FOOD PATHWAYS TO ANTIMICROBIAL RESISTANCE: A CALL FOR INTERNATIONAL ACTION

Policy overview

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Health Care Without Harm

CONTENTS

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INTRODUCTION

Due to its rising prevalence, antimicrobial resistance (AMR) is a global threat to sustainable development. Whilst there are many diverse factors influencing the development and spread of AMR, the use of antibiotics in food production is one that has long been unrecognised. Several food ingredients contribute to AMR through production, processing, and even preparation in kitchens, including hospital kitchens.

Hospitals and health systems are on the front line when it comes to treating infections, they therefore play an important role in leading global action to protect public health, the environment, and the economy, through the food they choose to procure and serve.

Whilst some actions have already taken place at international and regional levels to respond to this growing challenge, this publication will provide a closer look at legislation and campaigns in Europe and the U.S. that are reforming the use and monitoring of antimicrobials within the food supply chain. This overview also includes Health Care Without Harm (HCWH)'s recommendations on identifying what is still needed to address this global threat, and how hospitals and healthcare systems can contribute to a safer, healthier, and more sustainable food supply chain.

Food: an under-recognised pathway of AMR

There are a number of risks associated with the intensive use of antimicrobials in agriculture;[1] drug-resistant strains of microorganisms can be passed on to humans via:

1. Direct contact with animals on farms
2. Processing, transport, or handling of food animals and food
3. The environment (e.g. contamination of water and soil via manure or waste water discharge from plants manufacturing antibiotics)

What is AMR?

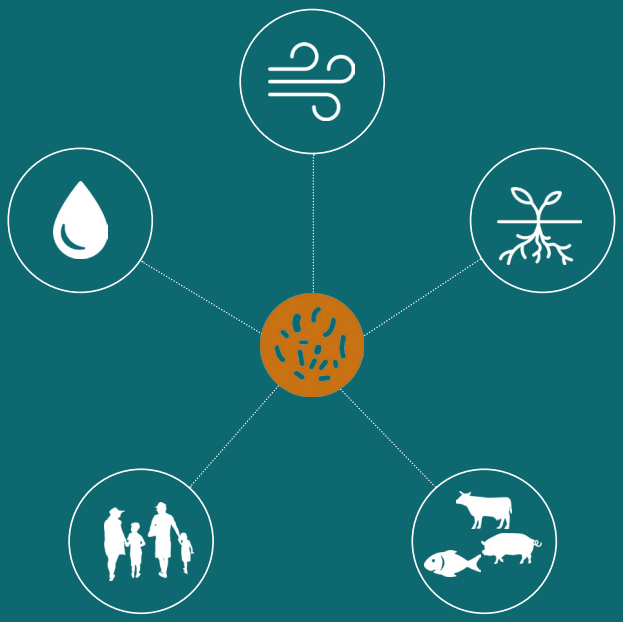
Antimicrobial Resistance (AMR) is a broad term describing viral, parasitic, fungal, or bacterial microorganisms becoming resistant to antimicrobial drugs. This leads to treatments becoming ineffective, infections persisting, and an increased risk of infections spreading.[2] Resistance to antibiotics is of particular concern: it is considered one of the greatest global threats to public health.[3]

FOOD AS A SOURCE OF AMR: THE FACTS

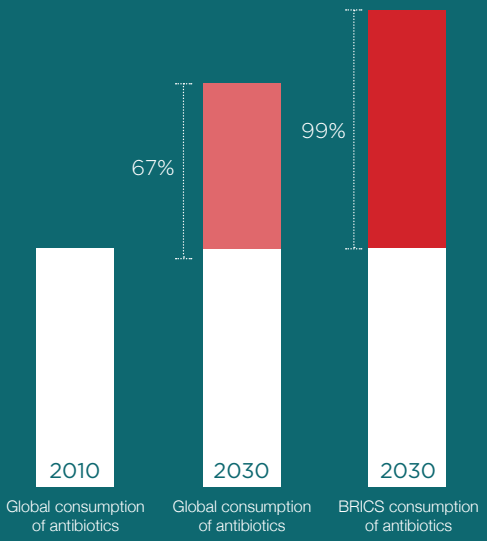
By **2050**, drug resistant infections will cause approximately

10 million deaths worldwide -

over 14 times the current number (700,000)[4]

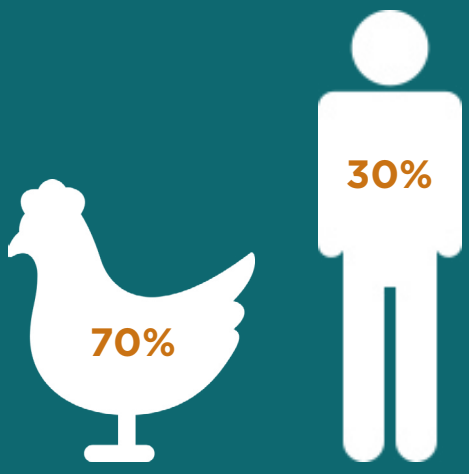


Antibiotic resistant bacteria can be found in soil, air, water, animals, and people [1]



Global consumption of antibiotics in agriculture will increase by 67% from 2010 to 2030. Consumption of antibiotics in BRICS countries (Brazil, Russia, India, China, and South Africa) will increase by 99% in the same period [5]

Across the world, the vast majority of medically important antibiotics for human health (by weight) are not used in human medicine, but in veterinary medicine



More than 70% of all antibiotics sold in the U.S. are used in livestock/animal agriculture [1]

The European Medicine Agency showed that approximately two thirds of all antibiotics used in 26 European countries were used in farm animals [6]

POLICY OVERVIEW

Notable policy instruments to tackle AMR in humans already exist at the international, EU, and U.S. levels but they are inadequate in addressing the increasing problem of antimicrobial resistant bacteria spreading in the environment. HCWH asserts that the healthcare sector should play a leadership role in the fight against AMR: taking action in their own facilities and advocating for effective and comprehensive policy measures.

Hospitals and health systems throughout the world can take a comprehensive approach to reduce AMR in humans and the environment by supporting actions that encourage medical professionals to safely minimise the prescription of antibiotics and implement healthy and sustainable food policies in their facilities.

INTERNATIONAL LEVEL

Due to intensified human mobility and trade of food and animals, antibiotic resistance is a problem that crosses national borders; overuse of antibiotics (and consequent resistance) in one region will undermine achievements in containing AMR elsewhere.[7] For this reason, all countries must pay greater attention to the spread of AMR – international, cross-sectoral, and collaborative action is needed.

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established in 2009 for future collaborations between the U.S. and the EU in order to increase information exchange, understand best approaches and practices, as well as develop peer relationships.[8]

To address the challenge of AMR at the international level and to fulfil the overall goal of the **Global Action Plan on Antimicrobial Resistance** (adopted in May 2015 at the World Health Assembly), the **World Health Organization (WHO)** in collaboration with the **Food and Agriculture Organization of the United Nations (FAO)** and the **World Organisation for Animal Health (OIE)**, has published multiple global strategies for AMR containment.

This Global Action Plan aims "to ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them."[9]

AMR and the SDGs

During recent decades, the issue and consequences of AMR have become part of the global health agenda, however, AMR has been omitted from the targets of the United Nations Sustainable Development Goals (SDGs) and is only mentioned in paragraph 26 of the 2030 Agenda for Sustainable Development:

> *"We will equally accelerate the pace of progress made in fighting malaria, HIV/AIDS, tuberculosis, hepatitis, Ebola and other communicable diseases and epidemics, including by addressing growing anti-microbial resistance and the problem of unattended diseases affecting developing countries".*[10]

As stated during the 71st meeting of the United Nations General Assembly (26th September 2016),[11, 12] AMR may impact upon the achievement of specific SDGs, including:

- **SDG 1:** End poverty in all its forms everywhere
- **SDG 2:** End hunger, achieve food security and improved nutrition, and promote sustainable agriculture
- **SDG 3:** Ensure healthy lives and promote well-being for all at all ages
- **SDG 6:** Ensure availability and sustainable management of water and sanitation for all
- **SDG 8:** Promote sustained, inclusive, and sustainable economic growth, full and productive employment, and decent work for all
- **SDG 12:** Ensure sustainable consumption and production patterns
- **SDG 17:** Strengthen the means of implementation and revitalise the Global Partnership for Sustainable Development.[13]

To manage the consequential risk arising from antibiotic use in agriculture, the WHO has also created (and continues to update) a list of

medically important antibiotics, as well as providing guidance on surveillance of antibiotic resistance and antibiotic use.[14, 15] The OIE also has numerous activities linked to antibiotic resistance, including a list of antibiotics important for animal agriculture and a global survey of veterinary antibiotics sales and use.[16, 17] Other OIE publications and resources are also available online for:

- Improving political and general awareness of AMR
- Promoting better practices in food and agricultural systems
- Ensuring prudent use of antimicrobials to help combat AMR

This risk management will be achieved in the spirit of a 'One Health Approach'* throughout the FAO's **Code of Practice to Minimize and Contain Antimicrobial Resistance**.[18] This Code of Practice focuses on antimicrobial use in food–producing animals and recognises that antimicrobial resistance is also an ecological problem; it will be reviewed and updated by a task force starting in October 2017.[19]

* **'One Health'** *is an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes.*[20]

EU LEVEL

The EU has been quick to recognise the importance of tackling AMR - reinforcing policies for animal health, as well as investing in research for more new antimicrobial molecules and alternatives. The EU supports numerous initiatives and programmes at a national level - such as supporting Member States in the development of national action plans on AMR.

To better coordinate and align worldwide AMR reduction efforts, the EU also works at the international level: collaborating with the WHO, OIE, FAO, and members of the G7. Despite the EU's strong position to act and its leadership in tackling AMR, there are still, however, areas for further research and improvement, e.g. negative impacts of AMR in the environment (particularly on food chains), and discrepancies between Member States' actions towards tackling AMR.

This section provides an overview of adopted and proposed EU legislation and guidelines to reduce the overuse of antimicrobials in animals, as well as the prevalence of drug-resistant bacteria. Unless the proposed policy actions at the European level effectively address all causes of AMR (including the overuse and misuse of antimicrobials within the food chain), Europe will fail to make further progress in coping with this increasing threat.

Adopted EU legislation

The following areas are covered by currently adopted EU legislation:

- Market authorisation rules for food and feed additives
- Quality of foodstuffs of animal origin
- Requirements regarding the prudent use of antimicrobials
- Monitoring of zoonoses (commutable diseases between vertebrate animals and humans) and zoonotic agents (pathogens of such diseases e.g. viruses, bacteria etc.).[21]

Regulation (EC) No 1831/2003[22] on additives for use in animal nutrition represents one of the most important achievements of current EU legislation: banning the use of antibiotics as growth promoters in animals. This ban has been in place since 1st January 2006.

Directive 2001/82/EC[23] **of the Community code relating to veterinary medicinal products** - Annex I of this Directive requires that the application file for marketing authorisation must provide data on the potential emergence of resistance.

Following referral procedures under Article 35 of this Directive, certain **Commission Decisions** are based on opinions of the European Medicines Agency (EMA) and Committee for Medicinal Products for Veterinary Use (CVMP) regarding critically important antimicrobials, such as:

- Quinolones – "ensure that the products identified [quinolones] are indicated only for appropriate conditions, that dosage strategies are set to minimise the likelihood of development of antimicrobial resistance, and that appropriate withdrawal periods are fixed to guarantee consumer protection" (2010).[24]

- Third and fourth generation cephalosporins – in 2012 the CVMP was positive regarding the inclusion of prudent use of these cephalosporins in food producing animals in the EU: they required that the risk associated with potential misuse in poultry and the need for specific measures, in particular the need for warning sentences in the product information, be addressed.[25]
- Polymyxins, the fifth most-sold antimicrobial class in 2014, account for 6.6% of total antimicrobial sales in 29 European countries.[26] More recently, the EU has adopted a tiered approach to curbing the use of polymyxin E, also known as colistin.
    - » Due to the potential serious health risk of colistin to both human and animal health, on 10th February 2010, CVMP adopted an opinion recommending that the market authorisation for individual medicinal formulations to be administered in drinking water for food producing animals should be specific to each formulation. Oral solutions, powders for injection, infusion, or inhalation that contain a 2,000,000 IU/ml concentration of colistin should each have a specific summary of the product characteristics (SPC), included in labelling and packaging. The aim is to ensure that correct dosage and withdrawal periods are observed (where applicable). The withdrawal period is a specific set period of time that must elapse between the last dose of veterinary medicine and when the affected animal(s) or animal products can enter the food chain.[27, 28]

Regulation (EC) No 470/2009 provides community procedures for establishing residue limits of pharmacologically active substances in foodstuffs of animal origin. This Regulation states that scientific risk assessments of pharmacologically active substances intended for veterinary medicinal products in the EU should examine the risk of microbiological effects to human beings.[29] In support of the existing pharmaceutical legislation, more detailed requirements on the quality of the medicinal products for veterinary use (including antimicrobials) have been provided in a series of guidelines at the EU level:

- **Volume 8** - Maximum residue limits guidelines (MRLs). In the general safety evaluation principles of residues concerning veterinary medicinal products in the EU, it is stated that "in the case of antibiotics and similar substances, the possibility of a microbiological risk addressing both the development of antimicrobial resistance in bacteria of the human gut flora and disruption of the colonisation barrier may also need to be considered."[30]

Directive 2003/99/EC on the monitoring of zoonoses and zoonotic agents sets an obligation for EU Member States to ensure that "monitoring provides comparable data on the occurrence of antimicrobial resistance in zoonotic agents and, in so far as they present a threat to public health, other agents."[31] This Directive amends Council Decision 90/424/EEC[32] and repeals Council Directive 92/117/EEC.[33]

Commission Implementing Decision 2013/652/EU on the monitoring and reporting of antimicrobial resistance in commensal* and zoonotic bacteria.[34] This document provides further information on:

- The sampling framework and collection of isolates (cultures of microorganisms isolated for study) by Member States
- How analysis by national reference laboratories should be achieved
- The assessment and reporting of the AMR monitoring
- The publication and confidentiality of data provided by the Member States.

Regulation (EU) 2016/429 on transmissible animal diseases (also known as 'Animal Health Law') complements the provisions in the veterinary medicines and medicated feed proposals; this regulation follows the EU Animal Health strategy principle "Prevention is better than cure".[35] It will be applied starting from 21st April 2021 and proposes:

- General preventive measures and behaviours that are aimed to contribute to reducing the use of antibiotics
- Rules on the prudent use of veterinary medicinal products (VMPs)
- Responsibilities, knowledge, awareness of operators and veterinarians

It also proposes some specific measures, such as that a "computerised interactive information system for the effective collection and management of surveillance data should be established at Union level for listed diseases and, when relevant, for emerging diseases or antimicrobial-resistant pathogens."[35]

** Bacteria that don't affect a human host i.e. non-pathogenic bacteria in a harmless symbiotic relationship*

On-going EU legislative proposals

The Regulation on veterinary medicinal products (VMPs) proposed by the European Commission is currently being negotiated within the European Council (since June 2017).[36] Whilst **Directive 2001/82/EC24**[23] scarcely mentions antimicrobial resistance, the Commission's current proposal contains a comprehensive package of specific provisions for addressing AMR, aiming to safeguard public health, animal health, food safety, and the environment. These provisions are based on two areas:

- The marketing authorisation of the antimicrobial VMPs: all antimicrobial products shall be subject to veterinary prescription, and the marketing authorisation will be refused if:
  - The product is presented as growth promoter
  - The "risk to public health due to AMR development outweighs the benefits to animal health"
  - The antimicrobial is reserved for treatment of certain infections in humans

  The proposed regulation on VMPs would empower the European Commission to establish rules for designation and designate antimicrobials reserved for humans (Art. 32(3)(4)). Additionally, the period of protection of technical documentation for new veterinary antimicrobials would be extended to 14 years.
- Post-marketing authorisation measures, which focus on the:
  - Collection of data on sales and use of VMPs
    - Relevant and comparable data shall be collected and sent to the EMA
    - The EMA shall analyse the data and publish annual reports
    - The European Commission shall establish detailed rules on methods of gathering data and of their transfer to the EMA
    - The European Commission may set up the format and the requirements for the data
  - Supply and use of VMPs
    - Prescribers (i.e. veterinary doctors) shall only distribute antimicrobial products for animals under their care, and only in the amount required for the treatment concerned
    - The European Commission may establish a list of products which cannot be used off-label (i.e. prescribing a drug outside of it's intended use) or can only be used subject to certain conditions
    - Whilst there are not specific advertising provisions for antimicrobial VMPs, they are included in the advertising provisions for VMPs in general. Advertising should not lead to overconsumption and should be banned for prescription-only products (except to prescribers and suppliers).

The Regulation on medicated feed (already revised by the European Parliament and European Council) is now awaiting progress on the Regulation on veterinary medicinal products.[37] A main objective of this proposed medicated feed regulation is to fight the misuse of antimicrobials by setting the following provisions:

- Banning the use in medicated feed for preventive treatment or as a growth promoter
- Requiring diagnosis of a disease prior to mandatory prescription for medicated feed
- Limiting treatment duration and the prescription's period of validity
- Establishing an EU-wide residue limit for veterinary medicines in ordinary feed.

Non-legislative tools at the EU level

In addition to adopted and proposed legislation, the EU also has some non-legislative instruments to support Member States in containing the development of AMR through prudent usage of antimicrobial drugs. These include the

European Commission's **Guidelines for the prudent use of antimicrobials in veterinary medicine** (September 2015)[38] or the European Medicines Agency (EMA) guidelines, recommendations, scientific advice, and joint reports with other EU agencies.

Under the coordination of the EMA, the **European Surveillance of Veterinary Antimicrobial Consumption Network (ESVAC)** collects information on how antimicrobial medicines are used in animals across the EU. The information is used to "identify possible risk factors that could lead to the development and spread of antimicrobial resistance in animals."[39]

The **Action Plan against the rising threats from Antimicrobial Resistance** was a five-year plan published by the European Commission in 2011.[40] Action two of this plan focussed on strengthening the regulatory framework regarding veterinary medicinal products and medicated feed. In 2017, the European Commission launched the **European One Health Action Plan against Antimicrobial Resistance (AMR)**[41] in which the Commission engages in addressing AMR. Several of the actions contained in the plan concern AMR in food and contribute to the following objectives:

- 2.1 Better evidence and awareness of the challenges of AMR
- 2.2 Better coordination and implementation of EU rules to tackle AMR
- 2.5 Stronger partnership against AMR and better availability of antimicrobials
- 3.1 Improve knowledge on detection, effective infection control, and surveillance
- 4.2 Stronger bilateral partnership for stronger cooperation
- 4.3 Cooperating with developing countries

European Antibiotic Awareness Day takes place annually on 18th November and aims to raise awareness about the public health impact of antibiotic resistance and the importance of prudent antibiotic use.[42]

Campaigns and educational material about AMR in food at the EU level

As part of the 'One Health' approach (see page 6), European regulations concerning AMR in humans, animals, and the environment must consider the work of different European organisations and alliances prioritising the issue of antibiotic abuse, including:

- **The European Public Health Alliance (EPHA)** is a European network that works to improve health and strengthen the voice of public health in Europe.[43] EPHA has examined the legal framework and opportunities (from both the human and animal point of view) to tackle antimicrobial resistance in the follow-up European Action Plan.
- **The Alliance to Save our Antibiotics** calls for EU-wide targets to reduce antibiotic use in agriculture - 50% by 2020 and 80% by 2050.[44] The alliance proposes urgent actions to ban routine preventative use of critically important antibiotics in groups of healthy animals; it works with farmers, food businesses, retailers, academics, policy makers, and human health organisations. The alliance also researches antibiotic use in different animal sectors (pig, poultry, dairy, etc.) primarily in the UK as well as other European countries, analysing best initiatives and discussing solutions and next steps. The organisation's latest research revealed the presence of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) in supermarket pork.[45]
- **The European Food Information Council (EUFIC) and The European Consumer Organisation (BEUC)** - two of the most important European consumer-oriented organisations - have produced educational materials to raise awareness about the causes of AMR.[46, 47] They also provide information on preventive measures for avoiding misuse or overuse of antimicrobials in livestock and human medicine. BEUC's **'From Farm to You'** campaign won the 2016 EU Health Award for NGO's fighting AMR.[48, 49]
- **ReAct Europe** is one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers.[50] ReAct has produced numerous educational resources and a toolbox aimed at students, communities, farmers, veterinarians, and health professionals, which is available in both English and Spanish.[51, 52] These resources explain the main contributing factors to the development of AMR, (particularly for the healthcare sector) in terms of

prescribing, dispensing, and other standard protocols, highlighting both the financial and health impacts of AMR.

- HCWH Europe's **Safer Pharma Campaign**[53] - HCWH Europe leads the only Europe-wide campaign addressing the issue of pharmaceutical residues in the environment and their environmental impact. The aims of the Safer Pharma Campaign are to:
  - » Challenge the pharmaceutical industry to clean up their production
  - » Raise awareness amongst healthcare professionals about the impact of pharmaceuticals in the environment, encouraging rational prescription practices
  - » Help citizens to understand the impact of pharmaceuticals in the environment and how to safely dispose of unused medicine
  - » Work towards transnational agreement to ensure the minimisation of pharmaceuticals in the environment

  Waste from the manufacture of antibiotics in the environment has been proven by scientists to be a reservoir for the spread of AMR, this campaign also aims at raising awareness about the environmental impact of AMR and advocates for actions to tackle the causes of this problem to be in place at international level.[54, 55]

U.S. LEVEL

During the past decade the U.S. has been responding to the highly complex problem of antimicrobial resistance by introducing legislation that strengthens the federal response to AMR through better coordination, leadership, surveillance, research, and prevention and control. Three U.S. government agencies take part in the oversight and regulation of antibiotic use in food production:

1. **The Food and Drug Administration (FDA)**[56] regulates and approves new drugs and drug use practices and enforces standards for antibiotic residue levels in food. The FDA's Center for Veterinary Medicine (CVM) supervises drug use in animals, approving drugs for use, and monitors safety and effectiveness of approved drugs.[57] The CVM also reviews reports on drug residues found by the Food Safety and Inspection Service (see below). Under the Federal Food, Drug, and Cosmetic Act,[58] the Animal Drug User Fee Act (ADUFA)[59] mandates reporting of all antibiotic sales for use in animal agriculture.
2. Multiple agencies within **The United States Department of Agriculture (USDA)** carry out research, surveillance, and labelling activities related to antibiotic use in agriculture.[60] These agencies collaborated in the development of the USDA Antimicrobial Resistance Plan (2014).[61] The degree to which they continue to collaborate, however, is unknown. USDA's Food Safety and Inspection Service (FSIS) is responsible for monitoring chemical residues (including antimicrobials) in meat, poultry, and egg products based on the tolerance levels set by the FDA.[62] Labelling claims related to use of antibiotics in animal husbandry (e.g. labels that state that the animal was raised without antibiotics) also fall under the jurisdiction of the FSIS. Data collected by the FSIS is analysed through the Public Health Information System (PHIS).[63] The USDA Agricultural Marketing Service (AMS) runs audit and accreditation programmes with independent third party auditors, and uses standards set by the International Organization for Standardization to verify claims, including those related to antibiotic use in agriculture.
3. **The Centers for Disease Control and Prevention (CDC)**[64] partner with the FDA and USDA through the National Antimicrobial Resistance Monitoring System (NARMS).[65] Under NARMS, these agencies, as well as state and tribal authorities, contribute to monitoring antimicrobial resistance of enteric (intestinal) bacteria found in animals, food, and humans. NARMS integrates and shares data on changes in the antimicrobial susceptibility of certain bacteria in ill humans, retail meats, and food animals.[66]

Adopted U.S. Regulation

This section provides an overview of adopted U.S. legislation and guidelines for reducing the prevalence of antimicrobial resistant bacteria and overuse of antimicrobials in animals, water, aquaculture, and crops. This overview provides the required knowledge for supporting progress on

antimicrobial resistance legislation in the U.S.

In 1977, The Food and Drug Administration (FDA)'s Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee proposed to withdraw the approvals for in-feed use of penicillin and two forms of tetracycline in animal production. Following the proposal, Congress requested and received additional data, but no legislation was enacted.[67, 68]

In 1994, the **Animal Medicinal Drug Use Clarification Act (AMDUCA)**[69] made off-label use of veterinary drugs legal, however, off-label use does not include in-feed or use for growth promotion.

The **1996 Animal Drug Availability Act**[70] made it easier to for the FDA to approve new animal drugs and medicated feeds and created the veterinary feed directive (VFD). The VFD was created to improve access to veterinary drugs in feed that require a veterinarian's order. (See opposite)

FDA Guidance for Industry #152 (2003) describes the process drug makers can use to show that new antimicrobial drug approvals are safe with respect to resistance.[71] The FDA applied this process to several existing drugs and found that their use in feed was inappropriate but did not act on findings.

- Ban on fluoroquinolones in Poultry (2005): The FDA withdrew fluoroquinolones (a type of broad-spectrum antimicrobial) from use in poultry water after the Center for Veterinary Medicine determined use of the drug was linked to the evolution of resistant Campylobacter species in poultry that poses a threat to humans.[72] Fluoroquinolones remain available, but only as injectable drugs with a veterinary prescription to treat and control of respiratory disease in cattle and swine.

FDA Guidance for Industry #213 (2013) set forth the process and timeline for implementing the **FDA Guidance for Industry #209 (2012**) which established a judicious use standard.[73, 74] Key components of that standard are:

- To end the use of medically important antimicrobial drugs in feed for growth promotion
- To engage veterinary oversight and consult in use of such drugs in feed and water by changing the status of certain antimicrobial drugs from over-the-counter to veterinary feed directive (VFD) or prescription[75]

FDA Guidance for Industry #213 also established a voluntary labelling change, which was fully implemented by 1st January 2017, with all drug sponsors making requested changes.[74] Once the labelling change took effect, medically important antibiotics (as defined by FDA) ceased being legally available for growth promotion purposes in animal production.

The Veterinary Feed Directive Final Rule (VFD) (2015)[75, 76] set forth the specific conditions for using veterinary drugs in feed (including all medically important antibiotics as of January 2017), that require a veterinarian's order. This rule amends the animal drug regulations established in the veterinary feed directive section of the **1996 Animal Drug Availability Act.**

Key provisions in the 2015 final rule include:

- A new standard for categorising VFD drugs, based on "likelihood drug will leave unsafe residue" – an existing standard for non-VFD drugs
- New recordkeeping requirements for clients, veterinarians, and distributors
- The VFD must be issued in the "context of a valid veterinarian-client-patient relationship", as determined by states, based on regulation of veterinary licensing and practice
- A requirement for VFD expiration date.

Animal feeding operations in the U.S.

The U.S. Environmental Protection Agency (EPA) defines Animal Feeding Operations (AFOs) as "agricultural operations where animals are kept and raised in confined situations." A Concentrated Animal Feeding Operation (CAFO) is an AFO that meets EPA thresholds concerning the quantity of animals and, in certain cases, the type of manure management system employed. An AFO that discharges manure or wastewater into a ditch, stream, or other waterway is defined as a CAFO regardless of the number of animals being raised.[77]

In compliance with the **Clean Water Act (CWA** and the **Safe Drinking Water Act**,[78] The United States Environmental Protection Agency (EPA) is responsible for regulating both ambient water quality and drinking water quality. For ambient water quality, a Total Maximum Daily Load may be established in impaired waterways for a given contaminant that has known adverse impacts on human health or aquatic ecosystems. For contaminants that are regulated under the Safe Drinking Water Act, a Maximum Contaminant Level is established indicating the highest level of a contaminant allowed in drinking water; both of these maximum levels/loads are enforceable standards.[79] Antimicrobials, other pharmaceuticals, and their by-products are not currently regulated as contaminants - they are considered Contaminants of Emerging Concern (CECs) and allowable limits in ambient and drinking water have not been established, even though antimicrobials are routinely detected in waterways.[80]

As well as antimicrobial contamination of water, antimicrobial resistant bacteria and antimicrobial resistance genes in water are also of concern to human health. While the EPA regulates level of contamination by monitoring several microorganisms, the monitoring of antibiotic resistant genes in the environment is lacking.[81, 82]

The U.S. EPA considers CAFOs point sources of pollution[83] as defined under **Section 502(14) of the CWA**.[78] CAFOs are therefore regulated under the **National Pollutant Discharge Elimination System (NPDES)**.[84] Antibiotics used in CAFOs and their by-products (from manure runoff or improper disposal of medications) can enter the ambient environment (i.e. water, soil, and air), contributing to the proliferation of AMR.

Animals raised in CAFOs are given routine, non-therapeutic doses of antibiotics in food and water to compensate for crowded and unsanitary conditions; this chronic exposure to low doses of antibiotics leads to antibiotic resistant bacteria developing in the gut of these animals. The resistant bacteria can then spread to humans through:

- Contaminated water or soil
- Direct contact with animals carrying resistant bacteria
- Contact with farmworkers who are carriers of antibiotic resistant bacteria
- Contact with or consumption of contaminated meat

According to the EPA, manure and wastewater entering ditches, streams, or other waterways from Animal Feeding Operations (AFOs) contribute pollutants, including antibiotics, to the environment.[85] NPDES permitting, however, only applies to AFOs that are considered CAFOs. **The Natural Resources Conservation Service (NRCS)**, an agency of the USDA, works in collaboration with the EPA to provide landowners with technical and financial assistance to take voluntary action to minimise the environmental impacts of manure storage facilities.[77]

In contrast to EU legislation, in the U.S. few antibiotics are approved for use in aquaculture; vaccines rather than antibiotics are used for disease prevention.[86] Medically important antibiotics are still used in US aquaculture, however, to treat diseases without available vaccines. In developing countries, where a significant portion of farmed seafood originates, use of antibiotics as a preventative measure is still common; vaccines have not replaced this practice.[87] As the scale and prevalence of aquaculture continues to grow worldwide to almost half of the global catch, the use of antibiotics in fish baths and feed to prevent disease is concerning.[86,88] Even low and legal levels of antibiotic use in domestic aquaculture can contribute significantly to antimicrobial resistance.[86, 89] This may be attributable to the fact that water provides an easy and constant medium through which antibiotics and resistant genes can disperse, increasing the impact of low level doses.

Little is known about the impacts of antimicrobial use in **fruit production**; since the 1950s, antimicrobials have been used to control plant diseases, including fire blight and citrus greening.[90] Since these antimicrobials are used as pesticides, they are monitored and evaluated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which regulates pesticide distribution, sale, and use.[91] The United States Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA) work with the EPA to test food and monitor pesticide residues on food.

The U.S. National Organic Standards Board disallowed the use of antimicrobial pesticides in organic fruit production in October 2014, however they are still approved for pesticide use in conventional fruit production. Two of the main antimicrobials used (streptomycin and oxytetracycline)

are also used in human medicine.[92] The extent of antibiotics used in fruit production is currently under-researched and therefore the impact on antimicrobial resistance is currently unknown.

Campaigns and educational materials about AMR and food at the U.S. level

Similar to the EU, there are organisations and alliances in the U.S. also conducting numerous campaigns and strategies to raise awareness and educate about the issue of antibiotic abuse.

Health Care Without Harm US & Canada has worked on this issue in the healthcare sector for the last 20 years, advocating for better antibiotic stewardship and a phase-out of purchasing meat raised with routine antibiotics in healthcare facilities.

- **U.S. Antibiotic Awareness Week** (formerly Get Smart About Antibiotics Week) organised by the United States Centers for Disease Control and Prevention (CDC) occurs annually to raise awareness about the threat of antibiotic resistance and the importance of appropriate antibiotic prescription and use.[93]
- **Keep Antibiotics Working (KAW)**[94] is a coalition of advocacy groups working to ensure that untreatable antibiotic resistant bacteria (a result of antibiotic- overuse on farms) do not reverse the medical advances of the past century. The coalition focuses on four key actions:
  - Introduce federal prohibition of using antibiotics on animals that are not sick
  - Implement humane changes to animal production
  - Create a federal programme to collect data on the use of antibiotics on farms
  - Support the US National Antimicrobial Resistance Monitoring System (NARMS)[65]
- **The Healthy Food in Health Care Program (HFHC)** is a national campaign of Health Care Without Harm US & Canada that focuses on antibiotics in animal agriculture.[95, 96] HFHC employs a combination of market-based and policy-based strategies to advocate for better antibiotic stewardship. Health Care Without Harm US & Canada, along with Practice Greenhealth, co-convenes a network of 14 large hospital systems, representing more than 300 hospitals, in a Market Transformation Group. The collective annual purchasing power of these hospitals is estimated at approximately $207 million (€195 million) for food and beverages, with approximately $40 million (€38 million) of that spent on meat and poultry. The HFHC team advocates for policy change by mobilising the healthcare voice to build support for antibiotics legislation and regulation. HFHC educates and activates a network of healthcare sector representatives who can take immediate action through sign-on letters, testimonials, and legislative visits. HFHC's key educational materials are:
  - Expanding Antibiotic Stewardship: The Role of Health Care in Eliminating Antibiotic Overuse in Animal Agriculture[97]
  - Antimicrobial Stewardship Through Food Animal Agriculture Toolkit Module[98]
- **Clinician Champions in Comprehensive Antibiotic Stewardship (CCCAS Collaborative)** is a joint committee of Health Care Without Harm US & Canada, the Paediatric Infectious Disease Society, and the Sharing Antimicrobial Reports for Paediatric Stewardship group.[99] The CCCAS Collaborative aims to increase knowledge within the clinical community of the link between antimicrobial resistance and antimicrobial use in agriculture and to promote policy action that supports judicious use.
- **U.S. Stakeholder Forum on Antimicrobial Resistance (S-FAR)** is a national partnership convened by the Infectious Disease Society of America (ISDA) with representatives from more than 100 healthcare organisations.[100] S-FAR stakeholders work together to ensure that U.S. government strategies to address AMR involve meaningful engagement with non-government experts and stakeholders throughout the policy development and implementation process.
- **The Faces of Antimicrobial Resistance Report**, developed by the Infectious Disease Society of America (ISDA), highlights individuals whose lives have been impacted by the antimicrobial resistance crisis. These stories demonstrate the need to combat antimicrobial resistance through infection prevention,

antimicrobial stewardship, surveillance, and research.[101]

- **Retail sector campaigns**: Several consumer and environmental advocacy groups: Center for Food Safety, Natural Resources Defence Council, Friends of the Earth, Consumers Union, Food Animals Concerns Trust, and the U.S. Public Interest Research Group - have organised joint campaigns. These campaigns request that targeted chain restaurants formally and publically commit to end the use of all medically important antibiotics in their meat and poultry for growth promotion, disease prevention, and non-routine disease control. The restaurants' policies should be publically available and provide a clear timeframe to which they will fully comply with their antibiotics policy for each species. The campaigns have achieved important gains to date, particularly with chicken - McDonald's converted its entire U.S. chicken supply to be raised without medically important antibiotics in 2016, Subway in 2017, and KFC will convert by the end of 2018.

CONCLUSION

Both the EU and U.S. have been adopting policies and measures to diminish the threat of AMR as well as developing strategies and campaigns. Legislation, however, has been proven to be inconsistent and unable to cope with the escalating threat of AMR (i.e. the increasing death toll and high associated health costs). The recommendations included in this policy overview aim to fill some of the current legislative gaps.

In spite of their different approaches to handling AMR, the EU and the U.S. should continue to commit to cooperative action. A cross-sectoral, multi-disciplinary "One Health" approach should be the next step in expanding the collaboration between these two regions to include more ambitious targets to tackle AMR in the environment and within food supply chains.

HEALTH CARE WITHOUT HARM RECOMMENDATIONS TO ADDRESS AMR IN FOOD

There are still many issues and challenges that need to be addressed at the international, European, and U.S. levels to reduce the risk of antimicrobial resistance in the environment and health. As experience and research grows, and as the shift towards improvements gains pace and supply chains adapt, new guidelines and norms are expected to develop. Health Care Without Harm (HCWH) proposes the following recommendations.

For international stakeholders and national/regional authorities

1. **The Transatlantic Taskforce on AMR (TATFAR) should support the goals and objectives of the WHO Global Action Plan on Antimicrobial Resistance**,[1] and within the high-level negotiations (UNGA).

2. **Ban antimicrobial use for growth promotion in agriculture and livestock at the national/regional level**, especially in the BRICS countries (Brazil, Russia, India, China, and South Africa), where this issue is most prevalent. This should also include the phase out of antibiotic use for disease prevention in food supply chains, and prohibit the use of colistin in animals.

3. **Include environmental criteria in national action plans on AMR globally**. National actions plans on Antimicrobial Resistance shall include actions to tackle AMR in the environment and address the foodborne pathways to spreading resistance.

4. **Commit to fight against unlicensed/illegal over-the-counter prescriptions, and Internet sales of antibiotics by working with the pharmaceutical industry, food producers and retailers**. Due to the increase in demand for animal-based food products, an increase in antibiotic use is also foreseen.

5. **Both the pharmaceutical and food industries should increase transparency and improve consistency along their supply chains**. Pharmaceutical and food companies should know their supply chains and should insist on consistently high quality standards throughout. Companies need to report publicly on their environmental and worker safety standards.

6. **Establish multidisciplinary antimicrobial stewardship programmes to encourage joint ownership of the problem**. More national initiatives like the Danish yellow card system,[102] the establishment of monitoring system and antibiotic use targets in The Netherlands,[103] and the NHS England General Practice Resilience Programme,[104] among other examples, are needed.

7. **Develop and support educational interventions on AMR for society, particularly for producers, procurers, and health professionals**. This includes medical and veterinary students, as they can play an important role in advocating for prudent use of antimicrobials and practice the "as little as possible, as much as necessary" axiom. It will be particularly important to highlight the risks related to inappropriate prescribing, dosage, use, and disposal of antibiotics.

8. **Fund research and develop evidence-based guidelines on alternatives to antibiotic use for prevention purposes in animals**. Alternatives to antibiotic therapy are both crucial and cost-effective in preventing the spread of infectious diseases. Further research and development are needed in this field.

9. **Fund research to close the knowledge gaps between the presence of resistant pathogens in the environment and the risks this poses to human and animal health**. Improved research is needed into the impacts of long term, low-dose environmental exposure of antimicrobials. Monitoring manure and sampling water, soil, and air from animal feeding operations for both antibiotic resistant bacteria and antibiotic resistance genes would provide improved analysis of the spread of AMR.

10. **Reserve last-resort and medically important antibiotics for human use only**. Last-resort antibiotics should not be prescribed for veterinary use, but only for human therapy. HCWH therefore calls on regulatory bodies and international organisations (WHO, FAO, and OIE) to agree on a harmonised list of last-resort antibiotics, critical to human health, which should be banned from agricultural use.

11. **Close knowledge gaps regarding safe and effective alternative treatments for antimicrobial use in crops**. Additional research is needed into treatments other than antimicrobial use that prevent crop loss from fire blight and other pathogens. Quantifying crop production's contribution to the spread of AMR (compared to other transmission pathways) will help prioritise strategies for curbing antimicrobial use overall.

12. **Improve aquaculture regulation**. Whilst HCWH recommends seafood sourcing from aquaculture operations be minimised overall, more rigorous guidelines for disease management in aquaculture production should be established to eliminate antimicrobial use.

For European policy-makers and governments

1. **Apply a holistic approach, creating a link between current/on-going European legislation and the necessary actions to tackle AMR in food**. This might enable consumers to identify products that comply with the standards of welfare through food marketing policies. Develop incentives for farmers, operators, and retailers to maintain (or improve) standards of animal welfare. Connect environmental, health, and labour protection regulations to control pollution in water sources - insufficient safety standards in industries, crops, or farms can generate antibiotic resistance.

2. **Align the advocacy role, joint work, and funding opportunities to tackle AMR** by enabling and encouraging dialogue between the European Commission, NGOs, academia, health professionals, farmers, and food producers and retailers.

3. **Promote the annual European Antibiotic Awareness Day** to increase awareness on how human health, animal health, and the food chain are connected in the framework of AMR.

4. **Stimulate shorter food chains and direct farmer marketing within European healthcare facilities** - follow Health Care Without Harm US and Canada's example – and guarantee that procured food meets the health, social, and environmental goals of healthcare facilities while fulfilling consumer preferences. This practice will impact the whole food supply chain, and will increase consumer awareness about the current industrial animal production systems.

5. **Provide further training for health workers on how to control infections more effectively**. Use rapid diagnostic tests, lab equipment, isolation units, and public information campaigns to contain the spread of resistance.

For U.S. policy-makers and stakeholders

1. **Institute a resolution and purchasing policy for hospitals to phase out the purchase of products raised with nontherapeutic antimicrobial drugs in production**. Work across institutional departments, engaging clinicians, administration, and food service employees, to discuss the importance of efforts to address AMR across the spectrum, from clinical to agricultural practices. Sample resolution and policy language for institutional procurement can be found in the CCCAS Antibiotic Stewardship Toolkit.[98]

2. **Amend FDA Guidance for Industry #213 to explicitly state how antimicrobials can and cannot be administered to food producing animals**. While Guidance for Industry #213 eliminates the use of medically important antimicrobials for growth promotion purposes and transfers the oversight of such medications to veterinarians, it does not adequately address the use of routine, non-therapeutic antibiotic use for disease prevention. As long as this practice continues, producers are still able to overuse antibiotics and reap the benefit of growth promotion, even if growth promotion is not the stated intent of administering the antibiotics.

3. **Strengthen Veterinary Feed Directive to ensure antimicrobials are only used on animals with diagnosed illness**. Promote FDA's strengthening of requirements to ensure consistent labelling of antimicrobial drugs and alignment with judicious use principles. Antimicrobial drugs should have clearly stated use indications and duration of use limits to prevent use in conflict with judicious use standards.

4. **Improve reporting on antibiotic use in animal agriculture**: Further data collection on the quantity of antimicrobial ingredients in products sold for food animal use would enhance efforts to curb AMR. The FDA should also collect data related to Veterinary Feed Directive. Continued support for data collection and tracking initiatives by the FDA and USDA (as outlined in the USDA Antimicrobial Resistance Action Plan) are imperative to increasing understanding of antibiotics use in animal agriculture and patterns in AMR emergence. The EPA should collect data on antibiotic use in crop production.

5. **Strengthen the regulation of CAFOs**: The EPA definition of Contained Animal Feeding Operation (CAFO) should be expanded so that more Animal Feeding Operations (AFOs) are regulated as point source polluters. This will allow for better monitoring of contaminants entering the ambient environment as well as improved manure management. All direct discharges from CAFOs into waterways should be prohibited; more effective wastewater treatment technologies such as ultraviolet radiation or ozonation should be used on any wastewater being eliminated from a CAFO. Lower animal density within AFOs and better nutrition should be prioritised to maintain animal health and reduce the need for antibiotics, rather than relying on antibiotics to compensate for overcrowded and unsanitary conditions.

6. **Labelling recommendations** – under current federal regulation, USDA's Food Safety and Inspection Service reviews and approves labelling claims for: raised without antibiotics, organic, grass-fed, and raised without use of hormones. Animal raising claims made for Process Verified Program undergo independent audit, however, process verified does not have one universal standard. Certified Responsible Antibiotic Use (CRAU)[105] is a new standard, verified by USDA, which limits medically important antibiotic use in poultry and entails certain data collection on antibiotics use. Greater transparency in inspection and audit processes by government agencies would facilitate accountability and adherence to stated claims. The CRAU standard could serve as a model for labelling improvements.

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Health Care Without Harm (HCWH) Europe is the European arm of a global not for profit NGO whose mission is to transform healthcare worldwide so that it reduces its environmental footprint, becomes a community anchor for sustainability and a leader in the global movement for environmental health and justice.

HCWH's vision is that healthcare mobilises its ethical, economical, and political influence to create an ecologically sustainable, equitable, and healthy world.

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