Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

Report on Recommendation 18

June 2016

"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 of* ***alternatives to antimicrobial drugs****."*

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Summary

In order to minimise the transmission of resistant bacteria from food-producing animals to humans we need to better understand how antimicrobial resistance arises as a result of antimicrobial drug use in the target animal species. While it is generally understood that the use of antimicrobial drugs in humans and animals selects for antimicrobial resistance in bacteria, the specific mechanisms by which resistance arises and is transmitted between animals and humans are incompletely known. Recommendation 18 was developed by TATFAR to address these issues. The working group responsible for its implementation agreed to adopt a “One Health” approach, bringing together expertise from both human and veterinary medicine.

The implementers conducted an assessment of existing work (research, surveillance and risk analysis) in order to identify knowledge gaps in the areas detailed above. These knowledge gaps were then attributed a priority level based on their potential for action and cooperation between the EU and the USA.

During the TATFAR meeting in Luxembourg (22-23 October 2015) the high priority knowledge gaps were reviewed to identify specific actions by which added benefit would be gained from transatlantic cooperation. Canada and Norway have provided comments to the report but are not included as co-authors since these countries became new TATFAR members only from December 2015. The identified actions form part of the next TATFAR implementation plan (2016-2020).

1. Introduction

1.1. Background of TATFAR

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was created in 2009 with the goal of improving cooperation between the EU and the USA in three key areas: appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, prevention of healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs in human medicine. TATFAR initially identified and adopted 17 Recommendations for future collaborations between the EU and the USA. These Recommendations have been implemented through increased communication (including regular meetings and workshops) and sharing of information (e.g., on approaches to common problems, best practices and methods).

Recommendation 18 was introduced in May 2014 (see Section 1.2) (TATFAR, 2014). It focused on the need to identify and address gaps in our knowledge of the emergence and transmission of antimicrobial resistance in bacteria related to veterinary uses of antimicrobial drugs and development of effective interventions.

The aim of this report is to provide an update of the status and outcomes of the implementation of Recommendation 18 following the TATFAR meeting, which took place on 22-23 October 2015 in Luxembourg, and to outline the actions that will form the basis of the next phase of implementation of TATFAR.

1.2. Recommendation 18

The following paragraphs, which are extracts from the "TATFAR 2014 progress report – Recommendations for future collaboration between the US and EU" (TATFAR, 2014), summarise the main aims of Recommendation 18:

> Establish a joint working group of international subject matter experts linked to EU and USA institutions 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 of alternatives to antimicrobial drugs**.
>
> The impact that the use of antibiotic drugs in animals has on the risk to man from antimicrobial resistance needs to be better understood. The use of antibiotic drugs in animals selects for antimicrobial resistance; however, the mechanism and frequency by which this resistance may be transferred to man and the extent of the threat that this represents to human health is less clear. Likewise, different control strategies to limit the risk to man from the use of antibiotic drugs in animals have been developed and a wide variety of alternatives to the use of antibiotic drugs are under development and evaluation. Adopting a "one health" approach, whereby expertise is brought together from both the human and veterinary domains, the working group will consider all uses of antimicrobial drugs in animals and will examine the evidence linking the resistance arising as a result of this use to infections in man with resistant organisms. The group will consider existing control strategies to limit the emergence and spread of antimicrobial resistance as well as the development of alternatives to antimicrobial drugs. The working group will identify the gaps in knowledge that exist and will develop concrete recommendations for filling these knowledge gaps, including suggesting specific research studies.
>
> - Implementers: FDA, CDC, USDA, EFSA, EMA, ECDC, DG SANTE, and DG RTD (see Annex 1)
>
> - Timeline: One year after adoption of recommendation

2. Data and methodologies

As a first step for the preparation of this report the implementers agreed to prepare an inventory of identified knowledge gaps, which is attached as Annex 2. It was further agreed that this inventory should be based on a collation and integration of conclusions and recommendations from existing reports and other relevant documents, rather than on a new review of the underlying scientific literature.

This inventory, which forms the basis for the output from Recommendation 18, addresses the following points:

- Listing of knowledge gaps identified in existing documents that are relevant to the objectives described in Recommendation 18;
- Identifying work already underway or planned by implementers (or others) to address these knowledge gaps, in particular where transatlantic cooperation is taking place;
- Highlighting knowledge gaps based on priority and feasibility, in terms of both potential for action and cooperation;

- Identifying existing documents produced by, or available to, the implementers to identify work already carried out in the areas covered by Recommendation 18.

The implementers organised teleconferences approximately every two months to monitor progress with Recommendation 18 and to discuss the status of the inventory and the report. From December 2015 Canada and Norway also took part in the discussions as new TATFAR members.

3. Assessment and identified knowledge gaps

3.1. Description of assessment

The assessment of knowledge gaps focused on two main areas:

I) understanding the transmission to humans of antimicrobial resistance that arises as a result of the use of antimicrobial drugs in food-producing animals, and

II) developing effective intervention measures to prevent this transmission, including alternatives to antimicrobial drugs.

I) The assessment of the level of understanding of the transmission to humans of antimicrobial resistance from the use of antimicrobials in animals was divided into three subparts due to its complexity:

> I.A. understanding the characteristics and extent of antimicrobial resistance in bacteria arising as a result of antimicrobial drug use in animals;
> I.B. understanding transmission to humans of antimicrobial resistance from animals, and
> I.C. underlying surveillance data needed to understand whether and how antimicrobial resistance in bacteria arises as a result of the use of antimicrobial drugs in animals and how it is transmitted to humans.

II) The assessment of the development of effective intervention measures was straightforward and consisted of a listing of interventions.

3.2. Outline of identified knowledge gaps

The inventory of the knowledge gaps identified through the assessment can be found in Annex 2. It is structured according to the sequential transmission pathways of antimicrobial resistance from animal to humans. Each knowledge gap was attributed a priority level according to their relevance for the aims of Recommendation 18 (see more details in Annex 2). The highest priority was given to those that were feasible via cooperation by TATFAR members, could produce measurable added value, and were achievable within TATFAR's 2016-2020 implementation period.

Below is an outline and summary of the findings of the assessment, which follows the same structure as the inventory. High priority areas (i.e., those recommended for the next phase of implementation of TATFAR) are identified with underlined text and numbers corresponding to their listing in the Conclusions (Section 4).

I. Understanding the transmission to humans of antimicrobial resistance that arises as a result of the use of antimicrobial drugs in food-producing animals

I.A. Understanding the characteristics and extent of antimicrobial resistance in bacteria arising as a result of antimicrobial drug use in animals

As the relationship between antimicrobial use in food-producing animals and the development of antimicrobial resistance is extremely complex and is currently being studied in both the EU and the USA through the development of analytic modelling frameworks, it was agreed not to recommend this as an area of high priority for additional collaboration.

- **I.A.1.** Risk factors for the occurrence of antimicrobial resistant bacteria in food-producing animals and/or the environment

It was recognized that the effect of co-selection on resistance to antimicrobials, resulting from antimicrobial use in food-producing animals, is an important knowledge gap but no immediate topic for cooperation in this area was identified.

The group also recognized that the subject of antimicrobial resistance disseminating from and to the broader natural environment is highly topical and there is research in this area ongoing in both the EU and the USA. However, due to the relatively early stage of this research and the long timescale for deriving meaningful conclusions, the group decided not to list this as a high priority for cooperation at this time.

- **I.A.2.** Relationship between antimicrobial consumption in food-producing animals and antimicrobial resistance in bacteria from animals and foodstuffs derived thereof

This was considered an important area for future cooperation as many activities are already taking place on both sides of the Atlantic. However, it was considered premature at the present time to include this in the current phase of TATFAR as no aspects were identified for immediate cooperation.

I.B. Understanding transmission to humans of antimicrobial resistance from animals

Foodborne transmission

This area was considered important given the significant knowledge gaps that remain, but not one in which a rapid result could be obtained. In other words, this it is not an area for short term collaboration but rather an area for long term, sustained research.

Whole genome sequencing (WGS) and bioinformatics are examples of two tools that can provide important data in this area. Much work is already underway, including cooperation through sharing sequencing data both within and between the TATFAR regions and implementers. It was agreed that epidemiological data are also needed to put the genetic data in context and ensure those are representative of bacterial populations.

How non-animal resistant bacteria (such as dissemination of resistant organisms via human travel) or their resistance genes enter and spread in the environment and to animals and food is not well characterised. Although this type of antimicrobial resistance is not the primary focus of Recommendation 18, which refers to antimicrobial resistance arising from the use of antimicrobials in food-producing animals, it is relevant as another source of emergence, a pathway for transmission, and as a potential confounder.

- **I.B.1.** Transmission of antimicrobial-resistant bacteria from food-producing animals to foodstuffs

Partially addressed under I.A.

This is an area in which there is already much information available but important knowledge gaps remain. It is not an area for short-term collaboration but for long-term sustained research.

- **I.B.2.** Transmission of antimicrobial-resistant bacteria from animals to foodstuffs through the environment

See above comment on I.A.1.

- **I.B.3.** Transmission of antimicrobial-resistant bacteria occurring in food-producing animals to humans through consumption of foodstuffs

The knowledge gap (1) *"Better understanding of transmission of bacteria resistant to certain classes of antimicrobials from food-producing animals to humans, notably through food consumption (I.B.3.1.)"* was selected by the working group as a high priority for collaboration (see Section 4.) in which exchange of communication between the EU and the US could help to make significant progress.

Direct transmission

Direct transmission covers risks factors and transmission routes involved in the direct transfer of antimicrobial resistance between animals and humans and *vice versa*.

- **I.B.4.** Direct transmission of antimicrobial-resistant bacteria from animals to humans (colonisation, infection)

Although transmission of antimicrobial resistant bacteria between food-producing animals and humans may occur by direct or indirect contact (e.g. transfer of Livestock-Associated Methicillin-Resistant *Staphylococcus aureus* (LA-MRSA)), the extent of this transfer has not been quantified. It is currently considered a lower priority when compared with the research gaps related to foodborne transmission of antimicrobial resistance from food-producing species.

There is limited information on antimicrobial resistance arising from transmission to humans from companion animals by direct or indirect contact. Transmission from companion animals is currently considered a knowledge gap but of lower priority when compared with the research gaps related to antimicrobial resistance from food-producing animal species. Therefore, companion animals as a source of zoonotic antimicrobial resistant bacteria are excluded from the scope of Recommendation 18 for this TATFAR performance period.

Environmental transmission (excluding the food chain)

- **I.B.5.** Transmission of antimicrobial-resistant bacteria from animals to humans through the environment

See above comment on I.A.1.

I.C. Underlying surveillance data needed to understand whether and how antimicrobial resistance arises in bacteria as a result of the use of antimicrobial drugs in animals and how it is transmitted to humans

- **I.C.1.** Surveillance of antimicrobial consumption in animals

Significant efforts are currently underway in the EU and the USA, to develop a transparent methodology for the stratification of sales data in order to obtain estimates on the consumption (use) of antimicrobials per the major food-producing species. This remains an important gap and represents

an opportunity for cooperation that should be given high priority. Collaboration could bring progress in a short period of time.

The group agreed it should also be possible to cooperate in the related area of measuring the impact on human and animal health of appropriate use of antimicrobial drugs (possibly including restricting use of certain antimicrobials) in food-producing animals for which consumption is measured. Antimicrobials of particular interest are those for which there is widespread agreement on their critical importance for human medicine (e.g., by WHO, OIE, FDA, and Canada) and for which a number of measures to restrict their use have been put in place in the USA and/or EU.

The knowledge gaps, (2) *"Information on antimicrobial consumption in animal species (I.C.1.1.)"* and (3) *"Impact on human and animal health of appropriate use of antimicrobials (including restricting use of certain substances) in food-producing animals (I.C.1.4.)"* were selected by the working group as high priorities for collaboration (see Section 4.)

- **I.C.2.** Surveillance of antimicrobial resistance in bacteria from animals and food

Monitoring of antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and foodstuffs is a high priority. There are a number of on-going efforts to build capacity for integrated antimicrobial resistance monitoring systems and to harmonise collection, analysis and reporting of representative data on antimicrobial resistance in the food chain. Antimicrobial resistance data also need to be supported by epidemiological data combined with genomic information (WGS data). Harmonisation of antimicrobial resistance monitoring in bacteria from food-producing animals is a gap that needs to be addressed, as such monitoring assists in assessing the impact of use of antimicrobials in food-producing animals. Multidisciplinary collaboration in this area is essential and should be encouraged.

There is also a lack of data on the occurrence of antimicrobial resistance in animal bacterial pathogens. Due to the difficulties in harmonising monitoring methodologies and the current lack of official monitoring for antimicrobial resistance in animal pathogens, it was not considered as a high priority during the current phase of TATFAR.

The knowledge gap (4) "*Coordinated/harmonised approaches for collection of data on antimicrobial resistance from humans, foodstuffs and food-producing animals are lacking (I.C.2.1.)"* was selected by the working group as a high priority for collaboration (see Section 4.)

- **I.C.3.** Surveillance of antimicrobial consumption in humans

Surveillance of antimicrobial consumption in humans is a critically important element in addressing the overall problem of antimicrobial-resistant infections in humans, as it is the foundation for our understanding where stewardship efforts in human medicine are working and where they need to be strengthened. In addition, complete data on antimicrobial consumption in humans are needed for meaningful comparisons with antimicrobial consumption in animals.

To obtain the full picture of antimicrobial consumption in humans, there is a need for a more complete participation of hospitals in and reporting of hospital data to national and supranational surveillance systems for antimicrobial consumption.

As recommendation 18 focuses on veterinary antimicrobial use, the collection of consumption data for antimicrobials in humans is of lower priority for this specific TATFAR activity.

- **I.C.4.** Surveillance of antimicrobial resistance in bacteria from humans

There is incomplete information on antimicrobial resistance in zoonotic pathogens and indicator bacteria in humans. This information would be of relevance to better understand antimicrobial resistance in zoonotic pathogens and indicator bacteria.

The knowledge gaps (4) "*Need for better and more comprehensive data on antimicrobial resistance in zoonotic pathogens and indicator bacteria from humans (I.C.4.1.)*", and (5) "*Need for continued efforts to develop and apply standardized in vitro antimicrobial susceptibility testing methods and use validated breakpoints for interpreting and reporting data (I.C.4.2.)*" were selected by the working group as high priorities for collaboration (see Section 4.)

- **I.C.5.** Attribution of antimicrobial consumption in humans to antimicrobial resistance in humans

Research into source attribution for all sources of antimicrobial resistance in bacteria from humans is a priority so that antimicrobial resistance arising from animal and other relevant (e.g. agriculture, environment) sources can be put in overall context of the human antimicrobial resistance burden.

This is an area of high priority but for which the data required would be extremely complex. It is therefore more suitable for inclusion as part of a possible future phase of the TATFAR activities.

II. Developing effective intervention measures to prevent this transmission, including alternatives to antimicrobial drugs

The group identified a list of interventions (prevention, diagnosis, treatment, alternatives, and control of spread of antimicrobial resistance) to prevent the emergence of antimicrobial resistance.

A promising area for the future is the research into alternatives to antimicrobials. There are several research projects ongoing and the market forces have already initiated efforts to bring some of the products developed to the market.

An important knowledge gap included control measures that can be introduced to stop transmission of antimicrobial resistance once it has emerged, such as environmental treatment and pre- and postmortem treatments. However due to its complexity, the group decided not to list this as a high priority for cooperation at this time.

- **II.1.** Prevention of animal disease

Although this is an area in which there are significant knowledge gaps, it is highly complex to find the links between prevention of animal diseases, its impact to reduce the use of antimicrobials and the impact of the decrease on the transmission of antimicrobial resistance.

- **II.2.** Diagnostic tests for animal diseases

Diagnostic tests for animal diseases are regulated differently in the EU and USA. Consequently it was decided not to include diagnosis of animal diseases in the high priority knowledge gaps and as above it would also be difficult to attribute or measure the impact on antimicrobial resistance of the use of diagnostics for animal diseases.

- **II.3.** Treatment of animals

Although this is an area in which there are significant knowledge gaps, it is not obvious how the collaboration could result in short term results on better understanding the transmission of antimicrobial resistance to humans as a result of the use of antimicrobial drugs in animals.

- **II.4.** Alternatives to use of antimicrobials

The EU and USA identified an opportunity to exchange information regarding the authorization of products which can serve as alternatives to antimicrobials or otherwise reduce their need. Where possible, the approaches to authorisation could be aligned to lessen the time to market for these products.

The knowledge gap (6) *"Impact of use of alternatives to antimicrobials on antimicrobial resistance (II.4.1.)"* was selected by the working group as high priority for collaboration (see Section 4). Veterinary regulatory agencies will discuss the particular challenges related to authorisation of novel veterinary therapies presented as alternatives to antimicrobials aiming to develop similar approaches to achieving regulatory approval, thereby accelerating access to market.

- **II.5.** Control options to prevent emergence/spread of antimicrobial resistance in humans

The group considered that the control options to prevent emergence/spread of antimicrobial resistance in humans had a wide scope that was already covered by other points.

4. Conclusions

The working group identified numerous knowledge gaps in understanding and stopping the transmission of resistant bacteria from food-producing animals to humans. The group assessed each in terms of (i) their feasibility for potential action and cooperation, (ii) the added value that could be expected to arise from cooperation between TATFAR members and (iii) the likelihood that results could be achieved within the relatively short timescale of the next TATFAR implementation phase.

Within this TATFAR exercise many areas for potential cooperation were identified but not all of them were deemed likely to produce measurable results in the short term and were therefore not considered as "high priorities". However, the working group agreed to retain these as areas of interest for reconsideration in the future (details can be found in the inventory table in Annex 2).

Given the work both currently underway and being initiated as a result of this recommendation, it is likely that the knowledge gaps and priorities will be revised in the future.

The working group agreed that the following knowledge gaps have high priority for transatlantic collaboration to provide evidence in the short term to understand and stop the transmission of resistant bacteria from food-producing animals to humans:

1. Better understanding of transmission of antimicrobial-resistant bacteria from food-producing animals to humans, notably through food consumption (I.B.3.1.)
2. Enhanced information on antimicrobial consumption in animal species (I.C.1.1.)
3. Improved assessment of the impact on human and animal health of appropriate use of antimicrobials (including restricting use of certain substances) in food-producing animals (I.C.1.4.)
4. Coordinated/harmonised approaches for integrated surveillance of antimicrobial resistance in zoonotic bacteria from humans, foodstuffs and food-producing animals are lacking (I.C.2.1.)

   Need for better and more comprehensive data on antimicrobial resistance in zoonotic pathogens and indicator bacteria from humans (I.C.4.1.)

5. Need for continued efforts to develop and apply standardized in vitro antimicrobial susceptibility testing methods and use validated breakpoints for interpreting and reporting data (I.C.4.2.)

6. Impact of use of alternatives to antimicrobials on antimicrobial resistance (II.4.1.) Veterinary regulatory agencies will discuss the particular challenges related to authorisation of novel veterinary therapies presented as alternatives to antimicrobials aiming to develop similar approaches to achieving regulatory approval, thereby accelerating access to market.

During the TATFAR meeting in Luxembourg (22-23 October 2015) it was decided to rename "recommendations" as "actions" to make it more explicit that concrete actions are expected by TATFAR collaborators.

The above mentioned high priority knowledge gaps were reviewed at this meeting and were translated into specific actions for the next TATFAR implementation period. The following table summarizes the connections between the high priority knowledge gaps identified in this document and the new TATFAR actions, with corresponding numbers allocated within the overall TATFAR action plan for further collaboration.

Table 1. Connections between the high priority knowledge gaps identified in this document and the new actions in the TATFAR action plan

High priority knowledge gaps (number in this document)	New TATFAR action (number in TATFAR list of new actions)*
1. Better understanding of transmission of antimicrobial-resistant bacteria from food-producing animals to humans, notably through food consumption (I.B.3.1.)	**1.5** Collaborate on implementation of the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance prepared by Codex Alimentarius.
2. Enhanced information on antimicrobial consumption in animal species (I.C.1.1.)	**1.4** (Veterinary) Cooperate in the development of methodology for measuring and reporting the consumption of antimicrobials per species in veterinary medicine.
3. Improved assessment of the impact on human and animal health of appropriate use of antimicrobials (including restricting use of certain substances) in food-producing animals (I.C.1.4.)	**1.6** Enhance information sharing on approaches to promoting and assessing the impact of appropriate use in veterinary communities.
4. Coordinated/harmonised approaches for integrated surveillance of antimicrobial resistance in zoonotic bacteria from humans, foodstuffs and food-producing animals are lacking (I.C.2.1.) Need for better and more comprehensive data on antimicrobial resistance in zoonotic pathogens and indicator bacteria from humans (I.C.4.1.)	**1.7** Cooperate in the areas of research and surveillance aiming to improve understanding of foodborne transmission of bacteria resistant to certain classes of antimicrobials. As part of this cooperation, exchange of information and methodology to enable the collection of better and more comprehensive data on antimicrobial resistance in zoonotic pathogens and indicator

High priority knowledge gaps (number in this document)	New TATFAR action (number in TATFAR list of new actions)*
	bacteria from humans.
5. Need for continued efforts to develop and apply standardized in vitro antimicrobial susceptibility testing methods and use validated breakpoints for interpreting and reporting data (I.C.4.2.)	**2.4** Encourage efforts to harmonise, to the extent possible, interpretive criteria for susceptibility reporting of bacterial isolates for contribution of data to the WHO Global Antimicrobial Resistance Surveillance System (GLASS)
6. Impact of use of alternatives to antimicrobials on antimicrobial resistance (II.4.1.)	**3.7** Veterinary regulatory agencies will discuss the particular challenges related to authorisation of novel veterinary therapies presented as alternatives to antimicrobials aiming to develop similar approaches and requirements, thereby accelerating access to market.

** Prefixes of new TATFAR action numbers: 1, Promote and assess the impact of responsible use; 2, Reduce need for antimicrobials; 3, Promote development of new antimicrobials or alternatives.*

The working group also agreed to create a forum for exchange of information in the content of implementing this set of TATFAR actions.

Annex

Annex 1. List of implementers and affiliations

European Union:

- European Commission Directorate-General for Research and Innovation (EC DG RTD)
- European Commission Directorate-General for Agriculture and Rural Development (EC DG AGRI)
- European Commission Directorate-General for Health and Food Safety (EC DG SANTE)
- European Centre for Disease Prevention and Control (ECDC)
- European Food Safety Authority (EFSA)
- European Medicines Agency (EMA)

United States of America:

- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)
- United States Department of Agriculture (USDA)

Annex 2. Inventory of knowledge gaps

I. *Understanding the transmission to humans of antimicrobial resistance that arises as a result of the use of antimicrobial drugs in food-producing animals*

I.A. Understanding characteristics and the extent of antimicrobial resistance in bacteria arising as a result of antimicrobial drug use in animals

I.A.1. Risk factors for occurrence of antimicrobial resistant bacteria in animals and/or the environment

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.A.1.1. Risk factors for occurrence of antimicrobial-resistant bacteria in animals and/or their environment	Intramural and extramural research agenda for antimicrobial resistance ecology EFFORT project: Antimicrobial consumption related risk factors at animal and herd level which influence antimicrobial resistance will be studied. CARB 2.4.3.: CDC and FDA will work with EPA to evaluate the risk of environmental uses of antibiotics on human health. CARB 4.2.: Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease. CARB 5.4.2.: Develop international collaborations to gather country-specific and regional information on drivers of antibiotic resistance, identify evidence-based interventions, adapt these strategies to new settings, and evaluate their effectiveness. CARB 5.8.: Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment guidelines related to the licensure and/or approval of veterinary medicinal products, including antibacterial agents, vaccines, and diagnostics, to the extent possible.		(CARB, 2015; EFFORT, 2015; EFSA, 2011; USDA, 2015)

I.A.2. Relationship between antimicrobial consumption in food-producing animals and antimicrobial resistance in bacteria from animals and foodstuffs derived thereof

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.A.2.1. Relationship between antimicrobial use in food-producing animals (measured at the population level) and the development of antimicrobial resistance	CARB 4.1.1: A National Institute of Mathematical and Biological Synthesis (NIMBioS) working group is developing an analytic modelling framework for assessing the relationship between antibiotic use in livestock (measured at the population level) and the development of antimicrobial resistance. EFFORT project: The relationship between antimicrobial consumption and resistance prevalence at animal, herd and sector level will be analysed and quantified. Quantification of AMR will be performed by conventional methods and metagenomics.		NIMBioS AMR Working Group (link) (ECDC/EFSA/EMEA, 2009; EFFORT, 2015; EMEA/CVMP/SAGAM, 2009)
I.A.2.2. Metaphylactic/ prophylactic/ nontherapeutic use of antimicrobials and its impact on antimicrobial resistance	none		(CARB, 2015; EMA, 2014)
I.A.2.3. Effects of co-selection on resistance to antimicrobials	Ongoing. The National Antimicrobial Resistance Monitoring System (NARMS) is publishing online the available data on its collection of bacteria – Salmonella, Campylobacter, Escherichia coli, and Enterococcus – that are found in the gut of animals and humans (enteric isolates), collected over the past 18 years, although data on all bacteria aren't available from all sample sources all years. NARMS is a collaborative effort of the FDA, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA) which gathers data from retail meat samples, human clinical samples, and slaughter samples, respectively.		(ECDC/EFSA/EMA, 2015; NARMS, 2015)

I.A.2.4. Impact of use of heavy metals (such as zinc) for animal treatments on heavy-metal resistance of bacteria in animals and the environment			(EFSA, 2013)

I.B. Understanding transmission to humans of antimicrobial resistance from animals

Foodborne transmission

I.B.1. Transmission of antimicrobial-resistant bacteria from food-producing animals to foodstuffs

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.B.1.1. Mechanism and pathways of dissemination of antimicrobial-resistant bacteria from animals to food	APHIS On farm sampling WHO-AGISAR 2016 EFFORT project: The ecology and transfer of antimicrobial resistance mechanisms in the food chain will be investigated.		(CARB, 2015; EFFORT, 2015; EFSA, 2011; EFSA, 2013; EMA, 2014; NARMS, 2015; USDA, 2015)

I.B.2. Transmission of antimicrobial-resistant bacteria from animals to foodstuffs through the environment

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.B.2.1. Mechanism and pathways of dissemination of antimicrobial-resistant bacteria from animals to food through the environment			

I.B.3. Transmission of antimicrobial-resistant bacteria occurring in food-producing animals to humans through consumption of foodstuffs

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.B.3.1. Better understanding of transmission of antimicrobial-resistant bacteria from food-producing animals to humans, notably through food consumption	Implementation of WGS (whole genome sequencing) into surveillance EFFORT project: The project will describe antimicrobial resistance patterns in samples from different sources, and will analyse relations with determinants at the farm level in order to quantify to humans through different potential routes (air and ingestion, direct contact with animals, exposure via food). CDC food source attribution analyses based on antimicrobial resistance data.	high priority	(EFFORT, 2015; EFSA, 2008; NARMS, 2015)

Direct transmission

I.B.4. Direct transmission of antimicrobial-resistant bacteria from animals to humans (colonisation, infection)

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.B.4.1. Risk factors and transmission routes involved in the transfer of antimicrobial resistance between companion animals, food-producing animals and humans and vice versa	USDA does not do companion animals Research on the characterization of antimicrobial resistance genes from the human microbiome and its interactions (e.g. transfer potential) with environmental, animal and food reservoirs of resistance determinants via the FP7 research project EvoTAR EFFORT project: The role of companion animals in antimicrobial resistance transmission is considered and included in human exposure modelling. American Veterinary Medical Association (AVMA) Task Force for Antimicrobial Stewardship in Companion Animal Practice: develop practice guidelines for implementing antimicrobial stewardship in companion animal practice. (link)		(CARB, 2015; EFFORT, 2015; EMA/CVMP, 2015; EvoTAR, 2015; USDA, 2015)

Environmental transmission (not involving food…)

I.B.5. Transmission of antimicrobial-resistant bacteria from animals to humans through the environment

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.B.5.1. Identification of the pathways for dissemination of antimicrobial-resistant bacteria and resistance genes from animals to the environment	Implementation of WGS into surveillance EFFORT project: Description of antimicrobial resistance in bacteria in different environmental samples and reservoirs (air, water, soil) and associations with farm determinants.	high priority for the future (not likely to produce measurable results in the short term)	(EFFORT, 2015; EMA, 2014; NARMS, 2015)
I.B.5.2. Identification of the pathways for dissemination of antimicrobial-resistant bacteria and resistance genes from the environment to humans	APHIS: On farm sampling EFFORT project: Description of antimicrobial resistance patterns in environmental samples, and analyse relations with determinants at the farm level in order to quantify transmission through the environment to humans through different potential routes (air and ingestion, direct contact with animals, food intake).		(EFFORT, 2015; WHO, 2015)

I.C. Underlying surveillance data needed to understand whether and how antimicrobial resistance arises in bacteria as a result of the use of antimicrobial drugs in animals and how it is transmitted to humans

I.C.1. Surveillance of antimicrobial consumption in animals

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.C.1.1. Enhanced information on antimicrobial consumption in animal species	ESVAC project is starting the collection of data by animal species. Some European countries collect and some are about to implement collection of data by animal species. Enhancement of existing on farm surveillance of management practices. Implementation of new surveillance streams on antimicrobial drug use on farms. The ESVAC project is about to publish EU wide DDDvet and DCDvet, principles for assignment of DDDvet and DCDvet have been published (EMA, 2015) EFFORT project: Methodological contribution on one-time collection of data on antimicrobial consumption including farm characterisation in nine European countries in pigs and poultry, and in 3 countries for turkey, veal and fish production and companion animals.. The project is in open dialogue with ESVAC to ensure compatibility of the results. CARB 2.4.2.: Enhance collection and reporting of data regarding antibiotic drugs sold and distributed for use in food-producing animals. In May 2015 the U.S. Food and Drug Administration is proposing revisions to its annual reporting requirements for drug sponsors of all antimicrobials sold or distributed for use in food-producing animals in order to obtain estimates of sales by major food-producing species (cattle, swine, chickens, and turkeys). (link) CARB 2.4.3: Implement voluntary monitoring of antibiotic use and resistance in pre-harvest settings to provide nationally representative data while maintaining producer confidentiality.	high priority	(CARB, 2015; ECDC/EFSA/EMA, 2015; EFFORT, 2015; EMA, 2014; EMA, 2015; FDA, 2015; USDA, 2015)

I.C.1.2. Changes in antimicrobial consumption	The ESVAC report, which is annually produced, includes a new chapter of trends in consumption of fluoroquinolones and 3rd- and 4th-generation cephalosporins per country. In October 2014 FDA enhanced its annual summary of antimicrobials sold or distributed in food-producing animals to include additional information, including data tables on the importance of each drug class in human medicine, provides aggregate data on the approved routes of administration for these drug products, whether they are available over-the-counter or require veterinary oversight, and whether they are approved for use for therapeutic purposes, or for production purposes or both therapeutic and production purposes. (link)		(EMA, 2014; EMA, 2015; FDA, 2015)
I.C.1.3. Lack of information on the off-label use of the antimicrobials	The Commission proposal for a new EU Regulation on veterinary medicines maintains the current requirement for veterinarians to keep specific records of off-label use which should be available for inspection by the competent authorities for a period of at least 5 years.		(EMA, 2014)
I.C.1.4. Improved assessment of the impact on human and animal health of restricting certain uses of antimicrobial drugs in food-producing animals	Joint EFSA/EMA opinion as requested by EC (EFSA/EMA, foreseen 2016) EFFORT project: The impact on animal health of multi-level interventions on poultry and pig farms to reduce and abolish antimicrobial treatments (in particular fluoroquinolones and cephalosporins) will be studied and implemented in experimental studies under farm conditions. Economic and welfare parameters will be included. CARB 1.2.2: Assess progress toward eliminating the use of medically important antibiotics for growth promotion in food-producing animals through enhanced data collection on antibiotic sales and use.	high priority	(EFFORT, 2015; EFSA, 2011; EFSA, 2013; EMA, 2014)

I.C.2. Surveillance of antimicrobial resistance in bacteria from animals and food

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.C.2.1. Coordinated/harmonised approaches for integrated surveillance of antimicrobial resistance in zoonotic bacteria from humans, foodstuffs and food-producing animals are lacking	Annual EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food (EFSA and ECDC). JIACRA reports will be produced regularly. NARMS Integrated Annual Report (FDA, CDC, USDA) (link)	high priority (likely to produce measurable results in the short term)	EU legislation on monitoring zoonotic and commensal bacteria, (ECDC/EFSA/EMA, 2015) EU surveillance reports by the 3 agencies; (NARMS, 2015; USDA, 2015)
I.C.2.2. There is currently a lack of information on the existence and prevalence of antimicrobial resistance in animal pathogens	Surveillance of antimicrobial resistance in target pathogens in the EU: the new Regulation on transmissible animal diseases ("Animal Health Law")[1] provides a legal basis for monitoring AMR in animal pathogens. This monitoring is a possibility and not an obligation (i.e. no specific start of monitoring is foreseen). Surveillance of key animal health pathogens via diagnostic laboratory networking. CARB 2.3.: Develop, expand, and maintain capacity in veterinary and food safety laboratories to conduct standardized antibiotic susceptibility testing and characterize selected zoonotic and animal pathogens CARB 2.4.1.: Enhance surveillance of antibiotic resistance in animal and zoonotic pathogens and commensal organisms by strengthening the National Antimicrobial Resistance Monitoring System (NARMS) and leveraging other field- and laboratory-based surveillance systems.		(ECDC/EFSA/EMA, 2015; USDA, 2015)

[1] Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law'), OJ L 84, 31.3.2016, P.1

I.C.2.3. Need for more epidemiological data allowing to assess the representativeness of antimicrobial resistance data within the framework of the surveillance of antimicrobial resistance (e.g. sampling plan; origin of the samples; domestic production vs. import vs. export)	Additional sampling of retail products and clinical salmonellae Implementation by the EU MSs of the new EU legislation on antimicrobial resistance monitoring in animals and food and of the EFSA technical specifications on randomised sampling for harmonised monitoring of antimicrobial resistance in zoonotic and commensal bacteria USDA-FSIS will expand its meat sample and cecal sample surveillance for antimicrobial resistance, in collaboration with FDA, NARMS, and other USDA offices. FDA will expand retail meat sampling to improve the representativeness of surveillance data on bacterial contamination of meat products.		(CARB, 2015; ECDC/EFSA/EMA, 2015; EFSA, 2011; EFSA, 2013; EFSA, 2014; NARMS, 2015; USDA, 2015) New EU legislation on antimicrobial resistance monitoring

I.C.3. Surveillance of antimicrobial consumption in humans

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.C.3.1. Need for better and more comprehensive data on antimicrobial consumption in health care settings	ESAC-Net Protocol for surveillance of antimicrobial consumption in hospitals in the EU planned for 2016 (ECDC) Expanded enrolment of US hospitals in National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance Surveillance (CDC) and the use of a proprietary data set to address this need in inpatient settings. For outpatient settings, national survey data (National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey) and proprietary antimicrobial consumption data are being used to characterize the volume of antimicrobial use, assess appropriateness, and identify the patient populations, provider types and geographic areas associated with higher prescribing.		(ECDC, 2014c; ECDC, 2014d) Latest data on antimicrobial consumption in the EU 2013 available from the ESAC-Net interactive database (link)

I.C.4. Surveillance of antimicrobial resistance in bacteria from humans

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.C.4.1. Need for better and more comprehensive data on antimicrobial resistance in zoonotic pathogens and indicator bacteria from humans	ECDC: EU protocol for harmonised monitoring of antimicrobial resistance in human Salmonella and Campylobacter isolates Improved data quality through annual AST EQA Contracted by ECDC. (First report to be published 2015). Expansion of NARMS testing of antimicrobial resistance in human Salmonella and Campylobacter isolates	high priority	(CARB, 2015; ECDC, 2014b; EFSA/ECDC, 2015; NARMS, 2015)
I.C.4.2. Need for continued efforts to develop and apply standardized in vitro antimicrobial susceptibility testing methods and use validated breakpoints for interpreting and reporting data	ECDC 4 year contract with EUCAST planned (2016-2019). Integrated surveillance programs continue to engage methods and breakpoint setting organizations such as CLSI and EUCAST.	high priority	(ECDC, 2014a)

I.C.5. Attribution of antimicrobial consumption in humans to antimicrobial resistance in humans

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
I.C.5.1. Need to investigate whether it is possible to develop statistical models to attribute the proportion of antimicrobial resistance in human infections, both overall and by pathogen, to specific human use, animal use, and plant and other uses of antimicrobials	Need identified and discussed. Will depend on the availability of data from other elements of this table, and not feasible until those inputs are developed.	high priority for the future (not likely to produce measurable results in the short term)	

II. Developing effective intervention measures to prevent this transmission, including alternatives to antimicrobial drugs

II.1. Prevention of animal disease

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
II.1.1. Analysis of the impact of good farming practices in animal husbandry and its results on reduction of antimicrobial resistance and use of antimicrobials	Joint EFSA/EMA opinion as requested by EC (EFSA/EMA, foreseen 2016) EFFORT project: The relationship between biosecurity and management characteristics as well as animal health and welfare factors and the antimicrobial consumption will be analysed and quantified. EU via the Research and Innovation Framework Programme Horizon 2020 has included a topic in its 2017 call on alternative production systems to address antimicrobial drug usage. EFFORT: (a) Development and implement practical and science-based assessment decision support (ADS) tools for poultry and pig farms in order to reduce use of antimicrobial treatments (including abolishment of the use of fluoroquinolones and cephalosporins) and (b) assess the effect of implementing those on antimicrobial usage, change in antimicrobial resistance patterns, animal health and welfare and related economic aspects. CARB 1.3.: Identify and implement measures to foster stewardship of antibiotics in animals.		(EFFORT, 2015; EFSA, 2011; EFSA, 2013; EMA, 2014)

II.2. Diagnosis of animal diseases

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
II.2.1. The ability to rapidly characterize newly emerged antimicrobial resistance in microorganisms and elucidate the underlying mechanisms; this knowledge is necessary to ensure that surveillance and diagnostic tools and methods remain current. Analysis of impact of better diagnose tools on transmission of antimicrobial resistance	Apply cutting edge technologies such as whole genome sequencing to antimicrobial-resistant microorganisms from humans, foods, animals and the environment (CDC, FDA, USDA). Provide forum for communicating emerging antimicrobial resistance findings and rapid detection methods among relevant clinical, diagnostic, and public health audiences (APHL, CDC, FDA, USDA).		(CARB, 2015; EFSA, 2011; EFSA, 2013; WHO, 2015)

II.3. Treatment of animals

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
II.3.1. Better treatment of common bacterial infections			(WHO, 2015)

II.4. Alternatives to use of antimicrobials

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
II.4.1. Impact of use of alternatives to antimicrobials on antimicrobial resistance	Joint EFSA/EMA opinion as requested by EC (EFSA/EMA, foreseen 2016) CARB 4.4: USDA, in collaboration with NIH, FDA, and the agriculture industry, will develop a research and development strategy to promote understanding of antibiotic-resistance and the creation of alternatives to (or improved uses of) antibiotics in food animals. CARB 4.4: USDA will solicit proposals that comprehensively develop research and outreach programs targeting development of novel alternatives to antibiotics for use in animals. CARB 5.5: USDA will establish or expand five collaborative international partnerships to facilitate research regarding development of alternatives to antibiotics, as well as vaccines and new antimicrobial drugs that are less likely to develop resistance. Proceedings of OIE meeting on alternatives to antibiotics recognised the particular regulatory challenges that such products will need to meet.	high priority (likely to produce measurable results in the short term)	(CARB, 2015; WHO, 2015), OIE alternatives to antibiotics meeting proceedings

II.5. Control options to prevent emergence/spread of antimicrobial resistance in humans

Knowledge gaps	Work underway or planned	Priority gap	Relevant documents
II.5.1. Need for assessing the effectiveness of control options to reduce public health risks caused by the transmission of antimicrobial-resistant bacteria through the food chain or via the food-producing animal environment to humans			(EFSA, 2011; EFSA, 2013)

Annex 3. Abbreviations and acronyms

AGISAR – WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMEG – Antimicrobial Advice ad hoc Expert group
AMR – Antimicrobial resistance
APHIS – Animal and Plant Health Inspection Service
AST – Antimicrobial susceptibility testing
CARB – U.S. National Action Plan For Combating Antibiotic-Resistant Bacteria
CDC – Centers for Disease Control and Prevention
CVMP – Committee for Medicinal Products for Veterinary Use
DANMAP –The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DCDvet – Defined Cure Dose Veterinary
DDDvet – Defined Daily Dose Veterinary
DG RTD – Directorate-General for Research and Innovation
DG SANTE – Directorate-General for Health and Food Safety
EARS-Net – European Antimicrobial Resistance Surveillance Network
EC – European Commission
ECDC – European Centre for Disease Prevention and Control
EFFORT – Ecology from Farm to Fork Of microbial drug Resistance and Transmission
EFSA – European Food Safety Authority
EMA – European Medicines Agency
ESAC-Net – European Surveillance of Antimicrobial Consumption Network
ESVAC – European Surveillance of Veterinary Antimicrobial Consumption
EU – European Union
EUCAST – The European Committee on Antimicrobial Susceptibility Testing
EvoTAR – Evolution and Transfer of Antibiotic Resistance
FDA – Food and Drug Administration
JIACRA – Joint Interagency Antimicrobial Consumption and Resistance Analysis
MRSA – Methicillin-Resistant *Staphylococcus aureus*
NARMS – National Antimicrobial Resistance Monitoring System
NIMBioS – National Institute of Mathematical and Biological Synthesis
TATFAR – Transatlantic Taskforce on Antimicrobial Resistance
USA – United States of America
USDA – United States Department of Agriculture
WGS – Whole genome sequencing
WHO – World Health Organization

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