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IMPLEMENTING WHO, EU AND UK AMR STRATEGIES AND ACTION PLANS:

HAS THE WORLD LIVED UP TO THE CHALLENGE?

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ANTIBIOTIC ACTION

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EXECUTIVE SUMMARY

In 2011 the World Health Organization (WHO) submitted a European Strategic Action Plan on Antibiotic Resistance to the WHO European Regional Committee with an aim of building on the momentum created by World Health Day. The Action Plan highlighted seven strategic objectives as guidance to national governments in European Member States to address the complex factors of antibiotic use and resistance. In response, both the European Union (EU) and the United Kingdom (UK) government set out to devise their own action plans to address the recommendations of the WHO policy document. This article reviews the recommendations in these three policy documents in the subject area of antibiotic resistance (AMR) and the extent to which they have been implemented in Europe and the UK.

Available evidence suggests that although some EU Member States have been successful in the implementation of many of the WHO recommendations, there are others that appear to have been overlooked. In particular, there was a conspicuous lack of evidence to suggest any activity to restrict non-prescription use of antibiotics by people or off-label veterinary use of certain new or critically important antibiotics to human medicine. Likewise, it appears that little has been done to evaluate the need for incentives to stimulate discovery, research and development of veterinary medicines to increase the likelihood that drugs will reach the market at the rate required to combat AMR.

Independent of the EU actions, the UK has taken significant steps to meet the objectives of the EU Action Plan, which in turn satisfies the WHO Europe Strategic Action Plan. However, the areas of the UK Action Plan that the UK has struggled to address include education and public awareness, veterinary and agricultural use, and incentives for antibiotic discovery, research and development. This may be due in part to a lack of action by regional authorities; however it may also be due in part to a lack of objective and tangible outcomes by which to measure success.

There is a lack of consistency between the strategies in terms of terminology, compliance areas and recommendations, which makes it difficult to discern whether the EU and UK regional action plans have successfully satisfied the overarching WHO Action Plan. The biggest weakness is the ambiguous nature of the terminology employed in the recommendations. This may have limited impetus for definitive government action in some areas and pose a challenge in finding evidence for fulfillment of the AMR strategy aims.

SUMMARY OF RECOMMENDATIONS

From the evidence outlined in this report and the conclusions presented above, the recommendations below are suggested for use by policymakers and other relevant parties for consideration in future action plans to combat AMR. These recommendations are as follows:

- Future strategies to combat AMR should incorporate S.M.A.R.T. targets (Specific, Measureable, Attainable, Relevant and Timely).
- Future regional and national strategies to combat AMR should clearly demonstrate compliance with the WHO Action Plan by aligning key areas with those of the WHO Action Plan.
- Develop a harmonised collection of educational tools aimed at educating all on the problems of AMR and antimicrobial stewardship practises for both the general public and those working in the healthcare and veterinary sectors.
- Begin carefully monitoring the efficacy of education campaigns through online channels.
- Coordinate a review into progress in the discovery, research, and development of new drugs including for the veterinary sector.
- Continue to tighten restrictions on the use of last resort antibiotics in veterinary medicine in EU member states in line with the EU Road Map action point two.

INTRODUCTION

Antimicrobial Resistance: A Global Problem

The discovery of sulphonamides and penicillin hailed the beginning of a golden age for medicine. These were the first of many agents that could successfully treat bacterial infections. Unfortunately, uncontrolled use of penicillin and other antibiotics has led to the evolution and spread of antimicrobial-resistant bacteria which are now commonly found across the globe. While antimicrobial therapy is essential to support modern medicine, current scientific thinking considers many routine uses in the human, veterinary, agricultural, and commercial sectors unnecessary, leading to an environment that drives the development and spread of antimicrobial resistance[1]. Over-use of antimicrobials coupled with a small drug discovery pipeline has resulted in a challenging environment with increasingly difficult-to-manage infections and a reduction in choice of therapies with which to treat bacterial infections. This report outlines some of the steps that are being taken globally to circumvent this problem and highlights areas that require further activity.

Action Plans: Global and National Strategies to Tackle Antimicrobial Resistance

In 2011 the World Health Organization (WHO) submitted a strategic action plan on antimicrobial resistance (AMR) to the WHO European Regional Committee aiming to build on the momentum created by World Health Day, 7th April 2011[2,3]. This WHO-Europe Strategic Plan set out seven strategic objectives to European national governments to address the complex factors of antibiotic use and resistance.

To meet the objectives of the Action Plan, the Commission to the European Parliament published an 'Action Plan: Against the rising threats from Antimicrobial Resistance' in 2011[4]. This document proposed twelve action points for implementation across European Union (EU) Member States. Subsequently, in December 2013, the European Commission launched an 'Action Plan Against the rising threats from Antimicrobial Resistance: Road Map'[5], hereafter referred to as the Road Map, which details activities, milestones and deadlines to satisfy each of the twelve actions points in the original EU Action Plan and is updated regularly.

The WHO-Europe Strategic Plan was seen around the world as an exemplar of good practice in tackling AMR and antimicrobial stewardship. As such, certain objectives have been implemented beyond European borders. In 2011, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established as a direct outcome of the EU-U.S. Summit Declaration[6,7]. TATFAR developed 17 key recommendations in the area of AMR, some of which were consistent with those included in the WHO-Europe Strategic Plan.

In 2013, the United Kingdom (UK) demonstrated its leading role in the call for action on AMR by publishing the UK Five Year Antimicrobial Resistance Strategy 2013 – 2018[8], which superseded the UK Antimicrobial Resistance Strategy and Action Plan of 2000[9]. This document goes beyond the EU initiatives with aims of increasing awareness, promoting stewardship of current therapies and stimulating the development of new therapies.

In 2015 the WHO published a Global Action Plan on Antimicrobial Resistance[10]. This global strategy was designed to be feasible for all WHO Member States, regardless of income and level of development. As a result, the standards and objectives set forth by this document, although more recent, are in general lower and less advanced than those described in the WHO-Europe Action Plan, which was developed for a more resource-rich region. For this reason, the 2015 Global Action Plan is outside the remit of this report, which has evaluated the success that Europe and the UK have had in implementing European-specific strategies to combat AMR.

AIMS

The aims of this report were to:

1. Review the recommendations and actions of policy documents on AMR published by the World Health Organization Europe, the European Union, and the UK Government.
2. Present evidence of implementation of these strategies by the UK, and by the UK through membership of the European Union (EU) or the Transatlantic Taskforce for Antimicrobial Resistance (TATFAR).
3. To highlight areas where there is little or no evidence of activities to deliver the policy document recommendations.

METHODOLOGY

For the purposes of this report, “evidence” was considered to include policy documents, government reports, or relevant publications in scientific journals that demonstrated implementation of the recommendations.

Evidence to support past or ongoing activities for recommendations or requirements for each document was sought in the primary literature, mainstream media, and publically available policy documents. Searches were performed in October 2014, November 2015, November 2016, and March 2017. An evidence review was performed using both Google and PubMed search engines.

Recommendations or objectives from the following documents were reviewed and evidence searched to determine proof of implementation:

1. WHO European Strategic Action Plan on Antibiotic Resistance, 2011.
2. The EU Road Map on AMR: to assess implementation of the WHO recommendations (Appendix 1; Figure 1).
3. The UK AMR Action Plan: to assess implementation of the EU Road Map (Appendix 2; Figure 1).
4. TATFAR recommendations and activities: to assess implementation of the WHO recommendations (Appendix 3; Figure 1).

This organization of regional and national strategies allowed for a coherent framework to analyse outputs of the relevant governing body and their contribution to meeting the WHO Action Plan on AMR recommendations. The relationships between the aforementioned Action Plans and strategies and the ways in which they satisfy the WHO Action Plan is represented diagrammatically in Figure 1.

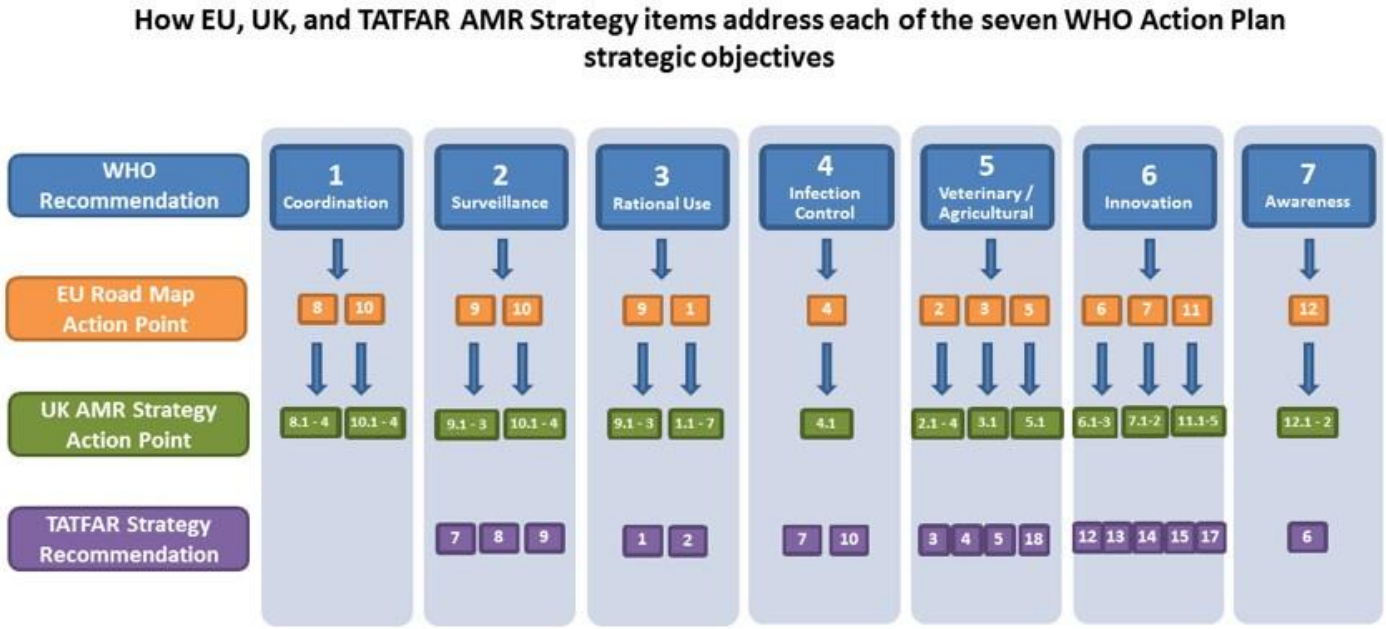

Figure 1. Visual representation of how action plans developed by each regional body meet the recommendations and action plans set out by their ‘parent’ body. This figure is derived from the authors’ interpretations of the similarities between action plans. Further information on each action plan can be found in appendices 1, 2 and 3, respectively.

Limitations

Milestones and deliverables set out in the EU Road Map were considered to be evidence demonstrating compliance with the EU Action Plan; however this does not indicate whether other EU Member States have implemented each recommendation uniformly.

A lack of identified evidence does not necessarily mean that no action has been taken. However, for the purposes of this report, a lack of evidence was assumed to translate to a lack of measureable activity. It was assumed that if no evidence of activity was found then the activities are either incomplete or not effective in their publication and communication. It was therefore deemed that the objective had not been achieved to a satisfactory standard.

Definitions

Action plans typically refer to ‘antimicrobials’, but many activities use the term ‘antibiotic’. When discussing activities this report has used the term from the source document for the purpose of consistency. It is noted that ‘antibiotic’ typically refers to antibacterial drugs, while ‘antimicrobial’ refers to drugs that are active against bacteria, fungi, parasites, or viruses.

IMPLEMENTATION OF THE POLICY DOCUMENTS ON ANTIBIOTIC RESISTANCE

The nature of AMR is such that action or lack thereof in one region can have significant consequences on regional, national and global transmission and spread of antimicrobial-resistant bacteria. It is therefore essential to have a 'One Health' approach in conjunction with ongoing monitoring of the effective delivery of policy and guideline recommendations. This report outlines the available evidence to support fulfillment of the WHO recommendations by the EU and by the United Kingdom, as a Member State of both the EU and the Transatlantic Task Force on AMR (TATFAR).

The development of policies, recommendations and guidelines is useful, but outcomes are only secured following their implementation. For this reason, it is important to highlight areas in which there is little or no evidence of action being taken to meet the policy objectives. By highlighting these shortcomings, governments can identify areas in which urgent work is needed to minimize the threat that AMR poses to global public health.

IMPLEMENTATION OF THE WHO EUROPEAN STRATEGIC ACTION PLAN ON ANTIBIOTIC RESISTANCE IN THE EUROPEAN UNION

The extent to which the recommendations stated in the WHO Europe Strategic Action Plan 2011 have been implemented in the European Union was investigated. In 2011, the EU published an action plan describing how it intended to meet the WHO recommendations during the period 2011-2016. Updates of EU progress are published in the EU Road Map which outlines strategies intended and projects completed to date[5]. A full list of EU Road Map strategies to fulfill the WHO Action Plan and indications of whether there is evidence of their implementation can be found in Appendix 1.

The Directorate-General for Health and Food Safety (DG Santé) of the European Commission provides leadership on European Union health-related policies, aiming to protect and improve public health[11]. It is responsible for coordinating and delivering the European Commission's work to address AMR and fulfill the WHO Action Plan and EU Road Map objectives and has highlighted AMR as a key challenge in its Strategic Plan 2016 – 2020[12]. In June 2016, DG Santé published an evaluation of the EU Action Plan which found that it has been successful in its relevance, effectiveness, efficiency, coherence, and added value[13]. However, the evaluation did not indicate the extent to which the EU Action Plan facilitated the implementation of the WHO Action Plan in Europe. The 70th World Health Assembly, which took place in May 2017, saw the launch of a database on the first global assessment of how countries perceive their progress on AMR[14]. This will be a useful resource in future as international regulatory agencies and national governments seek to evaluate their progress and improve their activities to address AMR. However, as indicated in this report, evidence of implementation and not perception is required.

WHO Action Plan Point 1: Strengthen national multi-sectoral coordination for the containment of antimicrobial resistance

The EU Road Map addressed national and multi-sectoral coordination in its eighth action point. Collaborative work within the EU and beyond its borders has been extensive since the Road Map was first published in 2011. Bilateral cooperation between the EU and China, Russia, and South America in the form of seminars, sub-groups and conferences is on-going. Most notable is the transatlantic cooperation following the formation of the Transatlantic Taskforce for Antimicrobial Resistance (TATFAR) in 2011. TATFAR have developed a discrete list of recommendations to address AMR (see page 11 for more information on TATFAR).

The EU has also supported the WHO in the development of its 2015 Global Action Plan and by aiding its neighbouring regions in implementing the WHO Europe Action Plan, particularly through support of the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) programme[15].

The EU is also officially collaborating with the World Organization for Animal Health through the revision of AMR chapters of the Terrestrial Code and to support of a conference on AMR by the Organisation[16].

Independent of the EU Road Map, the European Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) has been established to strengthen collaborative action to fill knowledge gaps on AMR with a One Health perspective[17]. As of 31 July 2017, this international partnership consists of 23 official member states, including 3 outside the EU and with as many hoping to join by 2018. It was established to pool national research efforts and make better use of Europe's public research and development resources. The JPIAMR liaises with the European Commission, the Innovative Medicines Initiative, and cooperates with the European Commission's DG Research, DG Santé, and other European health authorities and research agencies. The initiative has also developed a strategic research agenda to help countries align their AMR research agendas both nationally and internationally.

WHO Action Plan Point 2: Strengthen surveillance of AMR

Point two of the WHO Action Plan is addressed in the EU Road Map actions 9 and 10: strengthening AMR surveillance systems in human and animal medicine. The operational objectives of these action points include not only strengthening but also harmonizing surveillance systems and monitoring the occurrence of AMR and the consumption of antimicrobials in both humans and animals. To strengthen surveillance, the EU continues to publish reports from the European Surveillance of Antimicrobial consumption network (ESAC)[18], the European Antimicrobial Resistance Surveillance Network (EARS-net)[19], and the Antibiotic Resistance and Prescribing In European Children (ARPEC) project[20]. In addition the EU also implemented new case definitions for AMR and Healthcare-Associated Infections (HCAI)[21]. In particular, data arising from the report of the new case definitions for may highlight areas of particular concern, aiding future activity to combat AMR by focusing action and resources to prepare the relevant legislation that is needed to circumvent further problems associated with the spread of resistance.

To address the issue of harmonization of surveillance of antimicrobial use in animals, the EU has launched the European Surveillance of Veterinary Antimicrobial Consumption pilot project (ESVAC). This will collect standardized national sales data from all EU Member States[22]. This project established a legally binding regulatory framework for the collection of antimicrobial consumption data for veterinary medicines. It also harmonized surveillance and monitoring methodology in food-producing animals and created a framework for the monitoring of AMR in zoonotic and commensal bacteria. The EU has also made financial contributions to the harmonization of AMR monitoring in Member States (Table 1).

In January 2015, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the European Medicines Agency (EMA) published the Joint Interagency Antimicrobial Consumption and Resistance Analysis. This document provided an integrated analysis of antibiotic consumption and resistance in humans and food-producing animals[23]. With the exception of Salmonella spp, the analysis found associations between the volume of antimicrobial consumption and the prevalence of antimicrobial resistance in selected bacterial species investigated in animals, humans, and from animals to humans.

Measures to strengthen AMR surveillance are paramount, as careful surveillance will allow the identification of trends in the spread of AMR which will inform the necessary preventative and remedial actions. The EU has taken significant steps toward addressing the second WHO recommendation, but future use of harmonized data should follow so as to inform future governmental action.

WHO Action Plan Point 3: Promote strategies for the rational use of antibiotics and strengthen surveillance of antibiotic consumption

The EU Road Map addresses rational antibiotic use and surveillance in its first and ninth recommendations. These recommendations aim to stimulate the appropriate use of antimicrobials in human medicine, instigate research into improving appropriate antimicrobial use, support prescription-only requirements, develop educational and training programmes in nursing and long-term care facilities, and ensure the sustainability of the European Surveillance System of Antimicrobial Consumption (ESAC).

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) continues to publish reports[18]. The transfer in 2012 of its surveillance system to the European Centre for Disease Control and Prevention (ECDC) has improved the harmonization of data across WHO Member States. However, granular data on antibiotic consumption in these reports is lacking, making it difficult to discern the impact of interventions to improve education and prescribing practices, such as the 2012-2014 Preparatory Action on AMR project[24]. This EU-wide project targeted inappropriate use and sales of antimicrobials while raising awareness of AMR among stakeholders. No other EU-wide education projects were identified. Nonetheless, many Members States have implemented national projects such as the UK ‘Antibiotic Guardian’ campaign in the UK[25].

In the majority of EU Member States antibiotics can only be accessed with a prescription. Some countries, such as France, have significantly reduced prescribing through the implementation of a national campaign to cut antibiotic overuse[26]. Rational use remains an issue in countries where antibiotics are more freely available[27–29]. The provision of education initiatives to inform the public about the problems associated with antibiotic use should be a priority, especially where healthcare infrastructure is weak and antibiotics are available without a prescription.

Some research into improving appropriate use of antimicrobials in the medical sector has been done. This is evidenced by outputs of the EU Framework Programme for Research (Table 1). Most notably, a European Commission article titled, “The appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance” assesses the appropriateness of prescribing in nine European countries[30]. More research is required to inform the European Union on how best to improve antimicrobial use and prescribing in the future.

WHO Action Plan Point 4: Strengthen infection control and surveillance AMR in health care settings

Point four of the WHO Action Plan is addressed in point four of the EU Road Map. As indicated in the Road Map, one of the most significant outputs in this area has been the development of core competencies for infection control and hospital hygiene professionals in the EU[31]. An understanding of AMR by all staff in the health care sector is required to successfully coordinate actions to limit the spread of AMR infections in the clinical setting. Another important output was the publication of hospital acquired infection (HAI) surveillance reports and protocols by the ECDC[32].

WHO Action Plan Point 5: Prevent and control the development and spread of antibiotic resistance in the veterinary and agricultural sectors

The EU road map identified steps that should be taken to address this aspect of the WHO Action Plan in their action points two, three and five (Table 1). To address AMR related to the use of veterinary medicinal products and medicated feeds, there has been a revision of veterinary medicines legislation[33], harmonized limits have been set for veterinary medicines residues in non-target animal feed[34], and audits are being performed annually by the Food and Veterinary Office for Health Protection and Feed Hygiene teams. Seven audits are planned for 2017 in the animal health area and involving antimicrobial resistance[35]. Mediated feed legislation was proposed and adopted in 2014. However, proposed legislation on veterinary products has not yet been approved.

To further reduce the overall use of antimicrobials in the veterinary sector, guidelines have been developed for their prudent use[36]. Awareness has also been raised about responsible use of medicated animal feeds (references). The EU Road Map also proposed the creation of an animal health legal framework based on the principle that 'prevention is better than cure'. To achieve this, the European Parliament published the Animal Health Law, a Regulation on transmissible animal diseases in March 2016[37]. Although it is already in force, discussions regarding further provisions and implementation are ongoing.

The veterinary sector is a large reservoir for antimicrobial resistance genes[38] and for pathogens of clinical importance (e.g. Campylobacter jejuni, a major cause of foodborne gastroenteritis in humans[39]). Failing to address AMR in this sector can have downstream implications for the treatment of human disease, effectively working against activities to control AMR in the human medical sector.

Colistin is a drug of 'last resort' used in the treatment of multidrug resistant Gram-negative bacterial infections. In 2015, evidence emerged of colistin resistance in bacteria isolated from humans and animals[40]. Notably the genetic material coding for this resistance gene was located on bacterial plasmids, discrete, mobile sections of DNA with potential for transfer and therefore spread between bacterial species. In order to preserve colistin for human medicine and limit the spread of resistance genes the European Medicines Agency- Committee for Medicine Products for Veterinary Use imposed strict limitations on colistin use and recommended the withdrawal of marketing authorisations for all oral colistin in veterinary medicinal products[41,42].

WHO Action Plan Point 6: Promote innovation and research on new drugs and technology

The EU responded to this challenge from the WHO Action Plan with actions six and seven in their Road Map. These points recommend re-activating industry-led research and development (R&D) of new antibiotics and technologies through Innovative Medicines Initiative (IMI)-funded projects and JPIAMR funded projects[17,43,44]. Some progress has been made in this area (Table 1). The Road Map also recommended ensuring pricing conditions and other 'pull' measures that are needed for long-term sustainability of new antibiotic development through agreements with the European Federation of Pharmaceutical Industries and Associations (EFPIA) to promote sustainable business models and adequate conditions for the introduction of effective new antibiotics to market.

The Road Map also suggested assessing the possibilities for increasing the efficiency of the market authorization process in relation to new antibiotics. To meet these objectives, the IMI has launched the New Drugs for Bad Bugs (ND4BB) programme, consisting of seven projects to tackle the scientific, regulatory, and business challenges of developing new antibiotics. One such project is the COMBACTE project, which pioneers new ways of designing and implementing efficient clinical trials for novel antibiotics by bringing together leading scientists in the field of infectious disease to combat AMR in Europe[45]. Tangible outputs of COMBACTE include the publication of nine scientific articles covering topics relevant to AMR, the hosting of training events for healthcare professionals[46] and an up-to-date news feed that keeps scientists and the general public up to date on the latest progress in AMR research[45].

Another project, TRANSLOCATION, aims to increase understanding of how to facilitate the diffusion of antibiotics into MDR-Gram-negative bacteria[47], while the ENABLE project facilitates a platform for antibiotic drug development[48]. The majority of licensed antibiotics are not effective against Gram-negative bacteria, despite these being considered an

unmet public health need[49]. A detailed understanding of Gram-negative permeability delivered by the TRANSLOCATION project may help in the development of future drugs targeted against Gram-negative bacteria in a time when some of these bacteria are becoming pan-drug resistant.

The DRIVE-AB project is developing recommendations for new economic models that aim to provide incentives to drive investment in antibiotic R&D while ensuring the sustainable use and global access to antibiotics[50].

To date, however, these projects have not yet reached completion and so it is not possible to evaluate their ability to successfully satisfy the objectives set out in the EU Road Map. The potential benefits of DRIVE-AB are, however, significant. Outputs from DRIVE-AB have the potential to revitalize the drug pipeline, helping meet the need for novel antimicrobials to treat drug-resistant infections.

WHO Action Plan Point 7: Improve awareness, patient safety and partnership

The final action point in the WHO Action Plan is to improve awareness, patient safety and partnerships. To this end, the EU Road Map recommends action point 12, "assess and improve the impact of the EU awareness and communications initiatives around AMR" and "monitor evaluation of behaviour on AMR and prudent use in veterinary medicine". To reach these objectives, the European Commission has continued to support the ongoing annual European Antibiotic Awareness Day (EAAD), which aims to raise public awareness about AMR. However, a third Eurobarometer Survey on AMR in 2016 by the European Commission's DG Santé indicates that knowledge about AMR remains low across the EU51. Antibiotic consumption only decreased by 6% over seven years, raising questions about the efficacy of this initiative. The World Health Organization has initiated a global version of the awareness campaign, titled World Antibiotic Awareness Week, which aims to increase public awareness about the issue of AMR and to promote best practices[52].

HOW TATFAR ADDRESSES THE WHO EUROPE ACTION PLAN

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) is an EU-United States of America (USA) collaboration to combat AMR. Founded in 2011, TATFAR was established following the EU-USA summit in 2009. Involvement in TATFAR shows that the WHO Action Plan recommendation number one: "strengthen national multi-sectoral coordination for the containment of antimicrobial resistance", has, in part, been implemented. TATFAR aims to drive combative action in three areas:
(1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities,

(2) prevention of healthcare and community-associated drug-resistant infections, and (3) strategies for improving the pipeline of new antimicrobial drugs[53]. To achieve this, 18 TATFAR actions have been developed, many of which also meet the recommendations of the WHO-Europe Action Plan (Figure 1). In October 2015, TATFAR extended the collaboration to last until 2020.

The evidence summarized in Appendix 3 suggests that since its inception TATFAR has contributed to the implementation of each of the seven objectives set out by the WHO Action Plan.

TATFAR has continued to work towards implementing WHO Action Plan recommendations through a number of activities, including the harmonization of healthcare-associated infection point prevalence surveys and interpretive criteria for susceptibility reporting of bacterial isolates[54]. TATFAR has also developed terms of reference for how international communication and actions on AMR surveillance should occur[55]. Nonetheless, there remains a need for consensus on how best to evaluate the success of infection prevention and control mechanisms and programmes.

TATFAR has developed a common framework and process indictors for hospital antimicrobial stewardship programmes and organized two joint US/EU workshops in 2014 to propose standards for measuring antimicrobial use in hospital settings[55]. To prevent and control the development and spread of antibiotic resistance in the veterinary and agricultural sectors, TATFAR has facilitated the sharing of information between the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). TATFAR is also developing guidelines for AMR risk assessment for the Committee for Medicinal Products for Veterinary Use at the European Medicines Agency[56] as well as a guidance document which will utilize Codex Alimentarius and FDA guidelines[55]. Bilateral discussions have also been held between the FDA and the EMA to share information on prudent use and the EU Director General for Health and Consumer Affairs is finalising guidelines for the prudent use of antimicrobials in veterinary medicine[55].

TATFAR has facilitated the coordination of two public awareness initiatives, Get Smart: Know When Antibiotics Work and European Antibiotic Awareness Day, in the US and the EU, respectively. This supports the implementation of WHO action point seven: "improve awareness, patient safety and partnership"[55].

TATFAR has tackled WHO Action Plan recommendations on innovation and research of novel drugs and technology (Table 4; Appendix 3). TATFAR is facilitating cross-Atlantic collaboration on studies, research proposal calls and a strategic research agenda. One such agenda was developed with the Clinical Research Network on Antibacterial Resistance to identify the most important clinical questions in AMR and outlines clinical studies and trials to address these questions[55]. Both the EMA and the FDA recommendations on clinical trial designs for studying new antibacterial drugs have been published in the EMA's Guideline on the evaluation of medicinal products indicated for treatment of bacterial conditions as well as in the 2013 FDA guidance document for the food-producing animal husbandry[57]. The EMA and the FDA exchange information and practices in an effort to continue to achieve WHO Action Plan objectives.

To meet the WHO Action Plan action point four, "strengthen infection control and surveillance AMR in health care settings", TATFAR attempted to hold a workshop to bring together public health experts from the US and the EU to develop consensus evaluation tools for hospital infection control programmes[58]. However, as a result of regional differences in incentives and reimbursement models, as well as incompatibilities in the evaluation models for hospital infection control programmes in the US and the EU, this was cancelled. Work to address this particular TATFAR recommendation ceased following the completion of the 2014 TATFAR progress report[59]. It is unclear whether TATFAR will devise a new strategy to meet this objective of the WHO Action Plan.

There are two areas in which activities could be strengthened: improved coordinated action with respect to collaboration between the EU and U.S and enhanced infection control and surveillance activities in healthcare settings. Continued operation of TATFAR will be paramount in coordinating international action against AMR in the coming years. Further revisions of the TATFAR action plan should focus on identifying areas of collaboration between the US and EU health care systems with the aim of harmonising protocols for infection control.

UK IMPLEMENTATION OF THE EUROPEAN COMMISSION 'ACTION PLAN AGAINST THE RISING THREATS FROM ANTIMICROBIAL RESISTANCE: ROAD MAP'

The UK has already implemented or is in the process of implementing most of the actions detailed in the EU Road Map (Appendix 2). However there are areas where evidence of measureable activity is lacking. The UK Parliamentary Select Committee on Science and Technology Inquiry on AMR[60] and the All Party Parliamentary Group on Antibiotics[61] have been monitoring the implementation of the UK strategy to prevent and minimize AMR.

EU Road Map Point 1: Strengthen the promotion of the appropriate use of antimicrobials in all Member States

Significant action has been taken by the UK government to strengthen the promotion of appropriate antimicrobial use. However, objective 1.5 of the EU Road Map, "development of education and training for healthcare workers on all aspects of AMR", does not appear to have been addressed in full. Although this element has been included in the UK five-year strategy to combat AMR, no evidence was found to suggest that it has been fully implemented. A toolkit, 'Start Smart, Then Focus' has been developed for healthcare professionals across the UK on antimicrobial stewardship, however this does not address all aspects of AMR[62].

Other independent education initiatives operate in the UK, which go some way to addressing the gap left by the lack of governmental action in this area. One example of this is the British Society for Antimicrobial Chemotherapy Massive Open On-Line Course (MOOC) in AMR, which available for free on the online Future Learn platform[63]. Another example is the TARGET toolkit, developed by the Royal College of General Practitioners, which provides guidance and educational tools to help influence prescribers' and patients' attitudes and perceived barriers to optimal antibiotic prescribing practices[64]. The toolkit provides a range of resources that can be used to support responsible antibiotic use while helping to fulfill continuing professional development and revalidation requirements for healthcare professionals.

Evidence to support the fulfillment of the remaining action points including progress being made to promote the prudent use of antimicrobials at the national level is evidenced in the report published in 2015 by the European Commission (Table 2)[65], and the publication of the guidelines for prudent use of antimicrobials in the veterinary sector[66]. Further assessment of the EU framework should be conducted in coming months to determine its effectiveness in promoting prudent antimicrobial use.

EU Road Map Point 2: Strengthen the regulatory framework on veterinary medicines and on medicated feed via the review package foreseen for 2013

Except for the restrictions on the regular or off-label veterinary use of certain new or critically important antimicrobials for human medicine, all aspects of the existing UK regulatory framework on veterinary medicines have been strengthened (Appendix 2). Significant steps have been taken to tighten restrictions on the use of the regular or the off-label use of certain new or critically important antimicrobials for humans in the veterinary sector agents in the veterinary sector in other Member States including the Netherlands, Denmark, Sweden and France.

EU Road Map Point 3: Introduce recommendations for prudent use in veterinary medicine

Prudent veterinary use of antimicrobials is championed in the UK by the Responsible Use of Medicines in Agriculture Alliance, an alliance which produces a variety of resources aimed at disseminating good veterinary and antimicrobial chemotherapy agriculture practices[67]. In addition, the British Veterinary Association (BVA) and the British Small Animal Veterinary Association (BSAVA) produce resources outlining responsible veterinary practice[68]. The Department for Environment, Food and Rural Affairs is involved in the surveillance of veterinary medicine, which provides a useful resource for monitoring antimicrobial use in this sector[69]. One way in which the UK could further its efforts to satisfy the EU Road Map would be to establish a harmonized database of best practice recommendations for veterinary antimicrobial use.

EU Road Map Point 4: Strengthen infection prevention and control in healthcare settings.

Nursing homes and other long-term care facilities are significant reservoirs for antimicrobial resistant bacteria, in part due to the high rates of bacterial infections and subsequent antimicrobial prescriptions[70]. Infection prevention and control measures to prevent the spread of AMR within and outside of such settings are therefore extremely important. The most promising step in this area in the UK has been the introduction of the Infection Prevention and Control Commissioning toolkit[71]. This provides information for infection prevention and control commissioners and forms the basis of a healthcare associated infection reduction plan for healthcare commissioning organisations.

EU Road Map Point 5: Introduction of the new Animal Health Law

On 6 May 2013 the European Commission agreed to adopt a single, concise animal health law to effectively control infections in animals and to reduce the use of antibiotics[37]. The Regulation entered into force on 20 April 2016 and will be applicable on 20 April 2021.

EU Road Map Point 6: To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients

An indication that the UK is making substantial inroads into satisfying point 6 of the EU Road Map is that many research projects in the UK are undertaken in collaboration with other institutions across the European Union. However, the UK Action Plan also sets out the objective, “Ensure conditions for and implement fast track procedures for the marketing authorization of new antimicrobials” in order to satisfy point 6 of the EU Road Map. While various organizations and universities in the UK are involved in IMI projects aimed at developing novel antimicrobials to take to market, such as TRANSLOCATION[72], ENABLE[48], COMBACTE, and iABC[73], there is little evidence to suggest that there is any ongoing work to fast track novel antimicrobial development at the national level. Although the majority of novel antibiotics are discovered or developed in academia and small and medium enterprises (SMEs), these SMEs often lack the resources required to bring them to market[74]. Due to the constraints of patent and resource availability for any particular drug, fast tracking development is often difficult. Steps to incentivize fast tracked production, in conjunction with pressure on the relevant drug approval body should aide the rapid development of novel antibiotics.

Although the UK has not made any apparent substantial efforts in this area at the national level, a UK-based biomedical research charity, the Wellcome Trust, supports a US-based biopharmaceutical accelerator, CARB-X, which was established in 2016 following the 2015 US National Action Plan on Combating Antibiotic-Resistant Bacteria (CARB)[75,76]. This programme will accelerate a diverse portfolio of at least twenty antibacterial products towards clinical development, leveraging funds from the Biomedical Advanced Research and Development Authority and the Wellcome Trust over 25 years.

EU Road Map Point 7: Promote efforts to analyse the need for new antibiotics into veterinary medicine

This section provides evidence of implementation of point 7 of the EU Road Map. The EU officially requested advice on this subject from the EMA in February 2013 and final advice was published in 2014[77]. The UK Action Plan also recommended the evaluation of the need for, and possible introduction of, incentives to trigger development in veterinary medicines. The end goal of this recommendation is to increase the likelihood that innovations will reach the market within a reasonable time frame. No evidence could be found to suggest that the UK has implemented any activities to meet this objective.

EU Road Map Point 8: Develop and/or strengthen multilateral and bilateral commitments for the prevention and control of AMR in all sectors

Multilateral and bilateral commitments for the control and prevention of AMR include a UK-China antibiotic research partnership[78], three collaborative projects to support the development of frameworks for antibiotic stewardship education in India, Russia, and across Africa[79], the Newton Fund80 to develop international innovation partnerships, the Fleming Fund[81] to build laboratory capacity and surveillance networks in low- and middle-income countries, as well as TATFAR.

EU Road Map Points 9 and 10: Strengthen surveillance systems on AMR and antimicrobial consumption in human and animal medicine

The UK has taken measureable steps to implement the EU's recommended action points 9 and 10. In 2013, the Veterinary Antimicrobial Resistance and Sales Surveillance programme was launched by the national Veterinary Medicines Directorate[82,83], and Public Health England established the English surveillance programme for antimicrobial utilization and resistance (ESPAUR) in 2014[84], introduced an electronic reporting system in 2015 to improve surveillance of carbapenem resistance in Gram-negative bacteria[85], and continues to coordinate UK data for the European antimicrobial resistance surveillance network (EARS-Net[86,87]. Private institutions have also contributed. For example, the British Society for Antimicrobial Chemotherapy hosts an online open access, online project for monitoring resistance in respiratory and bacteremia isolates[88]. This project is easily accessible to all relevant bodies, including health care professionals, and provides a catalog of useful information including: Minimum Inhibitory Concentrations (MIC) of a given antibiotic, the cognate bacterial species, season in which the bacterium was isolated, and the frequency of isolation. Careful maintenance of this resource as well as awareness of its existence among relevant parties is paramount to inform development of future policy aimed at the containment of AMR.

The UK has not fully implemented the EU Road Map recommendation to assess ways in which to improve access to data on AMR at regional, local and hospital levels. In the UK, there are reliable data from National Health Services (NHS) prescriptions in primary care, but there are no data available from secondary or tertiary care or the private or voluntary sectors. As a result the UK remains reliant on point prevalence surveys as an indicator of antimicrobial consumption in secondary care. Future action should take this discrepancy with the EU Road Map into account and harmonize data from both the public and private sectors. This would allow for more informed preventative action.

EU Road Map Points 11 and 12: Reinforce and coordinate research efforts, and survey and comparative effectiveness research on awareness campaigns

The EU has taken several actions to address point 11; UK universities and research institutions are heavily involved with several IMI projects. These include involvement of the North Bristol National Health Service Trust in the COMBACTE project, the Universities of Liverpool and Bristol in the COMBACTE-MAGNET project, and the British Society for Antimicrobial Chemotherapy, University of Strathclyde, and University of Birmingham in the DRIVE-AB project. Continued outputs of UK universities in this field will be crucial to fulfilling the EU Road Map and hence the WHO Action Plan.Monitoring of these research outputs should continue. It is also important that antimicrobial resistance research is multidisciplinary and comprehensive. Research and development of novel antibiotics is not sufficient to curb the resistance threat; an understanding of other drivers of resistance such as exposure in healthcare, agriculture, and the environment are also necessary[89]. The UK research funders and NIHR have provided approximately £50million for interdisciplinary research spanning human medicine, veterinary medicine and the environment. Topics have included early drug discovery, understanding drug resistance, genomics, epidemiology of resistance, and social factors influencing appropriate use. The Fleming and Ross Funds have also been established[81,90]. These are to link UK scientists, clinicians, veterinarians, and healthcare professionals with those in low-medium income countries to help deliver the objectives of WHO Global AMR Surveillance System (GLASS) and build capacity in AMR research[91].

It is unclear whether the UK has been successful in implementing the Road Map's final recommendation, "survey and comparative effectiveness research". The Road Map states that by building on the findings of the 2010 AMR Eurobarometer survey, the European Commission will conduct a new EU-wide survey to assess the impact of national and EU awareness campaigns on AMR including the development of indicators by no later than 2015. The Road Map does not specify how it proposes that individual EU Member States achieve this objective, but there was no evidence available to indicate that an assessment of UK-wide or EU-wide awareness campaigns on AMR had been carried out. In 2015 an article was published in the Journal of Antimicrobial Chemotherapy by UK public health professionals about moving from professional engagement to public action[92]. However, this is not a national evaluation or a report on the monitoring of public behaviour and so is insufficient evidence to show that the UK has implemented this recommendation of the EU Action Plan. A clear understanding of the problems faced associated with AMR at both a public and professional level will be essential to gaining the momentum required to tackle the problem in all sectors. As little evidence was found to verify nationwide surveys aimed at assessing the effectiveness of public awareness

campaigns, future evaluation of campaigns will be required to identify key areas of weakness which propagate misconceptions about AMR and identify ways in which existing campaigns can be improved.

CONCLUSION

There are many barriers to effectively delivering action addressing regional, national and international health concerns, including effective coordination between international bodies. The recommendations outlined by the WHO in 2011 have effectively set into motion a series of actions to combat AMR, as outlined in this report. In particular, the EU Road Map and the UK Action Plan to address this Road Map have adequately met the majority of the seven WHO recommendations. However, there is a particular lack of evidence of activity in the UK in the following areas of the EU Road Map:

- To consider restrictions on the regular or the off-label use of certain new or critically important antimicrobials for humans in the veterinary sector.
- Evaluation of the need and possible introduction of incentives that trigger development in veterinary medicines to increase the likelihood that innovations reach the market within the review of the rules on veterinary medicines.

These areas of the EU Road Map correspond with the WHO Action Plan recommendation numbers two and seven, addressing the veterinary/agricultural and research and innovation aspects of AMR, respectively.

The relationship of each of the UK, EU and TATFAR action plans to the WHO Action Plan recommendations is demonstrated in Figure 1. This figure diagrammatically represents the lack of consistency between the four strategies. It should also be noted that there is significant inconsistency in terminology, compliance areas, and recommendations between the different regional strategies. This introduces risk for implementation and adherence as it is difficult to demonstrate whether a regional strategy, such as the UK or the EU, successfully addresses all compliance areas of its parent strategy, in this case the WHO Action Plan.

However the biggest weakness of all the AMR strategy and action plan documents is the ambiguous nature of the objectives. Subjective terminology employed throughout all strategies such as “improve”, “promote”, “strengthen”, and “assess” may have limited the impetus for definitive action by national and regional governments and authorities. This has certainly made the identification of measureable evidence for fulfillment of these aims difficult to find. Without measureable targets it is unrealistic to expect that governments will invest the necessary funds to deliver interventions with impact.

RECOMMENDATIONS

From the evidence outlined in this report and the conclusions presented above, the recommendations below are suggested for use by policymakers and other relevant parties for consideration in future action plans to combat AMR. These recommendations are as follows:

- Future strategies to combat AMR should incorporate S.M.A.R.T. targets (Specific, Measureable, Attainable, Relevant and Timely).
- Future regional and national strategies to combat AMR should clearly demonstrate compliance with the WHO Action Plan by aligning key areas with those of the WHO Action Plan.
- Develop a harmonised collection of educational tools aimed at educating all on the problems of AMR and antimicrobial stewardship practises for both the general public and those working in the healthcare and veterinary sectors.
- Begin carefully monitoring the efficacy of education campaigns through online channels.
- Coordinate a review into progress in the discovery, research, and development of new drugs including for the veterinary sector.
- Continue to tighten restrictions on the use of last resort antibiotics in veterinary medicine in EU member states in line with the EU Road Map action point two.

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APPENDIX 1

Table 1: EU Implementation of WHO European Strategic Action Plan on Antibiotic Resistance, 2011 (Data from EU Road Map[5])

WHO Action Point	Evidence of Activities in the EU
Action Point 1 **Strengthen national multi-sectoral coordination for the containment of antimicrobial resistance**	Addressed by EU Road Map Action 8 i. Maintain and deepen EU/US transatlantic cooperation addressing AMR through implementation of the 17 TATFAR recommendations and the bi-annual TATFAR audio-conference meetings and organisation of a face-to-face meeting to review progress and discuss follow-up. ii. Discussion with international partners including China, Russia, and South American countries to identify areas of cooperation. iii. Cooperation with WHO to support development of WHO Global Action Plan. iv. Implementation of the WHO 'Health Security Roadmap' identifying antimicrobial resistance as an area for cooperation including the Annual WHO-EURO/EC senior officials meetings and cooperation to support capacity building of surveillance laboratories in non-EU countries. v. Work with the World Organisation for Animal Health by supporting the conference on antimicrobial resistance organised by the World Organisation for Animal Health and through collation on revision of chapters on AMR of the Terrestrial Code and participation on the ad hoc groups AMR.
Action Point 2 **Strengthen surveillance of AMR**	Addressed by EU Road Map Actions 9 and 10 i. Strengthen surveillance systems on antimicrobial resistance and antimicrobial consumptions by publication of ESAC, EARS-net and PPS reports, implementation of new case definitions for AMR and HCAI, and completion of the APREC project. Publication in January 2015 of ECDC/EFSA/EMA integrated analysis of antibiotic consumption and resistance in humans and food-producing animals[23]. ii. Harmonised surveillance systems and monitoring on the occurrence of the antimicrobial resistance and consumption of antimicrobials including the European Surveillance of Veterinary Antimicrobial Consumption project, a pilot project collecting standardised overall sales data, and the collection of and reporting on overall national sales data from all Members. Finally, reinforcing the legal basis for collection of antimicrobials in regulatory framework for veterinary medicines. iii. Harmonisation of surveillance and monitoring of antimicrobial resistance in the food chain including the framework for monitoring of resistance in zoonotic and commensal bacteria and financial contribution from EU to harmonise AMR monitoring by Member States.
Action Point 3 **Promote strategies for the rational use of antibiotics and strengthen surveillance of antibiotic consumption**	Addressed by EU Road Map Actions 1 and 9 i. Support implementation of Recommendation 2002/77/EC regarding 'prescription-only' requirements, nursing and long-term care facilities and education and training programmes: 2012-2014. Preparatory action on AMR which addresses the misuse of antimicrobial agents in human medicine, awareness across the whole chain of stakeholders, sales of antimicrobial agents without a prescription, and the report on Antibiotic Prescribing and Resistance in European Children (ARPEC). Progress report on prudent use of antimicrobial agents in human medicine: third report on implementation of the Council recommendation published in 2016[93]. ii. Stimulate the appropriate use of antimicrobials in human medicines via meetings and workshops. iii. Research on improving appropriate use of antimicrobials including the EU Framework Programme for Research-funded project: 'Genomics to combat resistance against antibiotics in community acquired lower respiratory tract infections in Europe' and 'The appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance'[94]. iv. Ensure the sustainability of the European Surveillance system of Antimicrobial Consumption via the transfer of the European Surveillance system to ECDC and publication of ESAC reports.
Action Point 4 **Strengthen infection control and surveillance AMR in health care settings**	Addressed by EU Road Map Action 4 i. Monitor and support the implementation of the Council's recommendations on patient safety and HCAI with emphasis on development of guidance on infection prevention and control, strengthened surveillance of HAI, education and training of healthcare workers and information to patients. This has been demonstrated using reports from the commission on implementation of recommendations, the fact that HAI have been prioritised in the Third Health Programme Project call 2014, and the resources and publications produced by ECDC on infection prevention and control, strengthening healthcare-associated infections (HAI) surveillance, and training curricula for healthcare workers.

Action Point 5 **Prevent and control the development and spread of antibiotic resistance in the veterinary and agricultural sectors**	Addressed By EU Road Map Actions 2,3, and 5 i. To address AMR related to the use of veterinary medicinal products and medicated feeds including the revision of veterinary medicines legislation, the harmonisation of limits for residues for veterinary medicines in non-target animal feed (planned for end 2014), and the audits by Food and Veterinary Office Health Protection and Feed Hygiene teams. ii. Use existing tools to ensure prudent use of antimicrobials in the veterinary sector, including the Commission decision on referral in relation to 3rd and 4th generation cephalosporins, the recommendation from CVMP on need for further referrals of critically important medicines and the initiation of referrals on veterinary medicinal products taking into account the updated priority list for referrals established by EMA (Colistin referred in 2014), and the implementation and dissemination of scientific advice on use of last resort antimicrobials in veterinary sector. iii. Reduce the overall use of antimicrobials in the veterinary sector including the development of guidance with examples of prudent use published in September 2015[36]. iv. Guarantee responsible and efficient use of medicated feed by raising awareness. v. Create an animal health legal framework based on the principle 'prevention is better than cure', achieved by increasing responsibilities of operators to ensure the required level of animal health and biosecurity, clarifying the responsibility of veterinary and aquatic health professionals to adopt effective measures to prevent the spread of pathogens and to raise awareness, clarifying the responsibility of competent authorities to protect animal health, human health and the environment through reduction of the risks arising from the emergence, introduction or spread of pathogens, providing for an assessment, prioritisation and categorisation of diseases or disease agents including the ability to generate resistance to treatment as criterion to decide about appropriate measures, and clarifying obligations to ensure appropriate monitoring, surveillance and early detection of pathogens.
Action Point 6 **Promote innovation and research on new drugs and technology**	Addressed by EU Road Map Actions 6, 7, and 11 i. To re-activate research and development by industry for new antibiotics and related issues achieved by the Innovative Medicines Initiative (IMI) projects. ii. To ensure pricing conditions and other 'pull' measures needed for the longer term sustainability of new antibiotic development by setting up an agreement with EFPIA on a 'compact' on initiative to promote a sustainable business model and adequate conditions for the introduction of effective new antibiotics. iii. To assess the possibilities for increasing the efficiency of the market authorisation process in relation to new antibiotics by launching a dialogue and starting assessments. IMI Projects that have contributed towards compliance in these areas include: a. COMBACTE: pioneers new ways of designing and implementing efficient clinical trials for novel antibiotics. b. TRANSLOCATION: aims to increase understanding of how to get antibiotics into MDR-Gram negative bacteria. c. ENABLE: puts in place an antibiotic drug development platform. d. DRIVE-AB: develop recommendations for new commercial models that provide industry with an incentive to invest in antibiotic development whilst ensuring that new antibiotics are used wisely.
Action Point 7 **Improve awareness, patient safety and partnership**	Addressed by EU Road Map Action 12 i. Assess and improve the impact of the EU awareness and communication initiative on AMR achieved via the rollout of European Antibiotic Awareness Day. vi. Monitor evolution of behaviour on antimicrobial resistance and prudent use in human medicine via the Third Eurobarometer Survey on AMR. vii. Monitor evolution of behaviour on AMR and prudent use in veterinary medicine via the mid-term review of Commission's five year action plan in 2015.

APPENDIX 2

Table 2: UK Implementation of the European Union Antimicrobial Resistance Action Plan, 2011[4]

Action n° 1: Strengthen the promotion of the appropriate use of antimicrobials in all Member States.		
Action		**Evidence To Support Implementation of Action**
1.1	In cooperation with ECDC, the Commission will aim at ensuring that all the 2002 Council Recommendation on the prudent use of antimicrobial agents in human medicines are effectively implemented by the Member States with a particular emphasis on:	Addressed by EU Road Map Action 8 i. Maintain and deepen EU/US transatlantic cooperation addressing AMR through implementation of the 17 TATFAR recommendations and the bi-annual TATFAR audio-conference meetings and organisation of a face-to-face meeting to review progress and discuss follow-up. ii. Discussion with international partners including China, Russia, and South American countries to identify areas of cooperation. iii. Cooperation with WHO to support development of WHO Global Action Plan. iv. Implementation of the WHO 'Health Security Roadmap' identifying antimicrobial resistance as an area for cooperation including the Annual WHO-EURO/EC senior officials meetings and cooperation to support capacity building of surveillance laboratories in non-EU countries. v. Work with the World Organisation for Animal Health by supporting the conference on antimicrobial resistance organised by the World Organisation for Animal Health and through collation on revision of chapters on AMR of the Terrestrial Code and participation on the ad hoc groups AMR.
1.2	Improving the sustainability of national surveillance systems on AMR and access to surveillance data at local and regional levels.	- UK resistance surveillance data. - ESPAUR Report, 2016[84]. - Antimicrobial Use and Resistance in Humans, 2014 (Scotland)[95]. - Antimicrobial Resistance in Wales, 2005-2014[96].
1.3	Improving the implementation by all Member States of the prescription only requirements for antimicrobial agents.	- All parenteral antibiotics are Prescription only medicines (POM). - 'P' (pharmacy only) antimicrobials include oral fluconazole 150mg, chloramphenicol 0.5% eye drops and a number of topical antifungals. - No antimicrobials on the General Sales List.
1.4	Improving the implementation of control measures against AMR in nursing homes and long-term care facilities.	- HPA guidance document for local implementation[97] - EPIC 3: Guidelines for preventing HCAI in hospitals[98]. - Infection Prevention and Control Commissioning Toolkit aims to meet the challenge of reducing health care acquired infections (HCAIs)[71].
1.5	Development of education and training for healthcare workers on all aspects of AMR.	- Included in UK five year strategy. - Start Smart, Then Focus: a UK government toolkit on antimicrobial stewardship for healthcare professionals[62]. - TARGET toolkit: a Royal College of General Practitioners guidance toolkit on influencing prescribers' and patients' attitudes to prescribing practices[64].
1.6	Better assessment and monitoring at national level of the implementation and efficiency of the national strategies and control measures	- UK Interdepartmental High Level Steering Group. - All Party Parliamentary Group: Antibiotics[61].
1.7	The Commission will publish by 2015 at the latest a new report identifying progress made and shortfalls in promoting prudent use of antimicrobials at national and EU level and assess whether the existing EU framework for the promotion of prudent use of antimicrobials should be revised.	- Progress report published in March 2015[99]. - Guidelines on the prudent use of antimicrobials in veterinary medicine[100]. - EU Road Map, 2015[5].

Action n° 2: Strengthen the regulatory framework on veterinary medicines and on medicated feed via the review package foreseen for 2013, in particular:

Action		Evidence To Support Implementation of Action
2.1	To ensure appropriate warnings and guidance on the labels of veterinary antimicrobials.	- UK licensed products and UK dispensed products should fulfil UK legislation on labelling stated in the Veterinary Medicines Regulations (2011)[101]. - Summary of regulations and good practice statements[102].
2.2	To consider restrictions on the regular or the off-label use of certain new or critically important antimicrobials for humans in the veterinary sector.	- In UK 'Red Tractor' updated standards concerning fluoroquinolones and third and fourth generation cephalosporins in the poultry industry[103].
2.3	To consider amending the rules for the advertisement of veterinary antimicrobials.	- Legislation amended in June 2015[104].
2.4	To revisit the authorisation requirements in order to sufficiently address the risks and benefits of antimicrobial medicines.	- Guidance note on veterinary marketing authorisations was issued in July 2014[105]. No particular reference made to antimicrobials. This was updated in 2015 but makes no reference to antimicrobials. - Summary of UK Veterinary Prescribing Pressures Focus Groups[106].

Action n° 3: Introduce recommendations for prudent use in veterinary medicine

Action		Evidence To Support Implementation of Action
3.1	To include follow-up reports, using the same approach as 2002 Council Recommendation on prudent use of antimicrobial agents in human medicine.	- 2002 recommendation requires reporting to include six main strands, surveillance, control, prevention, education, information, research. - Prudent use advocating by Responsible Use of Medicines in Agriculture Alliance (RUMA)[107]. - British Small Animal Veterinary Association (BSAVA) guide to veterinary antimicrobial use[108]. - British Veterinary Association (BVA) advice on veterinary antimicrobial use[109]. - Surveillance by DEFRA[110]. - Zoonoses cases reported by DEFRA including surveillance, control and research[111]. - EU Guidelines on the Prudent Use of Antimicrobials in Veterinary Medicines.[36]

Action n° 4: Strengthen infection prevention and control in healthcare settings.

Conduct and publish by 2012 a report identifying the progress made by the Member States and gaps in implementing the 2009 Council Recommendations on patient safety, including prevention and control of health care associated infections, with a special emphasis on verifying whether:

Action		Evidence To Support Implementation of Action
4.1	Guidance on infection prevention and control is developed, surveillance of healthcare associated infections is strengthened, proper education and training of healthcare workers is organised.	- European Commission report published in November 2012[112]. - EPIC 3: Guidelines for preventing HCAI in hospitals[98]. - Infection Prevention and Control Commissioning Toolkit aims to meet the challenge of reducing health care acquired infections (HCAIs)[71]. - Public Health England Mortality Report: MRSA, MSSA and E. coli and C. difficile infection: 30 day all-cause fatality[113].

Action n° 5: Introduction of the new Animal Health Law

Action		Evidence To Support Implementation of Action
5.1	This will focus on prevention of diseases, reducing the use of antibiotics and replacing current Animal Health provisions based on disease control.	On 20 April 2016 a new and comprehensive animal health law from the European Commission entered into force[37].

Action n° 6: To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients by:		
Action		**Evidence To Support Implementation of Action**
6.1	Launching rapidly with EFPIA12, within the IMI-Joint Undertaking, a programme for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge.	On-going projects and IMI activities addressing these areas are discussed in detail in the EU Road Map.
6.2	Establishing an overarching framework agreement with the industry, defining objectives, commitments, priorities, principles and modes of action for public-private collaboration in a longer term perspective. Mobilising adequate resources, within IMI in particular (and its possible successor), FP7 and in the longer term the forthcoming research and innovation programme 2014-2020 (Horizon 2020), in order to support research and development work, based on criteria and modalities adapted to the specific needs and challenges of antibiotic development. Use the flexibility in the current pharmaceutical legislation to give rapid authorisation to new antibiotics and work with stakeholders and the Member States' authorities towards the establishment of adequate market and pricing conditions for new antibiotics.	On-going projects and IMI activities addressing these areas are discussed in detail in the EU Road Map.
6.3	Ensure conditions for and implement fast track procedures for the marketing authorisation of new antimicrobials.	On-going projects and IMI activities addressing these areas are discussed in detail in the EU Road Map.

Action n° 7: Promote efforts to analyse the need for new antibiotics into veterinary medicine		
Action		**Evidence To Support Implementation of Action**
7.1	Establishing request for scientific advice to clarify in particular whether the development of new veterinary antimicrobials would reduce AMR.	EU request advice from EMA in Feb 2013, final advice published in 2014[77].
7.2	Evaluation of the need and possible introduction of incentives that trigger development in veterinary medicines to increase the likelihood that innovations reach the market within the review of the rules on veterinary medicines foreseen in 2013.	No evidence identified.

Action n° 8: Develop and/or strengthen multilateral and bilateral commitments for the prevention and control of AMR in all sectors

Action		Evidence To Support Implementation of Action
8.1	***Multilateral cooperation:*** Cooperate with WHO EURO in implementing the new Regional Strategies against AMR and Multi Drug Resistant tuberculosis across the WHO EURO Region.	Regional plans from WHO[114].
8.2	Contribute to further development of the Health Codes of the OIE and promote the implementation of Codex Alimentarius internationals standards on AMR.	Support to the conference on Antimicrobial Resistance organised by the World Organisations for Animal Health.
8.3	Initiate cooperation on reduction of the environmental pollution by antimicrobial medicines particularly from production facilities.	Four antimicrobials included in EU watch lists for emerging water pollutants[115].
8.4	***Bilateral cooperation:*** Strive to maintain and deepen transatlantic cooperation against AMR through active participation in the TATFAR and the implementation of its recommendations. Set out and apply in a staged approach a plan to implement the 17 recommendations of TATFAR.	Update on progress on the 17 TATFAR recommendations[59].

Action n° 9: Strengthen surveillance systems on AMR and antimicrobial consumption in human medicine:

Action		Evidence To Support Implementation of Action
9.1	With the support of the ECDC, assess ways to improve access to data on AMR at all levels (regional, local and hospitals).	- Consumption data in secondary care remains reliant on point prevalence surveys. - Reliable data from NHS prescriptions in primary care but no data from the private sector. - ESPAUR Report, 2016[84]. - Antimicrobial Use and Resistance in Humans, 2015 (Scotland)[95]. - Antimicrobial Resistance in Wales, 2005-2014.[96]
9.2	Ensure the efficient transfer of the ESAC project to ECDC to secure the sustainability of the project.	Surveillance role transferred to ECDC[116].
9.3	With the support of the ECDC, support and monitor the successful development of the new EU funded surveillance project ARPEC – Antibiotic Resistance and Prescribing in European Children.	ARPEC up and running. Await results to determine its effectiveness[117].

Action n° 10: Strengthen surveillance systems on AMR and antimicrobial consumption in animal medicine:

Action		Evidence To Support Implementation of Action
10.1	Inclusion of a legal basis for the monitoring of AMR in animal pathogens in its forthcoming proposal for a new Animal Health Law.	On 6 May 2013, the European Commission has adopted a proposal for a single, comprehensive animal health law to replace the complicated animal health rules currently in place[37].
10.2	Promotion and extension of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) with the collaboration of EMA to obtain harmonised data on the usage per animal species and production categories as well as for different indications from all Member States.	- Data from UK includes animal species and medicine type however no data on indication has been published. - European Medicines Agency Report: Trends in the sales of veterinary antimicrobial agents in 29 European countries in 2014[118].
10.3	Review of the monitoring of AMR in zoonotic bacteria and/or indicators.	Veterinary Medicines Directorate report data on zoonotic bacteria: Zoonoses reports UK 2014 and 2015[119].
10.4	With the support of the relevant EU agencies, establish harmonization between human and veterinary surveillance to allow comparison of data.	Data on zoonotic bacterial infections includes data from animals and humans[119].

Action n° 11: Reinforce and co-ordinate research efforts

Action		Evidence To Support Implementation of Action
11.1	Promote further research aiming at better understanding of antimicrobial resistance and pathogenic-host interactions.	- UK Cross Funder Initiative[120]. - Fleming Fund[81]. - Ross Fund[90]. - The MRC represents the UK on the JPI AMR
11.2	Promote further research on the development of diagnostic tools, vaccines and other preventive measures.	- UK Cross Funder Initiative[120]. - Fleming Fund[81]. - Ross Fund[90]. - The MRC represents the UK on the JPI AMR
11.3	Support the launch of a Joint Programming Initiative 13 aimed at coordinating national research activities related to AMR.	- UK Cross Funder Initiative[120]. - Fleming Fund[81]. - Ross Fund[90]. - The MRC represents the UK on the JPI AMR
11.4	Support an analysis of the reasons for high usage of antimicrobials in countries with the highest occurrence of AMR in the human sector.	- UK Cross Funder Initiative[120]. - Fleming Fund[81]. - Ross Fund[90]. - The MRC represents the UK on the JPI AMR
11.5	Contribute to a global mapping of drug resistance.	- UK Cross Funder Initiative[120]. - Fleming Fund[81]. - Ross Fund[90]. - The MRC represents the UK on the JPI AMR

Action n° 12: Survey and comparative effectiveness research.

Building up on the findings of the 2010 AMR Eurobarometer survey, the Commission will by no later than 2015 conduct a new EU wide survey:

Action		Evidence To Support Implementation of Action
12.1	Assessing the impact of the national and EU awareness campaigns on AMR including the development of indicators.	No specific article identified.
12.2	Monitoring the evolution of the behaviour of the general public with regard to AMR and the appropriate use of antimicrobials.	Article in the Journal of Antimicrobial Chemotherapy, published 2015: "Antimicrobial resistance: moving from professional engagement to public action"[92]

APPENDIX 3

Table 4: US/EU Collaborative Implementation through TATFAR activities of WHO European Strategic Action Plan on Antibiotic Resistance, 2011.

Up to Date Information on Implementation of TATFAR Recommendations can be found on the TATFAR website[53]

WHO Action Point	Evidence of Activities in the EU
1. Strengthen national multi-sectoral coordination for the containment of antimicrobial resistance.	Establishment of and continuing meetings of TATFAR.
2. Strengthen surveillance of AMR	TATFAR Recommendations: 7, 8 and 9 - Consultation and collaboration on a point prevalence survey for HAI: CDC and ECDC protocols are not identical however additional variables have been added to each to enable comparison of results. - Develop a process for transatlantic communication of critical events that may signify new resistance trends with global public health implications: The terms of reference developed on how international communication and actions about critical AMR surveillance results will occur and which information should be communicated. Additionally, there are quarterly conference calls. - Encourage efforts to harmonise interpretive criteria for susceptibility reporting of bacterial isolates across surveillance programmes in the US and EU.
3. Promote strategies for the rational use of antibiotics and strengthen surveillance of antibiotic consumption	TATFAR Recommendations: 1 and 2 - Develop common structure and process indicators for hospital antimicrobial stewardship programmes. - Convene a joint US/EU working group to propose standards for measuring antimicrobial use in hospital settings.
4. Strengthen infection control and surveillance AMR in health care settings	TATFAR Recommendations: 7 and 10 - Consultation and collaboration on a point prevalence survey for HAIs: CDC and ECDC protocols are not identical however additional variables have been added to each to enable comparison of results. - Convene a workshop bringing together public health experts from the US and EU to develop consensus evaluation tools for hospital infection control programmes. Due to the different drivers, incentives and reimbursements and incompatibilities in the evaluation methods for hospital infection control programmes in the US and EU, activities will cease following completion of a landscape article.
5. Prevent and control the development and spread of antibiotic resistance in the veterinary and agricultural sectors.	TATFAR Recommendations: 3, 4 5 and 18 - Collaborate on collection of data on sales and use of veterinary antimicrobial drugs in food producing animals: FDA and EMA are sharing information on the development of units of consumptions of antimicrobial agents in food producing animals. - Collaborate on implementation of the Guidelines for the Risk Analysis of Foodborne Antimicrobial resistance prepared by Codex Alimentarius. A concept paper on a guideline for AMR risk assessment was adopted by the Committee for Medicinal Products for Veterinary Use at EMA. This work lead to a guidance document that will use the Codex Alimentarius and FDA guidelines. - Enhance information sharing on approaches to promote appropriate use in veterinary communities. Information on prudent use is discussed and shared during bilateral discussions.EU Director General for Health and Consumer Affairs is finalising guidelines for prudent use of antimicrobials in veterinary medicine. - Establish a joint working group of international subject matter experts to identify key knowledge gaps in understanding the transmission to man of antimicrobial resistance arising as a result of the use of antimicrobial drugs in animals and on the development of effective intervention measures to prevent this transmission, including the development to antimicrobial drugs.

6. Promote innovation and research on new drugs and technology.	TATFAR Recommendations: 12, 13, 14, 15 and 17 - Policymakers should strongly consider establishing significant incentives to stimulate antibacterial drug development examples include the IMI in EU whilst the FDA collaborating on a study to evaluate the economics of antibacterial drugs, diagnostic devices and vaccines for bacterial diseases and to evaluate the potential role of incentives to promote their development. - Increase communication between US and EU research agencies to identify common scientific challenges that may represent opportunities for collaboration. Periodic teleconferences to exchange information on ongoing and planned programs and to identify areas in which further discussion and collaboration is warranted. - Publicise funding opportunities to the EU and US research communities including calls for proposals and other resources for researchers on both sides of the Atlantic. Examples include: IMI, JPIAMR has developed a strategic research agenda and issues transnational research calls and the Clinical Research Network on Antibacterial Resistance17. Developed a research agenda identifying the most important clinical questions in AMR and clinical studies/trials to address these. - FDA and EMA will discuss ways to facilitate the use of the same clinical development programme to satisfy regulatory submissions to both agencies. The EMA and FDA recommendations on clinical trial designs for studying new antibacterial drugs have been published in the EMA's Guideline on the evaluation of medicinal products indicated for treatment of bacterial conditions, 2012 and in a number of FDA guidance documents. - Exchange information on possible approaches for developing drugs for bacterial diseases if limited drugs are available. FDA and EMA have exchanged information on possible approaches and each agency continues to update guidance documents on drug development programmes for antibacterial drugs to address unmet medical needs.
7. Improve awareness, patient safety and partnership	TATFAR Recommendation: 6 - Establish an EU/US working group to assess the evidence for effectiveness of communications tools in promoting behaviour change to increase appropriate use and to develop joint priorities. Examples include the US Get Smart Campaign and EAAD occur at same time. GSC and EAAD develop joint priorities and share information about their respective work.