (MDR) bacteria



Source: ENVIN-HELICS (1999-2014)
Note: Acin = Acinetobacter; Ps MR = Multi resistant Pseudomonas aeruginosa ; ESBL = Extended-spectrum beta-lactamase; MRSA = Meticillin-resistant staphylococcus aureus; VRE = Vancomycin-resistant enterococci; CPM = Carbapenemases

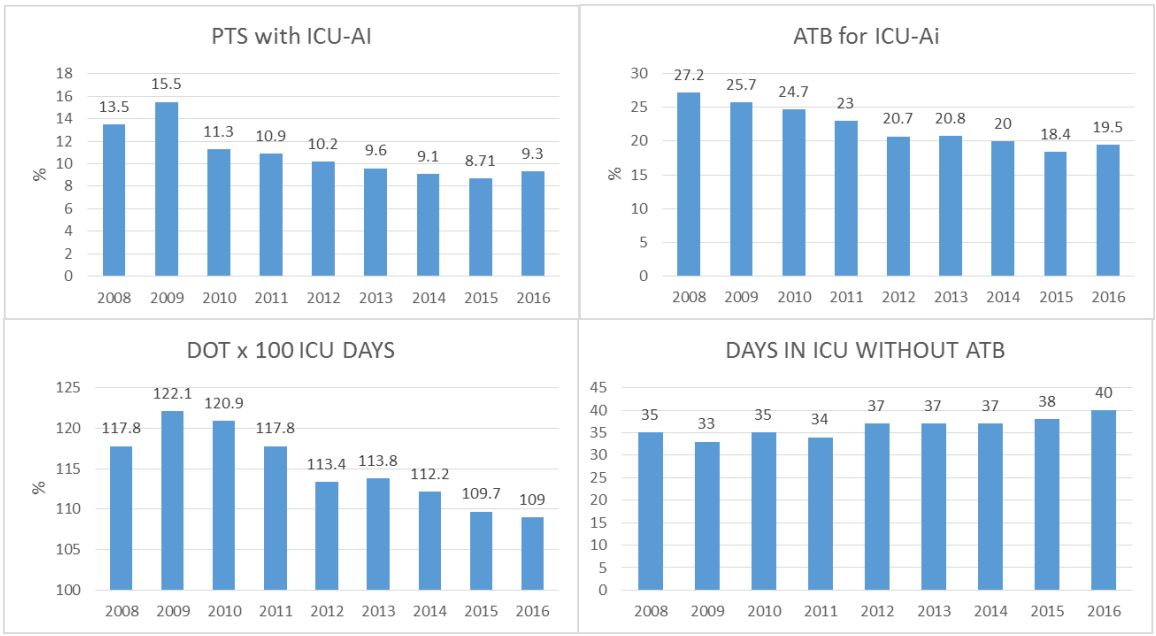
3) Identify, in each unit, a lead nurse responsible for infection control measures established to reduce transmission of MDR pathogens;
4) Perform an active search for the presence of MDR pathogens in all patients admitted to the unit and at least once a week throughout their stay;
5) Complete a 'checklist' at admission of patients to the ICU in order to identify those at high risk of carrying MDR organisms. Patients with one or more risk factors should be isolated pre-emptively by the application of contract precautions;
6) Comply with prevention measures, including those based on transmission mechanisms that should be systematically monitored (e.g. hand hygiene);
7) Develop a protocol for cleaning rooms occupied by patients with MDR pathogens (daily and also at patient discharge);
8) Create and update a file/ document specifying the existing clinical and technological material in the ICU and the cleaning protocol;
9) Introduce products containing 4% chlorhexidine in the daily hygiene of colonized/ infected patients with MDR micro-organisms;
10) Identify the causative organism with molecular genotyping methods if an outbreak is suspected;

The ZR targeted the MDR pathogens that had shown greatest resistance to antibiotics, from the Gram-positive (Staphylococcus aureus (MRSA) and Enterococcus) and Gram-negative classes (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter aumannii).

The ZR outcomes suggested that the rates of detection of MDR pathogens increased after 2014 in the ICUs where the programme was implemented, while the ICU-AI rate decreased. Additionally, it appeared that both detection and prevention of MDR pathogens was greater in the ICUs where ZR was adopted, compared to the ICUs with no ZR.

Figure 3 provides a perspective on the achievements of the programmes under the Zero Tolerance framework during the years of its implementation. Cumulatively, all the programmes have contributed to the gradual reduction of ICU-AI, with the largest improvement coming immediately after the introduction of BZ. This trend goes in the same downward direction, and at a similar rate, as the percentage of antibiotics used in ICU-AI. Another relevant and promising result of the programmes is the steadily increasing number of days spent by patients in ICUs without taking antibiotics.

Figure 3. Outcomes from BZ, NZ and ZR



Source: ENVIN-HELICS (1999-2014)
Notes: PTS = patients; ATB = antibiotic; ICU-AI = intensive care unit acquired infection; DOT = antibiotic days of treatment

The success of the Zero Tolerance programmes is observed through reduced rates of catheter-related infections, VAP, and ICU-AI by MDR. These have translated into considerable health care savings thanks to the high participation rates (70% of the ICUs) of hospitals. In other words, these results demonstrate the potential for hospital level interventions to reduce the spread of bacterial infections. However, long term improvements will depend on a culture founded on safety, prevention, training and education of health care professionals that will permanently change their approach towards a more teamwork- and evidence-based decision making. While high surveillance

will be needed to monitor the interventions, the stability of the whole programme will also rely on technical support and financial resources.

4. FIGHT AGAINST AMR. AN ITALIAN AND EUROPEAN PERSPECTIVE

Paola Testori Coggi, President, P&R committee, AIFA, Italy

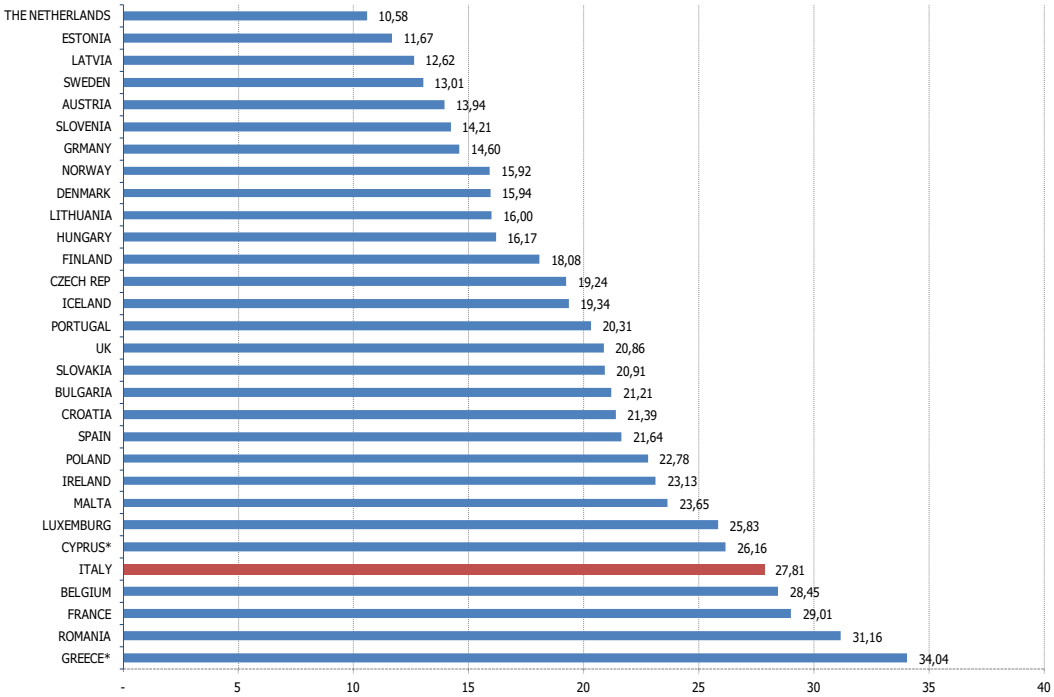
Dr Testori set out a description of the causes and social-economic consequences of AMR worldwide, using Italy as an example of sub-optimal consumption of antibiotics. After comparing global objectives for a successful fight against AMR with current European level activities and plans, she gave recommendations for an innovative HTA approach to appraise new antibiotics.

Trends in AMR and the Italian case

At the origin of increasing levels of AMR are a number of factors that have persisted over time generating a cumulative negative impact. First of all, there is a tendency to use antimicrobials inappropriately both in human and veterinary medicine. Secondly, innovative antimicrobial medicines are scarce both in the pharmaceutical market and in the development pipeline of the industry. Finally, poor prevention and hygiene practices aggravate the dispersion of infections. Examples of the medical areas threatened by the diffusion of antibiotic resistant pathogens are infectious diseases (e.g. pneumonia, tuberculosis), cancer, HIV/ AIDS and surgical procedures that are considered low-risk because they are currently supported by effective antibiotic treatments.

The present impact of AMR can be seen in both mortality terms, with over 25,000 deaths in Europe and 700,000 worldwide, and in economic terms, with over €1.5 billion of healthcare costs and productivity losses in the EU alone. Projections of the corresponding 2050 figures, if current rates of resistance continue, are alarming (European Commission, 2016).

Figure 4. Antibiotic consumption (DDD/1000 inhabitants)



Source: European Surveillance System (TESSy)
Notes: *Total use, including hospital consumption; DDD= Defined daily dose

Current trends are not reassuring: a large fraction of antimicrobials is being consumed by animals and the global share of consumption by livestock is projected to increase to 67% by 2030. Only 25% of countries worldwide are equipped with a national policy to tackle AMR and less than 40% have an active programme to prevent infections. Figure 4 shows the significant variation in the use of antibiotics across European countries, indicating the lack of a unified global strategy.

In a context where cross-country coordination on global policies is missing, Italy has not adequately addressed the levels of antibiotics consumption. This is despite the presence of a monitoring database collecting data at national and regional levels on pharmaceutical consumption, distinguishing between therapeutic categories and single active ingredients (Italian Observatory for Pharmaceutical Use, OsMed). A closer observation of the consumption patterns of antibiotics across the country reveals differences in use according to region, age and sex. Total consumption of antibiotics is highest in the southern regions (Campania, Puglia and Calabria), whereas the picture is reversed in the case of out-of-pocket consumption in the northern regions. This suggests that private consumption may be less well controlled in the north. Antibiotics consumption tends to be concentrated in the population aged below 4 and above 64 and more in women than in men. Recent years have witnessed a promising decrease in the inappropriate use of antimicrobials, particularly in acute respiratory infections and uncomplicated acute infection of the lower urinary tract, but, overall, rates remain high.

Good practice in the fight against AMR

Further steps must be taken to fulfil the global policy agenda. Areas of improvement involve:

1. Cooperation and coordination across countries and health areas: AMR is a 'cross-border health threat affecting human and animal health, as well as the environment.
2. Strong monitoring of antibiotic consumption globally in animals and in humans through specific databases such as the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) and the Epidemic Intelligence Information System.
3. Prevention and promotion of measures to reduce the occurrence of preventable diseases. Vaccines should be equally available and accessible across the population, while education and training programmes for healthcare professionals on the prevention of infections should be implemented. Provision of medical assistance should be made available to stop the spread of tropical and neglected diseases that are starting to emerge because of unprecedented migration of refugees and internally displaced persons, particularly in Southern Europe.
4. Promotion of collaborative research and public/private partnerships. Incentives for research in antimicrobials should also come through tax exemptions for the early stages of product development, particularly for rapid point-of-care diagnostic tests.

In the face of this broad approach, the European Union has started taking the first steps towards a new approach against the AMR threat. In terms of initiatives promoting cooperation, the newly created One Health Action Plan on June 29th 2017 and the related network of AMR experts will support member states in the fight against AMR. In order to monitor the levels of inappropriate consumption, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Strategy 2016-2020 provides guidelines on collection of data on sales and use in animals and humans. New guidelines on prudent use of antimicrobials and prevention of infections will also be created, along with new legislation on veterinary medicines and health. Antimicrobial research is expected to benefit from the Innovative Medicine Initiative (IMI), promoting a more collaborative research environment towards the understanding of the underlying causes of AMR and antimicrobial discovery. Horizon 2020 has also devoted €1 million to diagnostic development for respiratory diseases, specifically on the development of a diagnostic test for infections treatable with antibiotics.

At present, antibiotics are assessed through a traditional value-based HTA methodology that considers therapeutic need, added value, budget impact and impact on health care system and social costs. New antibiotics are also eligible for an accelerated procedure for pricing and reimbursement (100 days), and may involve 'exceptional relevance' for social impact and also address high therapeutic need. In light of the scale of the AMR problem, the criteria for an optimal HTA should go beyond those currently considered. In particular, extra value should be awarded to antibiotics that prevent transmission of infectious diseases, weaken AMR or introduce innovative elements of action.

5. TOWARDS A VALUE FRAMEWORK FOR ANTIBIOTICS

Adrian Towse, Director, Office of Health Economics, UK

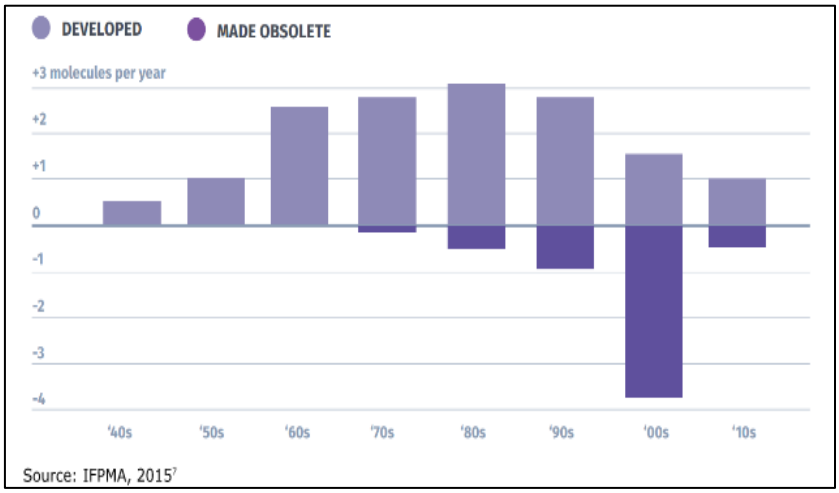
Professor Towse started the discussion with some background information about the challenges faced in the development of new effective antibiotics. Building on the recommendations of Dr Testori, he also discussed the reasons for the need for an

expanded HTA methodology, which currently does not include all potentially relevant dimensions of value. The elements of the presentation reflect the findings of a February 2017 Value Forum jointly organised by the Office of Health Economics (OHE) and the Academy of Infection Management (AIM), which focused on the identification of the relevant elements of value for new antibiotics for patients, payers and society (Karlsberg Schaffer et al., 2017).

The challenges for new antibiotics development and HTA

The past 30 years have witnessed a continuous fall in new antibiotic development. The availability of new antibiotics in the future may not grow at a fast enough rate to replace the obsolescence caused by the build-up of resistance.

Figure 5. Average number of new antibiotic molecules per year



Source: IFPMA, 2015

The first reason for this is of a scientific nature. The discovery and development of new antibiotics is becoming increasingly harder. As an example, the success rate for the development of new antibiotic high-throughout-screening (HTS) is four to five times lower than that of other therapy areas. From the economic perspective of the pharmaceutical industry, investments in novel antibiotics provide limited returns because the current 'price x volume' business model does not provide research incentives. Patents have expired before R&D costs can be fully recouped. At the regulatory and clinical level, the development of new antibiotics is hindered by the suboptimal design of clinical trials from an HTA perspective. Clinical superiority is difficult to prove, and the evidence available at launch does not reflect all of the expected utility of the new product. In addition, current HTA frameworks fail to capture the full breadth of benefits of new antibiotics, mainly because they do not assess the separate impact on public health of tackling the rise in AMR, over and above the immediate benefit to the patient.

Some European jurisdictions are trying to include and consider more value factors: France is giving a 5-year EU price guarantee to antibiotics that achieve an ASMR IV level (minor improvement compared to standard of care), while other, non-antibiotic, treatments are required to achieve at least an ASMR III level (significant therapeutic improvement) to qualify for a price premium over and above the prices of current therapies; in 2016, Germany proposed legislation to introduce new HTA measures to address AMR; the UK and Sweden both have a government-industry dialogue to create a new framework to evaluate antibiotics; the Italian Medicines Agency (AIFA) is looking at

the best way to pick up AMR in its HTA framework, as Dr Testori set out. In general, HTA for antibiotics should be adapted with respect to (i) value factors that capture benefits beyond patients treated, such as positive externalities on the success of other types of treatment, and (ii) the evidence requirements (to allow the acceptance of non-inferiority trials supplemented by evidence from non-clinical and microbiology data).

Additional elements of value of antibiotics

Error! Reference source not found. summarises the elements of benefit included in traditional HTA and other types of benefit of possible relevance to antibiotics.

Figure 6. Elements of Value Relevant to Antibiotics

Relevant benefits included in traditional HTA	**Other types of benefit of possible relevance to antibiotics**
Health gain	Insurance value
Unmet need	Diversity value
Cost offsets	Diagnostic value
Productivity benefits	Uniqueness or innovation value
	Enablement value
	Spectrum value

Among the type of benefits traditionally included in HTA we find:

1. Health gains in terms of both extension in life expectancy and improved quality of life. These are traditionally the main elements of value leading to successful HTA recommendations. New antibiotics struggle to demonstrate these because superiority is rarely achieved in clinical trials.
2. Unmet need, defined jointly by severity of the disease and availability of alternative treatments. This can be demonstrated using priority pathogen lists.
3. Cost offsets, based on the reduction of costs in other medical areas when a new medicine is made available. These can be shown with modelling studies or evidence from clinical trials.
4. Productivity benefits, corresponding to gains/ losses from the time spent receiving medical care or being unable to work. These can be estimated through modelling studies and evidence from clinical trials and observational studies.

The other benefits of possible relevance to antibiotics, not accounted for in typical HTA, are:

5. Insurance value, corresponding to having a treatment available in case of a catastrophic event, such as an outbreak of MDR pathogens that cannot be contained with existing drugs. According to the 'precautionary principle', having more options available to address the same risk can add to the overall insurance value.

6. Diversity value, which appears particularly important in the case of antibiotics because one antibiotic can only tackle a limited number of pathogen species, enabling the resistant pathogens to survive and proliferate (selection pressure). In relation to this, the 'selection pressure' can be attenuated if different antibiotics are used in different periods because the efficacy of the drugs can be preserved.
7. The value of an available diagnostic, which can speed up the diagnosis of the disease and allow an earlier start with the current antibiotic therapy. Arguably, this can be reflected in an HTA review of the diagnostic.
8. The uniqueness or innovation value, corresponding to the value of a new mechanism of action (MOA), has the potential to avoid problems of cross-resistance among classes and pave the way to the market for 'follow on' products which provide 'diversity' benefits. (It will be important not to double count these effects.)
9. The enablement value, which corresponds to protecting the safety profile of surgical procedures that rely on prophylactic or post-operation antibiotic interventions, and helping people whose treatment will leave them with compromised immune systems.
10. Spectrum value, because an antibiotic that covers a narrower spectrum of pathogens may be more valuable than one that targets a broader spectrum. Narrower spectrum antibiotics could for example prevent the 'collateral damage' to the microbiome and ultimately reduce the build-up of AMR.

It is important to note that some of these extra elements of value are not unique to antibiotics and may apply to the assessment of products in other medical areas, like the 'transmission value' in vaccines. The evidence may come from modelling studies, or by exploring the attitude of decision makers or the public towards risk. In general, it seems that the new dimensions could be integrated into existing frameworks with no need for completely new methods. Multi-criteria decision analysis (MCDA) or discrete choice experiments (DCEs) may represent a viable option to take into account an increased number of value dimensions in decision making. Alternatively, the new dimensions could be translated into standard HTA metrics, such as QALY equivalents.

In summary, the main message delivered by the OHE-AIM Value Forum was on the need to redefine existing frameworks by considering other potentially important dimensions of value. We also need to develop new payment systems for new antibiotics that would provide some reward to manufacturers even if sales volume during the period of patent protection was low. Additional thinking will be necessary to integrate new elements with the current approach. Such changes will only be possible in a collaborative environment of improved awareness of the importance of new antibiotics. This may require the engagement of international organizations, like the OECD and EUnetHTA.

6. SHARED PERSPECTIVES AND DISCUSSION

The last speaker of the symposium was Krzysztof Landa (Board of the National Centre for Research & Development, Poland), who concluded the session with some remarks on the preceding presentations.

He highlighted that the discussion around approaches to tackle AMR had been shaped by two main flows of ideas. First, the need to understand the rate at which AMR will grow in the future and how governments should respond to tackle AMR in the best way. It is

essential that obsolete antibiotics are displaced to save money and make room for the adoption of innovative and effective treatments. Educational programmes dealing with the 'behavioural' issue around prevention of infections and overconsumption of antibiotics are essential to stop the AMR growth, and they should involve both healthcare professionals and patients. The Spanish experience of the Zero Tolerance programmes, implemented at hospital level, proved that this type of programme can be successful and impactful when closely monitored. More collaborations, recommendations and surveillance at the European level are desirable.

The second issue relates to the new generation of antibiotics, and the approach that HTA bodies and payers will use to assess and reimburse them. Because R&D is usually driven by unmet medical need, and efficacious antibiotics currently exist for the majority of patients, future antibiotics are likely to target smaller patient populations that do not respond to available treatments. In other words, the focus of pharmaceutical research on antibiotics will be on the 'hardest' patients, whose conditions are rarer than average. In the case that these new antibiotics will be registered as orphan drugs, traditional HTA approaches that are based on economic evaluation may have to adjust in favour of more egalitarian approaches that value the reduction of health inequalities. Therefore, he argued, the HTA outcome should not be determined on the basis of cost-effectiveness thresholds alone. Market access bodies will have to ensure that the prices of antibiotics targeting smaller patient populations that are harder to treat, can adequately reward the investment in research. At present, the Polish system is using an egalitarian approach for the assessment of orphan medicinal products, including 'orphan antibiotics', and accepting high prices if efficacy is proven for a given condition. This has been made possible by the 'Drug Programmes' that provide separate budgets since 2005 for expensive drugs and for some antibiotics. In fact, even though economic analysis is required and assessed against a cost-effectiveness threshold (3xGDP/person/QALY in Poland), many orphan drugs are covered even if they do not meet this cost-effectiveness requirement.

In addition to the particular shape of the market for future antibiotics, the impact on AMR is another reason for assessing antibiotics with a different approach. When measuring the cost of new antibiotics, HTA bodies should include the reductions in future public spending from challenging the spread of AMR. Additionally, a dynamic HTA assessment would enable HTA bodies to take into account the changing value of antibiotics over time due to the development of MDR pathogens.

The final part of the discussion highlighted three main difficulties emerging in the choice of the optimal comparator for antibiotics HTA. First it was noted that despite the difficulties faced by antibiotics in demonstrating clinical superiority, the payer/ HTA body sees this evidence as particularly relevant in order to gain reimbursement. Secondly, the identification of the right comparator can be problematic when the antibiotic treatment belongs to the last line of treatment and patients' outcomes are influenced by previous treatments. Lastly, because the choice of the comparator and the patterns of treatment tend to follow country specific rules, it may be hard to draw lessons that can bear value across countries.

REFERENCES

APIC, A. S. i. P. C., 2014. *TARGET antibiotic toolkit* [Online]. Available: http://www.rcgp.org.uk/TARGETantibiotics [Accessed June 2017].

Ashiru-Oredope, D., Sharland, M., Charani, E., McNulty, C. and Cooke, J., 2012. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart—Then Focus. *Journal of antimicrobial chemotherapy,* 67 (suppl_1), i51-i63.

Cruickshank, M., 2011. Antimicrobial stewardship in Australian hospitals. *Sydney: Australian Commission on Safety & Quality in Health Care*.

Dellit, T. H., Owens, R. C., McGowan, J. E., Gerding, D. N., Weinstein, R. A., Burke, J. P., Huskins, W. C., Paterson, D. L., Fishman, N. O. and Carpenter, C. F., 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases,* 44 (2), 159-177.

ENVIN-HELICS, 1999-2014.

European Commission, 2016. AMR: A major European and Global challenge.

File Jr, T. M., Srinivasan, A. and Bartlett, J. G., 2014. Antimicrobial stewardship: importance for patient and public health. *Clinical Infectious Diseases,* 59 (suppl_3), S93-S96.

Future Learn, 2017. *Antimicrobial Stewardship: Managing Antibiotic Resistance* [Online]. Available: https://www.futurelearn.com/courses/antimicrobial-stewardship.

Karlsberg Schaffer, S., West, P., Towse, A., Henshall, C., Mestre-Ferrandiz, J., Masterson, R. and Fischer, A., 2017. *Additional Elements of Value for Health Technology Assessment Decisions*.

MacDougall, C. and Polk, R. E., 2005. Antimicrobial stewardship programs in health care systems. *Clinical microbiology reviews,* 18 (4), 638-656.

MacKenzie, F. M., Gould, I. M., Bruce, J., Mollison, J., Monnet, D. L., Krcmery, V., Cookson, B. and van der Meer, J. W., 2007. The role of microbiology and pharmacy departments in the stewardship of antibiotic prescribing in European hospitals. *Journal of Hospital Infection,* 65 73-81.

NHS Education for Scotland, 2015. *Antimicrobial Stewardship. Educational Workbook*. Available: http://www.nes.scot.nhs.uk/media/3239839/antimicrobial_stewardship_print_workbook_-_april_2016.pdf.

NICE, February 2015. *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use*.

O'Neill, J., 2014. Review on antimicrobial resistance. *Antimicrobial resistance: tackling a crisis for the health and wealth of nations*.

Palomar, M., Álvarez-Lerma, F., Riera, A., Díaz, M. T., Torres, F., Agra, Y., Larizgoitia, I., Goeschel, C. A., Pronovost, P. J. and Group, B. Z. W., 2013. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. *Critical care medicine,* 41 (10), 2364-2372.

Pronovost, P., Needham, D., Berenholtz, S., Sinopoli, D., Chu, H., Cosgrove, S., Sexton, B., Hyzy, R., Welsh, R. and Roth, G., 2006. An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine,* 355 (26), 2725-2732.

Shlaes, D. M., Gerding, D. N., John, J. F., Craig, W. A., Bornstein, D. L., Duncan, R. A., Eckman, M. R., Farrer, W. E., Greene, W. H. and Lorian, V., 1997. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance guidelines for the prevention of antimicrobial resistance in hospitals. *Infection Control & Hospital Epidemiology,* 18 (4), 275-291.