FINAL PROGRAMME
&
ABSTRACTS OF LECTURES AND POSTERS

3rd INTERNATIONAL CONFERENCE ON
RESPONSIBLE USE
OF ANTIBIOTICS
IN ANIMALS

29 September – 1 October 2014
Amsterdam, the Netherlands
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Key to the abstracts of lectures and posters:
- abstracts of lectures and posters are grouped separately;
- lectures are grouped according to the daily programme;
- posters are grouped in an alphabetical order according to the corresponding author.

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RESPONSIBLE USE OF ANTIBIOTICS IN ANIMALS – INTERNATIONAL CONFERENCE SERIES

WELCOME

Antibiotics are used worldwide both in veterinary and human medicine. The widespread use has heightened concerns about the emergence of antimicrobial resistance, which impacts animal welfare, public health, food safety and environmental exposure. The objectives of the 3rd International Conference on Responsible Use of Antibiotics in Animals are:

- to give an overview of the current status and ongoing activities with respect to the issue of antibiotic use in animals and antimicrobial resistance;
- to learn about the expectations of different parties involved;
- to identify the areas which need further action with respect to the current scientific knowledge and political expectations; and
- to open up possibilities for effective actions and co-ordination of activities.

The conference is designed for the animal health industry and the medical community; all users of antibiotics in animals, such as veterinarians, animal feed producers, livestock and aquaculture producers, and nutritionists; food processors and manufacturers, and retailers; policy makers and regulatory agencies; researchers in universities and research institutes; and others with an interest in resistance and in the sustainability of antibiotics, such as educators, agricultural extension staff, consultants, and consumer organisations.

The members of the Advisory Board of the 3rd International Conference on Responsible Use of Antibiotics in Animals are looking forward to meeting you and assure that your participation will be fruitful and productive!

CONFERENCE HISTORY

In 2005, the series started with the international debate conference ‘Antimicrobial Growth Promoters: Worldwide Ban on the Horizon?’ reflecting the state of AGPs and alternatives at that time. The second conference took place in 2011 and focused on exchanging views on the path forward. Key focuses of the third conference in 2014 are current insights, sustainable initiatives and transparency.

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Federation of Veterinarians of Europe and World Veterinary Association, Belgium
Prof.dr. Ching Ching Wu  
National Taiwan University, Taiwan
CONFERENCE DINNER

Tuesday 30 September 2014

As a special end to the 2nd day of the conference, there will be a unique dinner in ‘Het Grachtenhuis – The Museum of the Amsterdam Canals’.

The dinner is only open to participants who registered in advance when they booked for the conference. You have found your dinner ticket in your badge that you have received upon arrival at the conference.

The Amsterdam canals make the city. For centuries here, money has been earned, art created, feasts celebrated and life enjoyed. This is the story that the Museum of the Canals brings to life. The museum is situated in a monumental building on the Herengracht, where you are taken on a whirlwind journey through four hundred years of history. The Museum of the Canals shows you not only why the creation of the Amsterdam canals was so unusual, but also why they are still special today. This museum is for everyone who loves or is just about to fall in love with the city of Amsterdam. A journey through the Amsterdam canals begins here in the Museum of the Canals.

You will be ferried by a scenic canal boat to the dinner venue. The canal boats will leave opposite the conference venue at 18:15 h. The dinner will start at 19:00 h and end at 21:30 h.

IMPORTANT NOTE

Keep your personal belongings on Tuesday 30 September 2014 to a minimum! Do not leave your belongings in the conference venue! There will be no time to get back to your hotel after the lectures have ended and the conference dinner will start.
# PROGRAMME AT A GLANCE

## Monday 29 September 2014

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| 13:00 – 13:50 | Plenary Keynote Lectures  
*Promoting good antimicrobial stewardship* |                           |
| 13:50 – 17:45 | Plenary meeting  
*Trends in antibiotic use per animal species and sectors* |                           |
| 17:45 – 19:00 | The Lounge Party                                                        |                           |

## Tuesday 30 September 2014

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| 08:30 – 12:30 | Parallel session 1  
*Governmental initiatives and international collaboration* |                           |
|           | Parallel session 2  
*Antibiotic alternatives in animal production* |                           |
| 12:30 – 13:30 | Lunch break                                                            |                           |
| 13:30 – 17:30 | Parallel session 3  
*Stakeholder initiatives on responsible use of antibiotics* |                           |
|           | Parallel session 4  
*Progress in measures and research for control of antibiotic resistance* |                           |
| 17:30 – 18:00 | Drinks                                                                  |                           |
| 18:15 – 21:30 | Conference dinner (reservations only)                                   |                           |

## Wednesday 1 October 2014

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| 08:30 – 12:45 | Final plenary meeting  
*Animal production – the bigger picture* |                           |
| 12:45 – 13:00 | Conclusions & path forward                                              |                           |
| 13:00      | Conference closing                                                      |                           |
CONFERENCE PROGRAMME

MONDAY 29 SEPTEMBER 2014

12:45  Conference opening
       Dr. Christianne Bruschke, Chief Veterinary Officer – Ministry of Economic Affairs, the Netherlands

PLENARY KEYNOTE LECTURES – Promoting good antimicrobial stewardship

Until recently, the debate around antibiotic use in animals and antibiotic resistance in people has consisted largely of veterinarians and medics regarding each other as the main problem. Only over the last few years, this debate has become more grown up with both sides recognising their own responsibilities and the necessity of working together.

13:00  How to get promoted – promoting good antimicrobial stewardship in veterinary medicine
       Dr. Nicola Williams, Senior Lecturer – Department of Epidemiology and Population Health, Institute of Infection and Global Health, University of Liverpool, UK

13:25  Antimicrobial stewardship in human medicine within the One Health framework
       Dr. Margaret Stoddart, Department Medical Microbiology, Southmead Hospital, UK

PLENARY MEETING: Trends in antibiotic use per animal species and sectors

Chair:  Prof.dr. Johanna Fink-Gremmels, Utrecht University, the Netherlands

13:50  Role of selective and co-selective agents in persistence of antimicrobial resistance in food animal production systems
       Prof.dr. Wondwossen Gebreyes, Director of Global Health Programs – Department of Veterinary Preventive Medicine, The Ohio State University, USA

14:15  Prudent use of antibiotics by the poultry sector: wishful thinking or reality?
       Dr. Vincent Guyonnet, Scientific Advisor – International Egg Commission, UK

14:40  Responsible use of antimicrobials in swine health care: work in progress
       Alex Eggen, Director – AEVC, the Netherlands

15:05  New tools for an ancient war: antibiotics in the dairy sector
       Dr. Nico van Belzen, Director General – International Dairy Federation (IDF), Brussels, Belgium

15:30  Networking break

16:00  Responsible use of antibiotic in animals – initiatives of the meat sector (on behalf of the European Livestock and Meat Trading Union (U.E.C.B.V.):
       •  Global view and initiatives of the veal sector: Henk Bekman, M.Sc., The Dutch Meat Association and Product Board for Livestock, Meat and Eggs, the Netherlands
       •  Initiatives of the pork sector: Dr. Jan Dahl, Chief Advisor – Danish Agriculture and Food Council, Denmark

16:40  Aquaculture and antibiotics: does our (almost complete) ignorance matter?
       Prof.dr. Peter Smith, Department of Microbiology, National University of Ireland, Galway, Ireland

17:05  The aquaculture environment: the focus on sulfonamide and tetracycline resistance genes
       Prof.dr. Satoru Suzuki, Center for Marine Environmental Studies, Ehime University, Japan

17:30  Discussion/Q&A

17:45 - 19:00  The Lounge Party
TUESDAY 30 SEPTEMBER 2014

PARALLEL SESSION 1: Governmental initiatives and international collaboration

Chair: Dr. Thomas Shryock, Elanco Animal Health, USA

08:30  Policy and practice: how the European Union and Member States are attempting to improve responsible use of antibiotics
Prof. dr. Peter Borriello, Chief Executive – Veterinary Medicines Directorate, Department for Environment, Food and Rural Affairs, UK

08:55  Policy and practice: how developing countries are responding to increasing concerns about antibiotic use in animals
Dr. Delia Grace, Programme Manager – International Livestock Research Institute, Kenya

09:20  Latin America initiatives on veterinary drugs and antimicrobial resistance
Prof. dr. João Palermo Neto, University of São Paulo, Brazil

09:45  Overview of antimicrobial resistance prevalence and interventions in ASEAN countries
Dr. Rungtip Chuanchuen, Director – Center for Antimicrobial Resistance Monitoring in Foodborne Pathogens, Thailand

10:10  A One Health approach to antimicrobial resistance surveillance in animals in Australia
Dr. Darren Trott, School of Animal and Veterinary Sciences, The University of Adelaide, Australia

10:30  Networking break – sponsored by Neovia

CASE STUDY: U.S. Food and Drug Administration Guidelines for Industry and modernisation of the Veterinary Feed Directive
The major changes in feed antibiotics need to be understood by more parties. This is a significant shift in the practice of food animal medicine in the USA and will result in increased veterinarian oversight.

11:00  Implementing the new antibiotic guidance from FDA
Dr. Richard Carnevale, Vice-President, Regulatory, Scientific, and International Affairs – Animal Health Institute (AHI), USA

11:20  Veterinary oversight and the Veterinary Feed Directive
Dr. Joni Scheftel, State Public Health Veterinarian – Minnesota Department of Health, USA

11:40  What FDA Guidance 213 and the Veterinary Feed Directive mean on the farm – a pork producer’s perspective
Dr. Liz Wagstrom, Chief Veterinarian – National Pork Producers Council, USA

12:00  FDA’s antimicrobial resistance policies – the U.S. feed industry’s perspective
David A. Fairfield, Vice President of Feed Services – National Grain and Feed Association (NGFA), USA

12:20  Discussion/Q&A

12:30 - 13:30  Lunch break
TUESDAY 30 SEPTEMBER 2014

PARALLEL SESSION 2: Antibiotic alternatives in animal production

Chair: Dr. Piet van der Aar, Schothorst Feed Research, the Netherlands

08:30 Enhancing the power of the immune system
Prof. dr. Huub Savelkoul, Cell Biology and Immunology Group, Wageningen UR, the Netherlands

08:55 Current and future considerations for the veterinary antibiotic pipeline
Dr. Thomas Shryock, Senior Research Advisor, Microbiology – Global Regulatory Affairs, Elanco Animal Health, USA

09:15 Alternatives to antibiotics: recent scientific developments
Dr. Cyril Gay, Senior National Program Leader, Animal Health and Safety – Agricultural Research Service, U.S. Department of Agriculture, USA

09:35 Phytobiologics: using redoxigenic plant immunity to support the immune system in pigs
Prof. dr. Ching Ching Wu, Professor of Veterinary Microbiology – National Taiwan University, Taiwan

09:55 Can medicated feed be replaced by pre-/probiotics?
Dr. Joaquim Brufau, Director – Centre Mas de Bover, Investigación y Tecnología Agroalimentarias (IRTA), Spain

10:15 Growth promoting and health benefits by reducing inflammation and improving gut integrity
Dr. Albert van Dijk, Director of Species Support – Neovia, France

10:30 Networking break – sponsored by Neovia

11:00 Phage therapy versus antibiotherapy: can bacteriophages be effective alternatives for pathogen control?
Dr. Joana Azeredo, Centre of Biological Engineering, University of Minho, Portugal

11:20 From smallest to biggest feed additives: organic acids and enzymes in feed hygiene and gut flora management
Dr. Markus Matuschek, Global Marketing Animal Nutrition – BASF, Germany

11:40 Use of dietary quorum quenching enzymes as bacterial disease prevention in aquaculture
Prof. dr. Zhigang Zhou, Director – Feed Research Institute, Chinese Academy of Agricultural Sciences, China

12:05 I have developed a great product, now what? Regulatory issues!
Ruud Bremmers, Managing Director – Regal, the Netherlands

12:30 - 13:30 Lunch break
TUESDAY 30 SEPTEMBER 2014

PARALLEL SESSION 3: Stakeholder initiatives on responsible use of antibiotics

Chair: Gwyn Jones, Chairman – EPRUMA (European Platform for Responsible Use of Medicines in Animals) and COPA-COGECA (European Farmers and European Agri-Cooperatives), Belgium

13:30 Biocheck, a risk-based biosecurity scoring system
Prof. Dr. Jeroen Dewulf, Department of Reproduction, Obstetrics and Herd Health, Ghent University, Belgium

CASE STUDY: From disease prevention through disease detection and retrieving health status to improving health status – the EPRUMA scheme

14:00 Introduction to EPRUMA
Gwyn Jones, Chairman – EPRUMA, Belgium

14:15 The farmer’s role and management options regarding biosecurity, housing and nutrition

14:30 The veterinarian’s role and options regarding disease detection, diagnosis, treatment and prevention
John Blackwell, President – British Veterinary Association, UK

14:45 Partner in the challenges posed by the threat of antimicrobial resistance (on behalf of the European Manufacturers of Veterinary Diagnostics (EMVD)
Dr. Liesbeth Jacobs, Thermo Fisher Scientific/Prionics Lelystad, the Netherlands

15:00 The animal health industry’s role and options regarding veterinary medicines and other tools/services for treatment and prevention
Dr. Olivier Espeisse, Elanco Animal Health, Belgium

15:15 Networking break – sponsored by Neovia

SUBSESSION: National and international initiatives

15:45 GRSB’s approach to technology and Innovation
Ruaraidh Petre, Executive Director – Global Roundtable for Sustainable Beef (GRSB), the Netherlands

16:05 The Dutch approach for responsible veterinary use of antibiotics: the secrets to success
Dr. Hetty van Beers-Schreurs, Director – The Netherlands Veterinary Medicines Authority (SDa), the Netherlands

16:25 The Alberta Platform for the Responsible Use of Medicine in Animals (APRUMA)
Duane Landals, Senior Advisor – Alberta Veterinary Medical Association, Canada

16:40 Antimicrobial Consumption and Resistance in Animals (AMCRA) – the Belgian approach
Dr. Evelyne De Graef, Coordinator – AMCRA, Belgium

16:55 Vetresponsible: Spanish initiative for the promotion of responsible use of veterinary medicines
Pablo Hervás, Project Manager – Spanish Technology Platform for Animal Health (Vet+i), Spain

17:10 Responsible Use of Medicines in Agriculture (RUMA)
John FitzGerald, Secretary General – RUMA, UK

17:30 - 18:00 Drinks
TUESDAY 30 SEPTEMBER 2014

PARALLEL SESSION 4: Progress in measures and research for control of antibiotic resistance

Chair: Dr. Stephen Page, Advanced Veterinary Therapeutics, Australia

13:30  Pan-European resistance monitoring programmes encompassing foodborne bacteria and target pathogens of food-producing and companion animals
Dr. Hervé Marion, Secretary General – International Association Executive Animal Health Study Center (CEESA), Belgium

13:55  EFSA’s activities on antimicrobial resistance in the food chain: risk assessment and data collection
Dr. Ernesto Liebana, Acting Head – Unit on Biological Hazards and Contaminants (BIOCONTAM), European Food Safety Authority (EFSA), Parma, Italy

14:20  EFFORT: joining forces against antimicrobial resistance
Prof.dr. Jaap Wagenaar, Central Veterinary Institute and Utrecht University, the Netherlands

14:45  Relationships between antibiotic use in animals and increased antibiotic resistance in aquatic and soil environments
Prof.dr. David Graham, School of Civil Engineering and Geosciences, Newcastle University, UK

15:15  Networking break – sponsored by Neovia

CONTRIBUTED PAPERS

15:45  To which extent can we explain antimicrobial resistance patterns in Escherichia coli from animal derived foods by antimicrobial usage patterns in livestock?
Dr. Annemarie Käsbohrer, Department Biological Safety, Federal Institute for Risk Assessment (BfR), Germany

16:00  A qualitative approach to explore motivations for antimicrobial prescribing by veterinary surgeons in UK pig practice
Lucy Coyne, Institute of Infection and Global Health, University of Liverpool, UK

16:15  Antibiotic residue analysis in non-invasive animal matrices in the fight against bacterial resistance
Tina Zuidema, RIKILT Wageningen UR, the Netherlands

16:30  How the representation of antimicrobial consumption using different indicators can provide useful information about treatment strategies at farm level
Dr. Lucie Collineau, SAFOSO, Switzerland and BioEpAR, INRA / Oniris, L’UNAM, France

16:45  Antimicrobial reduction in pigs from birth till slaughter (-48%) and in breeding animals (-19%): a team effort without jeopardising production parameters
Merel Postma, Department of Reproduction, Obstetrics and Herd Health, Ghent University, Belgium

17:00  An estimation of the use of antibiotics in the Dutch small ruminant industry
René van den Brom, GD Animal Health Service, the Netherlands

17:15  Experience in practice: homeopathy in animal husbandry
Evelien van der Waa, M.Sc., Homeopathic Veterinary Practice Houten, the Netherlands

17:30 - 18:00 Drinks
WEDNESDAY 1 OCTOBER 2014

FINAL PLENARY MEETING: Animal production – the bigger picture

Chair: Prof.dr. Peter Silley, MB Consult Limited, UK / School of Life Sciences, University of Bradford, UK

08:45  Multidrug-resistant bacteria in meat products: how can we control this potential threat to public health?
Prof.dr. Luca Guardabassi, Department of Veterinary Disease Biology, University of Copenhagen, Denmark

09:10  Fostering cooperation to address the threat to human and animal health – what new approaches should be tried?
Dr. Stephen Page, Advanced Veterinary Therapeutics, Australia

09:35  Alone we can do so little; together we can do so much – Helen Keller
Dr. Michael Chaddock, Assistant Dean for One Health and Strategic Initiatives – Department of Veterinary Integrative Biosciences, College of Veterinary Medicine & Biomedical Sciences, Texas A&M University, USA

10:00  Sustainable intensification of agriculture needed to meet animal protein demand growth
Dirk Jan Kennes, Global Strategist Farm Inputs – Rabobank, the Netherlands

10:30  Networking break

11:00  Can public-private partnership help? The Innovative Medicines Initiative model
Dr. Angela Wittelsberger, Scientific Project Manager – The Innovative Medicines Initiative (IMI), Brussels, Belgium

11:25  Regular farm antibiotic use – does it advance or undermine animal welfare?
Peter Stevenson, Chief Policy Advisor – Compassion in World Farming, UK

11:50  Antibiotic use in livestock farming through the eyes of consumers
Marieke Meusen-van Onna, LEI Wageningen UR, the Netherlands

12:15  Trends and drivers in the food supply chain affecting the use of antibiotics in primary production
Dr. Roland Aumüller, Standards Management Livestock, GLOBALG.A.P., Germany

12:45  Conclusions & path forward

13:00  Conference closing
HOW TO GET PROMOTED – PROMOTING GOOD ANTIMICROBIAL STEWARDSHIP IN VETERINARY MEDICINE

Plenary keynote lecture

Nicola J. Williams

Institute of Infection and Global Health, University of Liverpool, UK
njwillms@liverpool.ac.uk

Antibacterials are extensively used in veterinary medicine for the treatment and prevention of bacterial infections in a wide range of animal species and in different contexts, from companion animals (including horses) to exotic species and, where use is greatest, in food-producing animals. With few new antibacterial agents in development and increasing antibacterial resistance in both commensal and pathogenic bacteria from animals, there is clearly a need to maintain the efficacy of the antibacterial agents currently available. Good antimicrobial stewardship is key to the preservation of broad spectrum agents including those critically important to human health. While veterinary clinicians have a duty to protect animal welfare, they also need to consider the potential societal impact of antimicrobial use on public health, through the food chain and direct contact with animals.

Good antimicrobial stewardship seeks to select the most appropriate drug, at the correct dose, route and duration of treatment, to provide a positive clinical outcome while having minimum impact on the emergence of resistance. Antibacterial use guidelines have been widely advocated in human medicine and shown to have a positive impact on stewardship and in reducing the use of antibacterials. Limited studies in the veterinary sector suggest that guidelines can also have a positive impact. Guidelines have been designed for companion animal (horse and small animal) practitioners (e.g., http://www.bsava.com/Resources/PROTECT.aspx, http://www.beva.org.uk/useful-info/Vets/Guidance/AMR), which encourage clinicians to consider their own in-house first line treatment of common conditions. Formularies are commonly used in human medicine, but less in veterinary medicine and have been shown to reduce the use of key antibacterial classes in human medicine. However, anything which restricts freedom of choice for prescribing may be unpopular, unless an industry or sector, positively adopt such changes. While the development of veterinary prescribing guidelines is a positive step, it is not known how widely they have been taken up or if they have led to sustained changes in prescribing behaviour. Furthermore, the promotion of good antimicrobial stewardship should be inclusive and not just involve clinicians, but animal owners and farmers. There is evidence within human medicine, and now emerging within the veterinary field, that clients influence the prescribing practice of clinicians, with perhaps the greatest impact in food animals where farmers can easily move their business between practices. It is important that farmers understand the importance of the prudent use of antibacterials, not just to protect public health, but to protect against the loss of that drug in animals.

Perhaps one of the main obstacles to promoting prudent use is that resistance is not currently perceived as a major problem within the veterinary sector: it is regarded as more of a human problem caused by widespread use of antibacterials in human medicine. However, it is likely that there is under-recognition of resistance in clinical veterinary settings. Although multi-drug resistant bacteria are increasingly being reported within veterinary hospital settings, those working in first opinion practices and with food animals may be less aware, as culture and sensitivity may not be undertaken routinely, and lack of efficacy and a necessity
to change drugs during treatment might not automatically be assumed to be due to resistance. Therefore, it is also important that surveillance of antibacterial resistance is undertaken and its outcomes made readily available to clinicians.

A further way to ensure good antibacterial stewardship is by monitoring and regulating use. Setting baseline levels of use, penalising farmers and veterinarians who continually exceed these levels, and/or removing the ability of vets to sell antibacterials so there is no profit component, have all been introduced in some European Union (EU) countries. Such approaches may have their problems, however; for example, monitoring daily doses could encourage cessation of antibacterial use as soon as an animal appears to be improving rather than finishing the course. Certainly monitoring antibacterial use and resistance is essential for determining the success or otherwise of any programme, regulatory or voluntary. The active development and promotion of guidelines, monitoring and self-regulation of antibacterial use by the veterinary sector may circumvent external regulation being put in place. This could be used in promoting why good antimicrobial stewardship is vital to continued unrestricted use of antibacterials in veterinary medicine.

Understanding veterinary prescribing behaviour is key in considering how best to implement strategies to promote good antimicrobial stewardship. In addition, it is important to understand the impact of interventions which may drive behaviour for sustained improvements in use. And as always, education, of veterinarians, farmers and other animal owners will be crucial to ensuring societal ownership of both the problem and any solution.
One of the major problems faced by the medical and veterinary professions is the increasing prevalence of antimicrobial resistance. This is being compounded by a reducing number of new agents entering clinical practice, and this problem is widely recognised as a major threat to public and animal health. Antimicrobial resistance is defined by the WHO as “loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines”.

Antimicrobial resistance can result from inappropriate use of antibiotics. In response, initiatives at the local, national, and international levels, are trying to promote ‘antibiotic stewardship’ with the goal of improving the appropriateness of antimicrobial use. Antimicrobial stewardship can be defined as an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobial drugs to preserve their future effectiveness. At a national level within the UK, the Department of Health has published a Five Year Plan (2013-2018) in regard to antimicrobial stewardship, the goal of which is to slow the development and spread of antimicrobial resistance using a multidisciplinary approach; it has 3 strategic aims:

- to improve the knowledge and understanding of antimicrobial resistance;
- to conserve and steward the effectiveness of existing treatments; and
- to stimulate the development of new antibiotics, diagnostics and novel therapies.

However, these initiatives rely on the continuing education of prescribers and patients to succeed, which in turn need to be supported by high quality research linking antimicrobial use to the emergence of resistance. Primary care is still responsible for the majority of antibiotics prescriptions and although some countries have been successful in reducing primary care prescribing of antimicrobials, levels of prescribing still vary widely within and between countries, suggesting that further reductions are possible. However there are barriers to further reductions from both medical staff and patients. This is largely due to lack of awareness of the problems that arise due to antimicrobial resistance and that resistance is not a real issue and does not apply to them.

There are several reasons for some of these misconceptions. A lot of research only investigates the relation between prescribing and resistance with population level data. When the primary concern of the doctor and patient will be the individual and any impact outside this will not be considered. It is important to educate all on the potential impacts of antimicrobial use beyond just immediate treatment. There is an expectation with both the doctor and patient that antibiotics will be prescribed if the patient is unwell and often this expectation is a driver for potential over prescription. There is a lack of knowledge on such areas as the residual effect that can occur after antibiotic treatment and that bacterial resistance can be found at different sites in an individual and that this can be detected up to 12 months after the initial antibiotic dose. Resistance can easily transfer between commensal organisms and potential pathogens and transient use of an antibiotic in an individual with resistant bacteria can have a major impact on the endemic level of resistance in the population. General principles recommended include using as few antibiotics as possible for
as short as possible. If further courses are needed, use another choice of antibiotic.

The main research implication is the need to strengthen the current evidence base, which is heavily reliant on observational studies, with more clinical trials. The opportunity to assess the effects of antibiotics on antimicrobial resistance should be considered whenever a placebo or 'no treatment' controlled trial is being designed. Further research is also needed on pharmacokinetics (PK) and -dynamics (PD) to optimise treatments for the individual – ill patients may respond differently to healthy patients on whom PK and PD work may have been determined; accurate diagnosis of infections and bacterial types, including resistance genes and new novel antibiotics, are still needed.
ROLE OF SELECTIVE AND CO-SELECTIVE AGENTS IN PERSISTENCE OF ANTIMICROBIAL RESISTANCE IN FOOD ANIMAL PRODUCTION SYSTEMS

Wondwosen A. Gebreyes

Infectious Diseases Molecular Epidemiology Laboratory, College of Veterinary Medicine, The Ohio State University, USA
gebreyes1@osu.edu

Antimicrobial resistance remains among the leading public health issues worldwide due to the emergence and persistence of antimicrobial resistant bacterial strains of public health significance. The abstract below and presentation on this conference will focus on the role of selective agents beyond the direct antibiotic selective pressure, including biocides and heavy metal micronutrients in various ecosystems, with a main emphasis on food animal production systems. Antimicrobial use in food animal, human medicine as well as other purposes, such as horticulture, imposes an important and significant selective pressure that enables the proliferation and transfer of antimicrobial resistant pathogens. The differential role of antimicrobial use and exposure to other co-selective agents, including heavy metal micronutrients and biocides (mainly disinfectants) in food animals as well as human medicine on the outcome, particularly the occurrence and persistence of resistant infections remains unclear. The use of molecular epidemiology allows better characterisation, understanding, tracking as well as to design effective prevention and control measures.

Non-typhoidal Salmonella serovars are among the most important foodborne bacterial pathogens with broad host range, including food animals and humans. According to the 2010 Foodborne Disease Active Surveillance Network reported by the Centers for Disease Control and Prevention (CDC), Salmonella infections were the most common cause of reported foodborne bacterial illnesses. Most strains of the commonly occurring serovars, such as Typhimurium, have been shown to exhibit multidrug resistance. The high occurrence of antimicrobial resistance in swine production units is well documented. However, the intricate relationship with various selective pressures that enable such MDR strains to persist is poorly understood. In the recent past, various investigations we conducted in swine production systems have shown the increasing occurrence of multidrug resistance among serovars that were historically not MDR including Agona, Havana, Infantis, Muenchen, Senftenberg, and Worthington.

In a recent study aimed at characterizing the role of heavy metal micronutrients in swine feed, we demonstrated the emergence of heavy metal-tolerant and persistence of MDR Salmonella [1]. This longitudinal study was conducted in 36 swine barns over a 2-year sampling period. The feed and faecal levels of Cu(2+) and Zn(2+) were measured. Salmonella was isolated at early and late finishing. MICs of copper sulfate and zinc chloride were measured using agar dilution. Antimicrobial susceptibility was tested using the Kirby-Bauer method and 283 isolates were serotyped. We amplified pcoA and ccdD genes that encode Cu(2+) and Zn(2+) tolerance, respectively. Of the 283 isolates, 113 (48%) showed Cu(2+) tolerance at 24 mM and 164 (58%) showed Zn(2+) tolerance at 8 mM. In multivariate analysis, serotype and source of isolates were significantly associated with Cu(2+) tolerance (P<0.001). Faecal isolates were more likely to be Cu(2+) tolerant than those of feed origin (odds ratio [OR], 27.0; 95% confidence interval [CI], 2.8 to 250; P=0.0042) or environmental origin (OR, 5.8), implying the significance of gastrointestinal selective pressure. Salmonella enterica serotypes Typhimurium and Heidelberg, highly significant for public health, had higher odds of having >20 mM MICs of Cu(2+) than did ‘other’ serotypes. More than 60% of Salmonella isolates with resistance type (R-type) AmStTeKm (32 of 53) carried pcoA; only 5% with R-type AmCISuTe carried this gene. ccdD gene carriage was significantly
associated with a higher Zn(2+) MIC ($P<0.05$). The odds of having a high Zn(2+) MIC ($\geq$8 mM) were 14.66 times higher in isolates with R-type AmClStSuTe than in those with R-type AmStTeKm ($P<0.05$). The findings demonstrate strong association between heavy metal tolerance and antimicrobial resistance, particularly among *Salmonella* serotypes important in public health.

We also found association between biocides (disinfectants) and MDR *Salmonella*. In a controlled study using four regimes of disinfection, including quaternary ammonium compounds (QAC), QAC-gluteraldehyde, per-oxygen blend, and a control hot water wash of the 36 barns listed above, we found that while *Salmonella* prevalence was significantly reduced when using the three biocides, the strains that survived post-disinfection were found to show significantly higher spectrum of MDR, particularly in the QAC+gluteraldehyde group and in some cases found to also be more virulent based on cell invasion assay, macrophage survival as well as mice killing assays. These findings were not unique to food animal production settings. In a previous study conducted on *Acinetobacter baumannii* collected from human hospital environments, we demonstrated a similar phenomenon strongly indicating the significance of disinfectant selective pressure that renders strains to be become highly MDR strains [2]. This is mediated primarily by the activation of multidrug efflux pumps, such as the ABE system [3]. We also found that the tolerance to biocides in *A. baumannii* is also associated with stronger biofilm formation, which further promotes its survival in the environment and persist.

In summary, while the role of co-selective agents in farm, hospital and other settings play an important role in persistence of antimicrobial resistance, it is equally important to fully understand the phenotypic mechanisms and genetic elements that encode for resistance and virulence and serve as vehicles for transfer of resistance as well as efficient expression of the genes and translation to functional proteins. Some of the known elements include plasmids, transposons, integrons, genomic islands and pathogenicity loci (PaLoc) on the chromosome and efflux pump systems. A better understanding of the mechanisms enables designing effective approaches for prevention and control of MDR in food animal production settings.

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PRUDENT USE OF ANTIBIOTICS BY THE POULTRY SECTOR: WISHFUL THINKING OR REALITY?

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For the past 20 years, various intergovernmental organisations and livestock organisations have worked together to minimise the negative public health impact of the use of antibiotics in food-producing animals, while at the same time providing for their safe and effective use in veterinary medicine. A number of guidelines published by the World Health Organization (WHO), the Codex Alimentarius and the World Organisation for Animal Health (OIE) have identified the role of regulatory authorities, veterinary pharmaceutical industry, wholesalers and distributors, veterinarians and food-animal producers in this shared responsibility for ensuring the prudent use of antibiotics in veterinary medicine.

For the poultry sector, the prudent use of antibiotics may be defined as ensuring both the effective treatment of birds for health and welfare reasons, the absence of residues above the permissible levels in eggs and poultry products, and the continued benefits of antibiotics to human and animals. The responsibility for prudent use of antibiotics in poultry must extend beyond farmers and poultry veterinarians, with feed millers and processors playing also a critical role. The work conducted by the poultry sector may be divided into five broad categories: (i) capacity building and awareness programmes; (ii) setting of industry codes of practices; (iii) development of internal (on-site/farm) evaluation and third-party verification systems; (iv) cooperation and partnership with governments; and (v) investment in the development of alternative options.

Capacity building must target both the issue of antibiotic usage as well as that of proper management practices, ensuring that the antibiotic treatment is not a substitute for good management, biosecurity and farm hygiene practices. Codes of practice are very useful tools to the poultry sector and have been developed in a number of countries. A system of evaluation and auditing is also critical to ensuring that codes of practices are being followed and progress is been made. In a number of countries, especially in the developing world, a strong partnership between the public and private sectors is critical to the implementation and monitoring of the prudent use of antibiotics in poultry. Finally, the poultry sector invests in research for alternatives to antibiotics, thus ensuring the sustainability of the sector. Work conducted by the poultry organisations from various countries will be presented to illustrate these five key areas.

Prudent use of antibiotics in the poultry sector is the result of the concerted approach by the various players of this sector (national producers and processors organisations, producers, processors, feed millers, poultry veterinarians) along with regulatory authorities, the veterinary pharmaceutical industry, wholesalers and distributors.
RESPONSIBLE USE OF ANTIMICROBIALS IN SWINE HEALTH CARE: WORK IN PROGRESS

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The title of this presentation could not be chosen better! Remarkable progress is accomplished in several countries in the past couple of years but the endpoint, which by nature of this dispute is a moving target, remains on a European Union (EU) level, ahead of us. Responsible use of antimicrobials is for many of us a synonym for reduction in the use of antimicrobials. This can be a consequence of the process but it does not exclude that a sick animal has the right to be treated, even with an antimicrobial! Responsible use of antimicrobials is much more related to the fact that the pork producing industry is actively working on expanding the number of intervention options that it can choose from to cure or prevent diseases. When you have choices, you need to motivate the option that you choose. This makes the manager responsible for the choice.

Antimicrobials are seen nowadays as one of the intervention options and not anymore as the only option. It only takes courage to leave a broad spectrum and relatively cheap option for a much more complex, often more expensive and not always failure proof, approach. During this conference, updates will be given on, for example, tightening biosecurity, enhancing the power of the immune system, next to other non-antimicrobial additives approaches as possible options for an alternative-to-antimicrobials intervention strategy. But how does this all work? Why are we considering more options than before? Of course this only works when there is (societal translated into political) pressure to leave old proven practices behind; and we need of course the development and implementation of new intervention strategies. Beside this, economic pressure is absolutely necessary to direct desired changes.

However, it should always be taken into account that there are major differences between the different segments in which antimicrobials are being used. Segments, for example, are the use of antimicrobials in humans (both in and outside hospitals), companion animals like dogs and cats, and livestock (including the use in fish farming). For having a clear and non-confusing discussion, one should always make sure to which segment one is referring to when making a statement. Cross-over observations between human and veterinary usage of antimicrobials for resistance genes are not necessarily equally related to all the different animal species. There are examples where resistance genes against a certain antimicrobial were found in a species for which that specific antibiotic was not even authorised. Hence, responsible use of antimicrobials (in general) in a certain species will not solve the issue of a specific resistance carrying gene against a specific antimicrobial that is not even used in that species! There are many other ways to spread microbes that may carry resistance genes.

In summary, although the discussion is highly influenced by societal and political motives, please try to keep the debate simple and focused, and suggest changes that are evidence-based, can easily be implemented, controlled and sanctioned.

In my presentation, I will briefly touch on achievements made in different countries in the past 3-4 years, and show you some examples how the swine sector actively is approaching the issue of responsible use of antimicrobials. Regarding the alternative intervention options, I will focus on the use of vaccines to help reducing the need for antimicrobials. At the same time, the information presented also provides a sound rationale for the use of antimicrobials, even on herd level. All examples are based on peer reviewed articles. PCV2 vaccine
introduction was a real eye-opener. PCV2 virus is strongly immune-modulating making the PCV2 virus-infected piglet much more susceptible for secondary infections. In a very short period of time, this (piglet-)vaccine reached a 70-80% penetration level. Due to the massive uptake of this vaccine, in a relative short period of time, the effect on the reduction of use of antimicrobials became clearly visible.

An immune competent piglet is better in controlling bacterial infections. This applies for both commensals that are normally present and suddenly turn into pathogens and for secondary invaders. An immune compromised piglet needs a treatment (with antimicrobials) to fight against secondary bacterial invaders. But it is not only PCV2 virus that has this effect on pigs. PRRS and influenza virus, both in their own way, also have a negative effect on the immune system leading to the same increased susceptibility for infections. Vaccines here can play a role but other management factors like biosecurity, pig density, housing and climate control, are also of importance.

In summary, remarkable progress in responsible use of antimicrobials has been achieved in those countries in which this strategy was accompanied by the development and implementation of alternative intervention strategies. As a consequence, this resulted in reductions of the use of antimicrobials in pork production in those countries.

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NEW TOOLS FOR AN ANCIENT WAR: ANTIBIOTICS IN THE DAIRY SECTOR

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Microbes have been living on earth for more than three billion years. They have outlived the dinosaurs and will probably outlive mankind as well. Under the intense pressure of competition and natural selection, it is not surprising that living organisms (including microbes) have developed antimicrobial substances, such as penicillin, and that microbes have developed resistance to them. Antimicrobial resistance genes have been isolated from 30,000-year-old permafrost sediments [1]; these were found to encode resistance to β-lactam, tetracycline and glycopeptide antibiotics. Thus, antibiotic resistance is a natural phenomenon that existed before the use of antibiotics by humans. However, our discovery and wide use of antibiotics has increased the selection pressure on microbes to acquire resistance.

Antimicrobial agents need to be used prudently to avoid selection of resistant bacteria as much as possible, and to minimise antimicrobial residues in milk and dairy products. The dairy sector is well aware of its responsibility and the International Dairy Federation (IDF) has published several documents on this topic. For instance, building on the ‘FAO/IDF guide to good dairy farming practice’ [2] and in collaboration with experts from the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), IDF published the ‘IDF Guide to prudent use of antimicrobial agents in dairy production’ [3] in 2013. The Guide collates the key practices supporting the prudent use of antimicrobial agents in the dairy sector, both for farmers, veterinarians, food processing companies, pharmaceutical companies and competent authorities.

Farmers are recommended to establish disease resistance herds, including selection of breeds and animals well suited to the local environment and farming system, determination of appropriate herd sizes and stocking rates, and vaccination as recommended by local authorities. They should aim to prevent entry of diseases onto the farm, and have an effective herd health management programme in place, including separation of milk from sick animals. Antimicrobial agents and veterinary medicines should be used as directed. Animals should be well watered and fed, and free from discomfort, pain, injury and disease. Veterinarians are recommended to assess the requirements for antimicrobial treatment, only supplying antimicrobial agents when necessary, selecting an appropriate agent and giving clear instructions on their use, and only use combinations of agents that are synergistic and approved by competent authorities for use together. Off-label use must only be undertaken if permitted under national legislation and if the risks can be adequately managed. Food processing companies are encouraged to provide clear specifications for raw materials and the quality management systems to help farmers meet them, provide guidance for on-farm milk testing and screening of farm supplies for the presence of antimicrobial agent residues. They should screen incoming supplies at processing facilities, adopt HACCP management and test products. Pharmaceutical companies are recommended to only supply antimicrobial agents through regulated channels and monitor after-market product performance. Competent authorities underpin the prudent use of antimicrobial agents by approving antimicrobial agents, implementing controls over their supply and use and monitoring for adverse outcomes, including resistance.

IDF covers all aspects of the dairy sector and has recently published guidance on detection of inhibitors and antimicrobial residues in milk and dairy products [4] as well as several related ISO/IDF guidelines and methods.
References
RESPONSIBLE USE OF ANTIBIOTICS IN ANIMALS – INITIATIVES OF THE VEAL SECTOR WITH A FOCUS ON THE NETHERLANDS

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Around 2005, human medicine and society became concerned about the trend of increasing patterns of antimicrobial resistance in animal husbandry in the Netherlands. At the same time, MRSA (LA-MRSA) was found at a pig farm in the Netherlands. Representatives of the veal sector discussed about a plan of action. This resulted in the Masterplan Rational Antibiotic Use in the veal sector in October 2007. The aim was firstly to demonstrate a rational use of antibiotics, including rules, protocols and verification of compliance at farm level, and secondly to start research for possibilities to stop the increasing antimicrobial resistance (AMR) and if possible even to reduce it. The plan was officially offered to the former Minister of Agriculture and contained the framework for other main animal production sectors in the Netherlands, i.e., poultry, pigs and dairy. This Masterplan has resulted in more than 50% reduction of antibiotic use in the veal sector today!

First actions in the Masterplan were:
- to upgrade the existing quality assurance system (integrated chain management programme (IKB) veal calves), with special attention to antibiotic use and registration, including rules for veterinarians;
- to monitor antibiotic use in the veal sector in about 10% of the veal farms (at random);
- to start research risk factors for AMR and the effect of intervention strategies; and
- to start research for the molecular epidemiology of (multi)resistant bacteria.

In December 2008, the Masterplan further developed into a ‘Convenant AMR Animal Production’ that was concluded between government and the four animal production sectors mentioned above. Parties agreed to fight antimicrobial resistance. Important targets were responsible, prudent use of antibiotics (e.g., one-in-one relation between farmer and veterinarian) and full transparency in antibiotic use (all antibiotic use to be registered).

The Minister of Agriculture, under pressure of the Dutch Parliament, simplified the AMR-topic to a reduction of antibiotic use in animal production. In April 2010, she set reduction targets for antibiotic use of 20% in 2011 and 50% in 2013, both compared to 2009. The animal production sector involved incorporated these targets in their activities. The veal sector decided to create a database for collecting all prescription by vets for all veal farms. It was introduced in 2010 and the IKB-schemes required registration of all prescriptions from the beginning of 2011. This registration was done by the veterinarian. IKB-inspections at farm level stimulated registration reliability in a short time to a high level. In 2011, a Product Board for Livestock, Meat and Eggs (PVV)-regulation came in force for all (veal) farmers in the Netherlands. Additional requirements were introduced in the IKB-scheme, such as an animal health plan at farm level (BGP) and an animal treatment plan at farm level (BBP).

At the end of 2010, the Netherlands Veterinary Medicines Authority (SDa) was established by the animal production sectors involved and the Royal Dutch Society for Veterinary Medicine. This independent agency defines benchmark indicators for responsible antibiotic use in animal husbandries and checks whether the information in the databases meets the quality requirements. The SDa also monitors any improvement measures implemented by livestock farmers and their veterinarians in order to reduce antibiotic use and justify their
usage of certain types of antibiotics.

While in the beginning the AMR-topic was simplified to a reduction of the quantity of antibiotics used in animal production, in August 2011, the report of the Health Council of the Netherlands put forward recommendations for the quality of antibiotics used to minimise the risk of AMR-spread from animal production to human health. Based on these recommendations, the veal sector decided to ban cephalosporins in the IKB-scheme and put further restrictions on the use of fluoroquinolones.

In 2012, the Dutch government decided to abolish the Product Boards (PB). The PBs were recognised as an important party for initiatives in combating AMR in animal production. The PBs had the opportunity to collect funds for research activities but also general programmes for establishing antibiotic registration databanks and supporting private initiatives by legislation (e.g., central registration of all prescriptions). Representatives of animal production are concerned about their remaining possibilities to take initiatives, a typical element in this Dutch approach that was, after all, the fundament of the results achieved up to now.

In 2013, the veal sector decided to an accelerated implementation of additional requirements to improve the robustness of the veal calf entering the veal sector and for housing conditions after arrival of young calves. In cooperation with dairy farming, new ideas are explored to improve the transition phase of the young calf from the dairy farm to the veal farm.

Major results of the Masterplan are:
- awareness of negative effects of antibiotics use on AMR in the veal sector;
- full transparency of antibiotics use in the veal production sector;
- 50% reduction of antibiotic use;
- 95% reduction of the use of cephalosporin’s and fluoroquinolones; and
- preliminary indications of reducing AMR-levels.
RESPONSIBLE USE OF ANTIBIOTIC IN ANIMALS – INITIATIVES OF THE PORK SECTOR

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Antibiotics are used to treat infectious diseases. Treatment will inevitably lead to antibiotic resistance, both in the target organism, but also in organisms present in the animals, without causing disease, including zoonotic organisms. Antibiotic use in the pig sector is a complex issue. There are large differences in quantities and types of antibiotics used between types of production, between countries/regions in the European Union (EU), and outside the EU. The drivers of antibiotic use in the pig production are a complex mixture of pig health, regulatory systems, availability and price of antibiotics, availability, price and quality of vaccines and probably more important than we realise – tradition.

Initiatives
Initiatives can be divided up into two groups:

- Initiatives to reduce resistance-development by reducing antibiotic usage generally or for specific antibiotic classes.
  Several organizations working in the primary sector have set up the EPRUMA stakeholder platform, promoting responsible use of antibiotics in animals. The pig sector in several countries has implemented voluntary restrictions on the use of some of the critically important antibiotics, including 3. and 4. generation cephalosporins and fluoroquinolones. These antibiotics are critically important for the treatment of zoonotic infections like salmonellosis, campylobacteriosis and human pathogens. An important part of reducing the need for antimicrobial treatment is improved animal health. Vaccines, management, improved feed and hygiene, and implementation of herd health schemes to control the introduction of new diseases are important factors. SPF systems declaring which diseases are present in individual herds help limiting the spread of infections from herds with infections to herds without infections.

- Initiatives to reduce transfer of antimicrobial resistant microorganisms or genes from animals or meat
  Good slaughter hygiene limiting the spread of zoonotic agents will also reduce the spread of resistant microorganisms. In the beef industry, use of decontamination strategies, such as use of lactic acid, is allowed. For the pork industry, similar protocols can be implemented. Some resistant microorganisms, such as MRSA, can spread from live animals, including live pigs. Modern pig production facilities have implemented hygienic locks to prevent the introduction of infections into pig herds, demanding change of clothes, shoes, shower-in, etc. But focus is now shifting to also include an effort to avoid carrying out pathogens with a zoonotic impact. Shower-out, change of clothes will become good practice in many herds in the future.

Wishes for the future
The last decade much research has been conducted in the area of problem finding, describing the spread of antimicrobial resistant microorganisms or genes from the animal population to humans. But in reality, very few studies have demonstrated the impact on human health.

There is a proven and clear link between the use of antimicrobials in animals and antimicrobial resistance in zoonotic pathogens, such as Salmonella and Campylobacter. And
circumstantial evidence also indicates beyond reasonable doubt that MRSA CC398 became methicillin-resistant in pigs. But for many possible threats the evidence is relatively poor, based on comparing resistance genes from one organism to another. And in many cases the results are conflicting. ESBL genes from coli isolated from Dutch animals or meat indicate a possible connection because of some similarities between these genes and genes from coli isolated from humans. But results from Denmark, Norway and Sweden show a remarkable difference in ESBL genes from coli from animals and humans, indicating that only at worst a very small proportion of human ESBL-genes potentially could be of animal origin.

A better understanding of the interactions between the animal population and the human population is important. Research has to move from showing the possibility of transfer to quantifying the effect. There is a lack of collaboration between epidemiologists and microbiologists here. Because of this lack of knowledge and because it is easier to communicate a reduction in total antibiotic consumption, there is a risk that not the most cost-effective targets and interventions will be implemented in the future, with the risk of compromising porcine health and welfare.

Research in animal/porcine health has been reduced in many countries. This paradox – increased focus on reducing antimicrobial use and antimicrobial resistance but reduced research in animal health – is limiting the possibilities for new, innovative solutions. New innovative vaccines could have a large potential here. A balanced approach is necessary, acknowledging that antibiotics will also be needed in the future to treat sick pigs. Improved treatment strategies, using the appropriate antibiotics with less impact on problematic resistance, is another area of promising research. Understanding the interaction between the animal population, the pathogen and the treatment has a lot of potential for optimising treatment.
After thirty years of working on the issue of antibiotic use in aquaculture and as I approach the end of my scientific life, the temptation to review the progress we have made is difficult to resist. When I started to address the issues, I was aware that our ignorance was vast. As I prepare to leave the field it is very difficult to avoid the conclusion that it still is.

We have little idea how much antibiotics are used, nor which antibiotics are used in global aquaculture. It is true that for certain regions, we do have accurate information. The regions for which we have this information, mainly northern Europe and northern America are, however, responsible for only 5-10 % of global aquaculture. There are, however, reasons for suspecting that in these highly regulated regions the amounts of antibiotics used per ton of production are considerably lower than the global average.

We have very little quality information on the frequency of resistance in bacteria resulting from antibiotic use in aquaculture. There have been many studies published which suggest, as would be expected, that antibiotic use in aquaculture has been followed by the emergence of strains of the target bacteria with reduced susceptibility to the agent that was used therapeutically. The value of these studies is, however, limited by the lack of standard susceptibility test protocols, the lack of any quality control of the performance of the tests and importantly the lack of internationally agreed criteria to aid the interpretation of the meaning of the data generated by the tests. We have a lot of data but very little information.

Given this continuing lack of basic data, it is unsurprising that we have failed to answer the question of the risks that this use of antibiotics presents for human health. In this situation, it is reasonable to ask whether there are reasons why we should not be concerned by our failure.

If aquaculture were globally a small industry, its potential impact may be, in the general scheme of things, insignificant. This argument is, however, untenable. Globally aquaculture is a vast (60 mt per annum) and rapidly growing (6% per annum) industry.

If the pathways by which antibiotic resistant bacteria or resistance determinants could travel from the aquaculture environment to the human environment were very restricted, this would limit the risk. It is true that, in contrast to those of terrestrial animals, the microorganisms associated with aquatic animals are very much less likely to include human pathogens. It is plausible to argue that the transfer of resistant zoonotic bacteria from aquatic animals to humans might not be a major risk. If aquaculture was considered to be largely an activity practiced in small farms in low income food deficient counties, it might be postulated that the risks consequent on antibiotic use might be local. It is true that approximately 80% of global production derives from small farmers and there are ethical considerations in applying first world regulatory frameworks to such operations. However, the fact that 40% of aquaculture production is traded internationally argues that resistant bacteria selected in small farms cannot be considered to have only local consequences.

These two arguments may have relevance to the possible risks to humans mediated by resistant bacteria selected for during aquacultural use of antibiotics, but neither have much relevance to the risks mediated by the movement of resistance determinants. In 1971, Watanabe [1] established that resistance determinants in bacteria isolated from farmed fish...
could transfer to bacteria capable of infecting humans. This observation raised the spectre that antibiotic use in aquaculture could impact on human health. How big this risk was, became a valid question. Forty year later, although we can posit the question in more sophisticated language, we are arguably no nearer to an empirically based answer. Our current understanding is that the ultimate source of resistance determinants in human pathogens is the environmental resistome. All human uses of antibiotics, in humans, terrestrial animals and plant and in aquatic animals, take place in an open environment and they all have the potential, by selecting for increased frequencies of resistance determinants, to increase the size of the environmental resistome. It is argued that there is an urgent need to develop our understanding of the complex processes involved in these pathways. Such understanding might allow us to design experiments that would generate data that would facilitate some evidence-based assessment of the risk

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THE AQUACULTURE ENVIRONMENT: THE FOCUS ON SULFONAMIDE AND TETRACYCLINE RESISTANCE GENES

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Although a lot of newly developed antibiotics have been available in human, classical antibiotics, sulfonamides and tetracyclines, are still frequently used in animal husbandry and aquaculture [1]. Especially low-income countries in Asia, use sulfonamides as human medicine too. In case that wastewater treatment systems do not work properly, antibiotic contamination in aquatic environment is of concern. The aquatic environment becomes a mixing and transferring place of antibiotic resistance genes (ARGs) derived from human, animal and aquaculture. Thus, the aquatic environment should be a ‘sink and source’ of ARGs. As an example of aquatic environment, lagoon of tropical Asian animal farms is a place of gathering, exchange and spreading of ARGs, which can be metaphorically spoken as ‘ARGs bazaar’ [2]. We should consider the importance of aquatic environment as ARGs reservoir.

Here, I would focus on aquaculture environment. Sulfonamides have been used several decades ago and tetracyclines are now major antibiotics in aquaculture. We have been monitoring sul genes and tet(M) as representative ARGs in aquatic environments. The sul genes are known to be widely present in environmental bacteria and tet(M) is the widest host range gene among ribosomal protection protein (RPP) genes [3]. RPP is suspected as an ancient resistance gene against chemical stresses in bacteria since before the divergence of prokaryote and eukaryote [4]. In the Baltic Sea aquaculture site, it was found that the sul and tet(M) genes are not ubiquitous in the water column but retained in the sediment, where antibiotics have not been used for a decade [5,6]. On the other hand, Taiwanese and Japanese aquaculture sites showed a high copy number of these genes in the water column, where oxytetracycline is used every spring to summer. Antibiotic administration, even at low concentration, gives ecological selection pressure to the environmental bacterial community, which leads to remaining of the ARGs. Among sul genes, sul3 could only be detected in natural assemblage, but not in culturable bacteria. This suggests that sul3 is conveyed in non-culturable community members.

It is beyond doubt that the aquaculture site is a reservoir of ARGs, and non-culturabl community members should play an important role in spreading and remaining of ARGs in the aquatic environment. The non-culturable bacteria occupy more than 99.9% of the marine bacteria. The silent majority should be paid attention to as a black box of ARGs ecology in the environment.

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POLICY AND PRACTICE: HOW THE EUROPEAN UNION AND MEMBER STATES ARE ATTEMPTING TO IMPROVE RESPONSIBLE USE OF ANTIBIOTICS

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Both at the level of the European Union (EU) and at the level of Member States a range of mandatory and voluntary approaches have been taken or recently initiated to improve the responsible use of antibiotics. This has ranged from the historical ban of antibiotics as growth promoters across the EU, to the recent provision of responsible use guidelines. Within that range there are a variety of actions inclusive of national action plans, improving education and raising awareness, improving information, setting broad-based arbitrary reductions in total use, mandated and voluntary reduction/prohibition of certain antibiotics, suspension of marketing authorisations of some products, national farm use league tables, improvement of data and/or surveillance on antibiotic use and veterinary pathogen antibiotic susceptibilities, decoupling of veterinary prescription and sales, tightening the farmer-vet relationship, control of illegal internet sales, developing treatment guidelines, improved biosecurity, enhanced susceptibility testing, restrictions on off-label use, limitations on medicated feed, greater implementation of herd health and herd treatment plans, vaccination programmes, and the making of certain resistances notifiable.

The range of activities within countries and differences in activities between countries makes it difficult to monitor and compare the influence of any individual action (and therefore its relative importance compared to other actions) on outputs and outcomes. Most measures of success are based on measures of reduction of use (crude or denominator based) due to the difficulties of measuring outcomes and of linking actions to the outcomes.
POLICY AND PRACTICE: HOW DEVELOPING COUNTRIES ARE RESPONDING TO INCREASING CONCERNS ABOUT ANTIBIOTIC USE IN ANIMALS

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There is increasing consensus that resistance to antimicrobials used in human healthcare has been generated in animals, is spread to humans, and has the potential to cause major harm to human health. Antimicrobial resistance (AMR) also imposes costs on the livestock sector. Most of the studies on antibiotic use and AMR come from developed countries, but developing countries are increasingly concerned about the impacts of AMR. Moreover, in a globalised world, AMR created in one country can easily spread to others. We present three case studies from different developing country contexts and discuss the implications for policy and practice.

In east Africa, the majority of livestock are kept by smallholder mixed farmers or in traditional pastoralist systems. In body mass, sheep and goats predominate (51 million TLU) followed by cattle (45 million), pigs (3 million) and poultry (1 million). Even in Kenya, where livestock intensification is most advanced, only 14% of poultry are intensively reared. In east Africa, AMR is common in human pathogens. Many studies have found antibiotic residues present in meat and milk at levels above those permitted by national standards. Probably, most drugs given to livestock are administered by untrained people, but by global norms, antibiotic use in livestock is low. Antibiotics are not added to feed for growth promotion and prophylactic use is minimal (4 kg per year for all Kenya). In some cases, AMR bacteria in livestock probably result from antibiotic use in livestock (for example, tetracycline resistant Streptococcus agalactiae in Kenyan camels emerging after decades of pastoralists using tetracycline in camels). In other cases, AMR bacteria are most likely the result of exposure to antibiotics in human faeces (for example, multiple drug resistant Salmonella in smallholder swine that scavenge for food in communities with inadequate latrines; these pigs are rarely or never treated with antibiotics). There is no evidence of AMR in humans caused by antibiotic use in livestock. A regulatory framework exists in most east African countries; implementation of importation regulations is reasonably good but implementation of regulations on use is weak or non-existent.

In India, most livestock are kept by smallholders. Cattle predominate (321 million TLU), followed by sheep and goats (228 million), and pigs and poultry (10 million each). There are no government regulations to control antibiotic use in animals and little is known about use of antibiotics in livestock. High levels of AMR bacteria have been found in livestock products and livestock faeces, even when antibiotics were not used on the farms. Other studies focus on resistance patterns in bacteria isolated from livestock, antibiotic residues in livestock commodities, and surveys on farmers use of antibiotics and perceptions of their efficacy. A Task Force in the National Centre for Disease Control, convened in 2011, established the need for an intersectoral coordination committee to review and generate data and develop regulations on veterinary antimicrobial use.

In Vietnam, most livestock are kept by smallholders. Pigs predominate (27 million TLU) followed by cattle (9 million TLU), poultry (3 million) and sheep and goats (1 million). Antibiotics are widely used in pork and poultry production. They are commonly present in
feed, probably as a growth promoter as well as for prophylactic and therapeutic use. A regulatory framework has been put in place since 2000, regulation of importation, lists of permissible antibiotics and an action plan on antibiotic resistance to 2020.

These three cases studies, East Africa, India and Vietnam together cover around 1.5 billion people and 2 billion livestock. Although smallholders predominate in all systems, intensification in terms of input use (including veterinary drugs) is low in India and east Africa but high in Vietnam. In India and east Africa, where access to sanitation is poor and many animals are unconfined, it is likely that livestock are exposed to antibiotics and AMR bacteria in human faeces; antibiotic usage in humans may be driving AMR pathogens in animals. However, animals and livestock products may then play a role in retransmission to people. In Vietnam, it is possible that antibiotic use in animals is driving AMR pathogens in people.

However, these are speculations and a main finding from our case studies has been the very limited evidence on antibiotic use and AMR pathogens in livestock and the implications for human and animal health. We can confidently say that, in the countries studied, most antibiotic use is by untrained people, regulations even when present do not translate to practice, and AMR pathogens are common in livestock and livestock products. This suggests that further evidence generation and action are needed to address what is potentially a problem of major significance for global health and the well-being of people and their livestock in poor countries.
LATIN AMERICA INITIATIVES ON VETERINARY DRUG AND ANTIMICROBIAL RESISTANCE

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The control of antimicrobial resistance has recently become a health priority in Latin America. Bacterial populations with multiple forms of resistance and cross-resistance between antibiotics and many other chemicals, are extremely diverse and several selectors drive their resistance. There is overwhelming evidence that antibiotic use has been a powerful selector of resistance. Given the broad range of animal species under veterinary care and the enormous variety of infectious agents, a complete range of antimicrobials is needed in veterinary medicine. Having fewer products available, either through the occurrence of resistance or through prohibition of their use, will have serious consequences for the health and welfare of all animals. It will also seriously affect people who depend on these animals.

Latin America governmental authorities, aware of the key elements of any strategy to stop the growing trend of antimicrobial resistance, took several independent initiatives to keep the use of antimicrobials as transparent and responsible as possible and safeguard the effectiveness of antimicrobials in the future. The harmonised data requirements established by VICH, i.e., standards for the scientific studies on quality, safety and efficacy that are required to obtain a marketing authorization for a veterinary medical product as well as for their post-marketing safety monitoring, are being used in the majority of our countries. By another way, to provide for science-based policy recommendations regarding public and animal health surveillance programmes are now in place in many Latin America countries, to follow trends in resistance development as well as in the consumption of veterinary antimicrobials. Specific texts developed by the FAO/WHO Codex Alimentarius on antimicrobial resistance are being followed in Latin America, particularly the ‘Code of Practice to Minimize and Contain Antimicrobial Resistance’ (CAC/RCP 61-2005) and the ‘Guideline for Risk Analysis of Foodborne Antimicrobial Resistance’ (CAC/GL 77-2011). Other Codex texts on antimicrobial resistance, such as the ‘Code of Practice on Good Animal Feeding’ (CAC/RCP 54-2004), the ‘Code of Hygienic Practice for Egg and Egg products’ (CAC/RCP 15-1979) and the ‘Code of Practice for Fish and Fishery Products’ (CAC/RCP 52-2003) are also being followed. Worth noting that Latin America food chain authorities are putting across the best of their efforts to follow the measures and recommendations on prudent use of antimicrobial agents in veterinary medicine, especially on those specified in the ‘OIE Terrestrial Animal Health Codex’ document. Relevant to point out the contribution given by Latin America governmental and non-governmental authorities to almost all Codex initiatives on this subject, such as, and for instance, the ‘FAO/OIE/OMS Codex Intergovernmental Task Force on Antimicrobial Resistance’.

Although it is not possible to generalise the measures taken up by the different Latin America countries to manage antimicrobial resistance, it is felt the eight risk management options that came out from the ‘FAO/OIE/WHO Expert Meeting on non-Human Antimicrobial Usage and Antimicrobial Resistance’ (WHO/CDS/CPE/ZFK/2004-8) are been carefully considered and applied were appropriate. For all of that, it seems reliable to state Latin America regulatory authorities, veterinary pharmaceutical industries, wholesale and retail distributors, veterinarians and food-animal producers, clearly understand their roles and responsibilities in antimicrobial resistance restraint. There is a common perception in Latin America that only by mobilising all countries to improve the quality of antimicrobials, introduce antimicrobial resistance surveillance and implement measures for the responsible use of antimicrobials, will it be possible to halt the spread of antimicrobial resistance.
OVERVIEW OF ANTIMICROBIAL RESISTANCE, PREVALENCE AND INTERVENTION IN ASEAN COUNTRIES

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To date, foodborne diseases are still common in ASEAN countries. *Salmonella enterica*, *Campylobacter* and pathogenic *Escherichia coli* appear to be the most common causative agents. Unfortunately, antimicrobial resistance (AMR) has increasingly evolved for essentially all antimicrobials currently approved for use in human and veterinary medicine. This problematic situation has become more complicated due to the frequency of new emerging resistance phenotypes occurring among many bacterial pathogens and commensal bacteria. By 2015, the ASEAN Economic Community (AEC) will be fully established and recognise the evolving threat of AMR in bacterial foodborne pathogens as a major food safety priority.

Like in other world regions, livestock is considered a major source of resistant bacteria for humans in ASEAN countries, the strongest connection to animals being food originated from these animals. AMR has arisen for both common and clinically important antibiotics in bacteria associated with food animals and derived products throughout the region, e.g., Thailand [1], Malaysia [2], Philippines [3], Vietnam [4], and Cambodia [5]. Of particular concern is that healthy animals and retail meat appear to be a significant source of AMR bacteria (particular *Salmonella* and *E. coli*) [6]. As a major pathogen, AMR in *Salmonella* has been most extensively studied. The most frequent resistance is to common antibiotics, e.g., ampicillin, tetracycline, streptomycin and sulfamethoxazole, trimetoprim [1,3,7], while quinolone resistance varies. Resistant *Campylobacter* has been reported in broilers and pigs from farm-to-fork in Thailand, the Philippines and Cambodia [3,5,8].

Despite the fact that antimicrobial use (AMU) creates a selective pressure for resistant bacteria, antibiotics are still commonly used in ASEAN livestock due to widespread of bacterial infections, lack of better alternatives for infection treatment and animal welfare. Type and extent of AMU is different from one country to another depending on animal species, type of farm, economy, level of development, animal husbandry and existing regulation. Such data are neither systematically recorded nor clearly stated in most countries. No formal AMU data in livestock could be reached in certain countries, e.g., Indonesia, Laos and Myanmar. Based on the available data, the major antimicrobial classes used in livestock include β-lactams, tetracycline, fluoroquinolones, aminoglycosides, macrolides and sulphonamides; most are imported from other Asian and European countries. Counterfeit drugs are a serious challenge in some countries, e.g., Vietnam [9].

Recognising the public health crises due to AMR, different ASEAN countries have taken action to counteract the problem through different strategic plans with different degrees of intensity and success. Therefore, there are wide variations in efforts, surveillance capacity, monitoring practice and regulation. Systemic surveillance of AMU and AMR is still lacking in ASEAN countries at either national or regional level. Consequently, the true root and cost of AMR remain largely unclear. Non-standardised and non-harmonised AMR monitoring is recognised as a primary weakness in comparison of AMR monitoring data across the regional countries. Together with ineffective public health system, combined surveillance of antimicrobial use and resistance seems far away for the region. AMU is generally not well regulated. There are limited data published on national regulation policy; some existing publications are usually in native languages. Responsible use of antimicrobials in food animals has not been seriously encouraged. Currently, only two ASEAN countries (i.e.,
Thailand and Philippines) have started assembling guideline for judicious use of antimicrobials in livestock.

To address AMR control and management in ASEAN countries, regional cooperation is needed for immediate and long-term developing and implementing effective AMR monitoring, control and prevention approaches. The regional strategy for the containment of AMR providing a framework of interventions to minimise the emergence and spread of AMR is imperative and through: (i) raising AMR troublesome situation to be of national/regional concern; (ii) encouraging training on and application of standardised antimicrobial susceptibility testing methods and AMR monitoring protocol; (iii) developing national AMR surveillance and follow-up system to ensure its effectiveness and success; (iv) enforcing regulation and legislation on veterinary drug use; (v) encouraging rational use of veterinary drugs; (vi) developing the AMR recording and reporting system; (vii) providing regular financial resources from governmental and private sectors; (viii) endorsing collaboration between regulators, public health officials and stakeholders for AMR management; (ix) enforcing the prescription for veterinary drugs; (x) increasing number of veterinarians and veterinarian services in remote areas; and (xi) encouraging research on new drugs and vaccines and new technology for diagnosis.

References
A ONE HEALTH APPROACH TO ANTIMICROBIAL RESISTANCE SURVEILLANCE IN AUSTRALIA

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Australia is a large, isolated island with diverse climate and geography, a sparse human population (22.7 million, 2.9 people per km² with over 60% living in cities of greater than 1 million people), significant populations of food-producing animals (e.g., 74.7 million sheep; 28.5 million cattle) and a substantial meat export industry. In line with restrictions on fluoroquinolone use in humans, Australia is the only country that has legal measures in place to exclude the use of this class of antibiotic in food animal species. Label constraints for third generation cephalosporin use in Australian food animals are very strict by international comparison (for example, they are not registered for use in poultry). There also are large differences between Australia and other countries with respect to animal production (a stronger reliance on extensive production without housing), quarantine bans on the importation of fresh meat and live animals, and the fact that Australia is geographically isolated with no shared land borders.

Whilst Australia also does not currently have a national, federally funded antimicrobial resistance and antibiotic usage surveillance programme focused on animals, a number of notable one-off surveys have been conducted in recent years. These studies have consistently confirmed a low public health risk in the food animal sector related to resistance against critically important drugs, such as fluoroquinolones. Through funding from the federal Department of Health and Aging, The Australian Group on Antimicrobial Resistance (AGAR) has been conducting national surveillance and reporting of antimicrobial resistance and antibiotic usage in humans since the mid 2000s. In 2014, the federal Department of Agriculture provided funding to develop a detailed report on how antimicrobial resistance and antibiotic usage surveillance could be conducted in animals in Australia, given the considerable differences and challenges outlined above. The report comprises an extensive critical review of existing surveillance systems adopted throughout the world, a summary of recent survey activity in Australia and a list of recommendations to move towards an integrated, 'One Health' surveillance system.
IMPLEMENTING THE NEW ANTIBIOTIC GUIDANCE FROM FDA

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For more than 40 years, antibiotics used in the feed of food-producing animals have been available without a prescription and approved by the U.S. Food and Drug Administration (FDA) for four distinct labelled uses; individual or group treatment of active bacterial infections, control of infections to prevent further spread, prevention of infections in at risk populations, and to increase weight gain or improve feed efficiency. FDA identifies the first three indications as therapeutic indications. The decision to allow these products over the counter was one made many years ago when legislation was passed to regulate animal drugs. The lack of veterinary services in rural areas of the country and the lack of the communication technologies available today were some of the reasons for permitting farmers and producers to have access to these medications to keep their animals healthy.

In April of 2012, the FDA announced its policy for ‘The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals’. The policy advised that those antibiotics that FDA has classified as medically important and have dual use in both animals and humans be marketed only for therapeutic indications under the control of a licensed veterinarian. In 1994, the U.S. Congress passed the Veterinary Feed Directive requiring that all new antibiotics for use in feed be labelled as a VFD drug, which is essentially the counterpart to prescription pharmaceuticals. At that time, the VFD was not retroactive so that all antibiotics that were originally approved remained over the counter. With the new policy, FDA is proposing to apply the VFD requirement to older medically important antimicrobials at the same time they are asking sponsors to withdraw production claims. FDA has since issued more detailed guidance to the industry explaining the process for changing the labels to reflect the new policy. Companies could also petition the agency to add new therapeutic indications to the label if they can provide the necessary documentation through scientific studies supporting the disease claim and target pathogen. The intent of the agency is to complete labelling changes on medically important antimicrobials within 3 years but a key milestone that must be met is publication of a final regulation revising the current VFD provisions to accommodate these changes. The FDA has requested the drug sponsors voluntarily cooperate to change the labelling on these products and is working with trade associations and drug sponsors in a collaborative manner. The Animal Health Institute (AHI), the Generic Animal Drug Association, and independent sponsors have all committed in writing to work with the FDA to effect the policy change. The change in labels and market access to feed use antimicrobials will take much effort and coordination between the drug manufacturers, feed mills, producers, and government authorities in order to maintain availability to important therapeutic products while these changes are being effected. When all changes are in place, medically important antibiotics as defined by FDA will be used only for prevention, control, and treatment of disease under the control of a veterinarian.
The U.S. Food and Drug Administration (FDA) is addressing the issue of antimicrobial resistance by adopting two overarching policies. The first is to increase veterinary oversight of the use of antimicrobials in food animals and the second is to phase out production uses of antimicrobials (for growth promotion and feed efficiency). In FDA Guidance 209, FDA states that the use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health. These are treatment, control, and prevention. Production uses of antimicrobials will no longer be allowed.

There are three categories of drugs regulated by FDA: over-the-counter (OTC) drugs, prescription drugs and Veterinary Feed Directive (VFD) drugs. The VFD is the primary mechanism for veterinary oversight of antimicrobials administered in feed. They are prescription-like, but they are for feed only. VFDs are federally regulated, whereas prescriptions are regulated by states. Currently, there are only 2 VFD drugs: tilmicosin for control of swine respiratory disease and florfenicol for control of swine respiratory disease and for control of certain bacterial diseases in aquaculture. (Most U.S. veterinarians have never issued a VFD.) FDA plans to increase veterinary oversight of the use of antimicrobials in food animals by transitioning medically important antimicrobials delivered in water from OTC to prescription status, and antimicrobials delivered in feed from over-the-counter (OTC) to Veterinary Feed Directive status.

A 5-member American Veterinary Medical Association (AVMA) Steering Committee for FDA Policy on Veterinary Oversight of Antimicrobials (VOSC) was appointed by the AVMA Executive Board in April of 2011. The Committee’s charge was to work with FDA to identify workable strategies for increasing veterinary oversight of the use of antimicrobials in food animals through modifications to the VFD. The VOSC met with FDA in Washington D.C. in June 2011 to learn about FDA’s plan for the VFD and how we could contribute. The committee then spent the summer discussing the issue and in a September 2011 meeting with FDA, the VOSC recommended that there be a requirement that veterinarians be licensed in the state in which the animals reside and that the requirement for a total amount of feed or drug be dropped from the VFD so that a veterinarian would order drug A to be given to these animals at x dose for y duration because the total amount of feed had proven to be difficult to predict.

The current VFD contains a reference to the federally defined, codified veterinary-client-patient relationship (VCPR) found in the Animal Drug Use Clarification Act (AMDUCA), the federal regulation addressing extra-label drug usage. However, any extra label use of antimicrobials in feed is currently, and will continue to be, illegal and strictly prohibited in the U.S. In addition, the VFD is a federal regulation; whereas the definition, enforcement, and control of veterinary professional conduct (including adherence to a VCPR) is a state function through licensure and state practice acts. State licensing boards have the authority to invoke penalties and revoke licenses. For these reasons, the VOSC agreed with the FDA plan to defer the VCPR to the states’ authority. With this change, regulation of veterinary professional conduct regarding medicated feeds would be consistent with regulation of prescription injectables and prescription antimicrobials delivered in water.
The VOSC saw that as veterinary oversight is increased, it was important that the AVMA’s Veterinary Client Patient Relationship (VCPR) be updated to reflect the diversity of practice types and changes that have occurred in the profession. We reviewed the AVMA’s VCPR found in the AVMA’s principles of Veterinary Medical Ethics, and other AVMA policy. After much debate, an updated AVMA VCPR was passed by the AVMA House of Delegates in January of 2013, and included a phrase on veterinary oversight: “The veterinarian provides oversight of treatment, compliance and outcome.”

In early June 2014, AVMA hosted a one-day Veterinary Feed Directive Summit that included approximately 100 attendees representing all food animal practice types and regions of the U.S. The purpose of the programme was to exercise the use of Veterinary Feed Directives under the proposed new FDA regulations in common practice situations to identify what is likely to work well and where adjustments may need to be made. Stakeholders identified small improvements in the process that could be made, however overall, the VFD process appeared practical, and no large problems with its use were found.

The VOSC continues to engage with FDA as the tenets of FDA Guidance 209 and 213 are implemented, and we look forward to supporting the process as it moves forward.
WHAT FDA GUIDANCE 213 AND THE VETERINARY FEED DIRECTIVE MEAN ON THE FARM – A PORK PRODUCER’S PERSPECTIVE

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In December 2013, the U.S. Food and Drug Administration (FDA) published final Guidance for Industry #213 and proposed modifications to the Veterinary Feed Directive (VFD) rule. Guidance for Industry #213 asks animal health manufacturers (sponsors) to relinquish their label claims for production uses (growth promotion or improvement of nutritional efficiency) for antimicrobials that are in classes of antimicrobials that are also used in human medicine. The changes to the VFD Rule will require all therapeutic uses of these same classes of antimicrobials in feed to be under a veterinary order. Water administration of these same classes will require a veterinary prescription. All sponsors of the affected antimicrobials have indicated their intentions to comply with the Guidance. The changes required by these regulatory actions are expected to be fully implemented by the end of 2016. This will require significant changes on farm by U.S. pork producers.

Background
Prior to implementation of the changes described above, farmers in the United States have been allowed to utilise a range of antimicrobials to improve growth or nutritional efficiency without veterinary prescription. Many of these antimicrobials were also in classes that are used in human medicine, e.g., tetracyclines, macrolides, lincosamides, etc. However, the critically important fluoroquinolone and cephalosporin classes have never been used for production improvement purposes or as feed additives in the United States.

Certain antimicrobials in feed – tilmicosin and fluorphenicol – have only been allowed for use in feed under a veterinary order under the existing VFD rule. The current VFD regulations require that the veterinarian sign an order stating not only the indication and dose, within an approved dosage range, but also an estimated tonnage of feed they estimate will be consumed by the animals during the treatment time. In addition, the restrictions in the current VFD regulations on electronic transmittal are difficult to comply with, requiring in many cases the delivery of the original signed order to the feed mill. The requirements of the current VFD rule have been problematic to many small and large producers alike.

Antimicrobials administered in feed can only be used as labelled. This restriction is included in the Animal Drug Use Clarification Act (AMDUCA) legislation. In short, it is against the law to use any antimicrobial in feed in an extra-label manner. Since administering an antimicrobial for a different indication than on the label is considered extra-label, after the growth promotion/nutritional efficiency labels are discontinued it will be illegal to use these antibiotics to promote growth even in the case when the former growth promotion dose overlapped with the dose for metaphylaxis.

Impact on the farm
The implementation of Guidance 213 and the revised VFD rule will change how antimicrobials are used in U.S. pork production. Simplistically, many feel that the success of these changes should be measured by a decrease in pounds of antimicrobials sold in the U.S. However, it is uncertain how much clinical disease is being prevented by the current uses of antimicrobials for growth promotion. If there is significantly more clinical disease that occurs following the removal of the growth promotion uses, more antimicrobial use – at higher doses – may subsequently be utilised for disease treatment.
The requirement for the therapeutic uses of antimicrobials in feed and water to be under veterinary oversight will also impact pork producers of all sizes. It is expected that the revisions to the VFD rule will make the process of writing and filling a VFD more user friendly. However, in spite of those changes it is expected these changes will impose a burden on farmers and veterinarians. Many small farms use a veterinarian sporadically, and the costs of a veterinary farm call to write a prescription or VFD will need to be spread over a relatively smaller number of animals. While large farms generally have veterinarians that develop standard operating procedures for use of animal health products, it is uncertain how much impact the increased regulatory burden of writing orders for those uses will be. Since there are relatively few veterinarians practicing swine medicine in the U.S., the burden to provide and document the veterinary orders may be substantial.

**Conclusion**

The FDA Guidance for Industry #213 and the changes to the VFD rule will have substantial impact on antimicrobial use decisions on farm and add to the burden to document judicious use of therapeutic antimicrobials by producers who utilize them on their farms.
FDA’S ANTIMICROBIAL RESISTANCE POLICIES – THE U.S. FEED INDUSTRY’S PERSPECTIVE

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For more than 50 years, antibiotics have been used in the United States within animal agriculture to facilitate a wholesome and safe food supply and improve animal health and welfare. During this time period, most antibiotics used in animal feed have been available on an ‘over-the-counter’ basis, being distributed and used in accordance with established regulations. However, the U.S. Food and Drug Administration (FDA) in 2010 announced policy changes that will transition the use of animal antibiotics that are important to human medicine to a status requiring enhanced veterinarian oversight. In addition, FDA’s policy change will eliminate subtherapeutic use of such antibiotics that previously were approved by the agency for improving animal production.

The U.S. feed industry recognises the public health importance of issues concerning antibiotic use in food-producing animals, and supports policy and regulatory decisions regarding such use that are based upon objective and substantive scientific evidence. As such, the U.S. feed industry has in the past and continues to rely on the FDA to make sound public health policy decisions, including those pertaining to antimicrobial resistance, in view of the best available scientific information. From a practical standpoint, commercial feed manufacturers in the United States – those that are not involved in animal production, but sell feed products to animal producers – generally have no direct monetary interest in adding antibiotics to animal feed. Commercial feed manufacturers receive margin for their products based upon nutritional value and supporting services rendered, not from the addition of an antibiotic to the feed. Antibiotics are added to feed at the request and for the benefit of the animal producer.

However, as an industry aligned with producers of animal-based foods, U.S. feed manufacturers have an overarching interest in producing for consumers both in the United States and around the world a safe, economical and wholesome supply of meat, milk and eggs. Regarding international customers, the continued ability for U.S. producers to market animal-based food products globally is of vital importance to their livelihood. As an example, the percentage of U.S. meat production that is exported has grown dramatically over time and now represents a very significant portion of overall demand. Therefore, the industry strongly supports U.S. requirements that no animal drug be used unless its safety and efficacy have been demonstrated, so as to provide all consumers with assurance about the safety of U.S. animal based-foods. And in that regard, the industry believes that human health considerations should be uppermost in the decision-making process.

The transition within the United States of the use of animal antibiotics that are medically important to enhanced veterinary oversight will not be without significant challenges. The U.S. animal agriculture and feed industries are large and diverse. There are many issues to be considered and addressed, ranging from the practicalities associated with the number of available veterinarians, to the possibilities of disruptions of necessary medications to animal producers if their suppliers choose to stop distributing feeds with antibiotics due to an increased regulatory burden.

FDA’s Veterinary Feed Directive (VFD) has and will continue to serve as the regulatory framework for providing veterinary oversight for the use of antibiotics in animal feed within
the United States. The VFD requirements squarely place the regulatory burden of appropriately distributing medicated animal feed on the feed industry. This regulatory burden under the current VFD regulation is significant and will grow significantly as the number of animal drugs subject to VFD requirements is dramatically increased. As such, the feed industry has been actively engaged with FDA during its on-going VFD rulemaking process to explore options to minimise the regulatory burden while still ensuring judicious and responsible use of antibiotics.

Moving forward, the U.S. feed industry believes that a workable regulatory framework to provide for the continued availability of antimicrobial drugs for use in animal production plays a vital role in maintaining the health of humans and animals, and the safety of animal-based foods. While the industry does believe it is possible to revise and enhance the current VFD process, the increased regulatory burden likely will be very significant. As an outcome, it is likely that those most affected by the increased burden will be small operations, whether they be animal producers or feed distributors. Therefore, it is likely that the pending transition to enhanced veterinary oversight of the use of antimicrobial drugs will be a factor that contributes to further consolidation of the animal agriculture and feed industries within the United States.

To assist in assuring the best outcome for all stakeholders, the U.S. feed industry will continue to be an active and constructive participant as all interested parties work to further promote the responsible use of antibiotics in animals.
ENHANCING THE POWER OF THE IMMUNE SYSTEM

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The immune system is involved in host defense against infectious organisms and in assuring tolerance to sources of non-threatening antigens. Impaired immune function can be associated with increased susceptibility to infectious agents and increased severity of infections necessitating the therapeutic use of antibiotics. Malnutrition and specific nutrient deficiencies impair immune function and increase susceptibility to infection. There is some evidence that various micronutrient deficiencies – for example, deficiencies of zinc, selenium, iron, copper, folic acid, and vitamins A, B₆, C, and E – alter immune responses in animals in vitro. However, the impact of these immune system changes on the health of animals is less clear. Variations in intake and status of certain nutrients and dietary constituents (e.g., long-chain n-3 fatty acids, micronutrients, plant flavonoids, low-digestible oligosaccharides and probiotics) among livestock may account for observed variations in immune function. The evidence for many dietary factors is, however, inconclusive, with some studies reporting effects and others not, e.g., the effect of fish oil supplementation on immune parameters in healthy subjects. Furthermore, the sensitivity of the immune system to dietary interventions may be different in individual animals with an inflammatory condition compared with healthy individuals, for whom the immune system may be buffered to a larger extent against modulation by such intervention.

Livestock performance and feed efficiency are closely interrelated with the qualitative and quantitative microbial load of the animal gut, the morphological structure of the intestinal wall and the activity of the immune system. In-feed antimicrobial growth promoters have made a tremendous contribution to profitability in intensive husbandry but as a consequence of the increasing concern about the potential for antibiotic resistant strains of bacteria, feed antibiotics are banned. There are a number of non-therapeutic alternatives, including enzymes, (in)organic acids, probiotics, prebiotics, etheric oils and immunostimulants. Antimicrobial peptides, part of native host defense, have emerged as novel potential antibiotic alternatives. Immunostimulants in nutritional interventions should enhance the activity of the immune system but there are many laboratory measures of immune function and these show large inter-individual variation. There are paradoxical effects of vitamin D on immunity. Experiments in animals support a suppressive effect of vitamin D on inflammation but not other aspects of immunity including host resistance to infectious disease. The vitamin D and the vitamin D receptor are both required for the development and function of at least two regulatory populations of T cells, invariant NKT cells, which are early producers of cytokines and CD4/CD8α intraepithelial lymphocytes found in the gastrointestinal tract. Protective immune responses that depend on these regulatory T cells are therefore impaired in the absence of vitamin D or the vitamin D receptor leading to an increase in gut-associated inflammation and reduced performance.

In light of the current situation of a worldwide spread of antibiotic resistance, therapeutic alternatives beyond antibiotics have been investigated during the last years, including vaccines, probiotics, photodynamic inactivation, phage therapy and phytomedicine. Probiotics are live organisms or produced substances that are orally administered to promote health. Probiotics mostly prevent antibiotic side effects, such as diarrhoea, as well as improve eradication rates. Indeed, probiotics can act in several ways in the gut microbiota, for instance by direct antagonism to pathogens through the production of inhibitory substances, competition for adhesion or nutrients, host immune modulation or inhibition of
toxins. Phytotherapy, also described as herbal therapy or botanical therapy, consists in the use of plants or plant extracts for medicinal purposes. The active ingredient is not always identified; sometimes the group of compounds, but not the exact formula, is identified. Flavonoids are widely distributed in plants and are recognized as the pigments responsible for the colours of leaves, especially in autumn (yellow). The flavonoids are recognised to possess anti-inflammatory, antioxidant, hepatoprotective, antithrombotic, and antiviral activities. The flavonoids are phenolic compounds and, therefore, act as potent metal chelators and free radical scavengers. The risks and benefits of herbal medicine are incomplete, complex, and confusing. There is a need for further controlled clinical trials addressing the potential efficacy of herbal medicine, together with understanding the mode of action and implementation of legislation to maximize their safety and quality.

In this presentation some recent findings, background mechanisms of action and implications of immune strengthening dietary components as alternatives to the use of antibiotics are discussed.
CURRENT AND FUTURE CONSIDERATIONS FOR THE VETERINARY ANTIBIOTIC PIPELINE

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Antibiotics are molecules that inhibit or kill microorganisms; typically meaning bacteria. Antimicrobial agents include molecules directly active against viruses, fungi, parasites and/or bacteria. Antibiotics are approved for therapeutic indications of treatment, control and prevention; in some countries antibiotics may be used for performance (e.g., feed efficiency or daily gain) indications. The current marketplace is approximately $4.8bn USD, with 65% of sales in the U.S. and Europe.

The regulatory pathway for therapeutic or performance label indications requires demonstration of effectiveness (clinical outcome matched with dose, duration and route), safety (including human food safety) and quality of product; regardless of the origin of the active component. A novel antibiotic would ideally need to have effectiveness comparable to or better than the market-leading product, preferably no human use potential, bactericidal, ‘low’ resistance potential, short withdrawal time or a unique safety profile. Sources of novel chemistry includes newly discovered agents, unusual fermentation products, analog approaches for existing molecules or repurposed old antibiotics. Approximately 10 years and $100M USD are invested to bring a new product to the market. The commercialisation pathway generally requires about 3-4 years to identify and affirm acceptable characteristics sufficient to progress it to the next phase of registration quality studies, which may take 4-5 years and then regulatory submission and review of approximately 3 years.

Current external factors that influence antibiotic development include a conservative approach by regulatory agencies to label approved products with narrow conditions of use and a prohibition or restriction of use of certain classes of critical importance to human medicine. In the future, additional factors may include implementation for a cascade approach or for holding newly approved products ‘in reserve’ to be used only as a second or third line therapy, formularies and the increased marketplace availability of low-cost generic products.

An additional consideration that may be detrimental to new antibiotic development is the perception that no new antibiotics are necessary, because it is possible to replace antibiotics with ‘alternatives’ that will have equivalent effectiveness and will be less risky in some way. To date, treatment of clinical disease is only possible with antibiotics, hence it is unlikely that an ‘alternative’ for this use would be commercialised. Disease prevention may be achieved, or performance may be enhanced, by non-antibiotic interventions; equivalent to or exceeding the ‘gold standard’, which is likely to be an antibiotic product with such a label indication. Since disease prevention is the initial step in clinical practice guidelines for responsible antibiotic use, alternative approaches (that are non-antibiotic) for disease prevention are needed, since not all antibiotics have prevention indications. These types of products may decrease the prevalence of disease and thus the overall amount of use of therapeutic antibiotics; however, disease outbreaks will still occur and the need for antibiotics will continue and have an essential role in disease intervention to ensure animal health and welfare.
ALTERNATIVES TO ANTIBIOTICS: RECENT SCIENTIFIC DEVELOPMENTS

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Antibiotics are one of the most important medical discoveries of the 20th century and remain an essential tool for treating animal and human diseases. However, antibiotic resistance among bacterial pathogens and concerns over their extensive use in animals has garnered global interest in limiting their use in animal agriculture. There is therefore a critical need to explore the scientific breakthroughs and novel technologies that provide alternatives to antibiotics. The international symposium Alternatives to Antibiotics in Animal Production (http://www.ars.usda.gov/alternativestoantibiotics) was organised to assess promising research results and novel technologies that could potentially provide alternatives to antibiotics in animal agriculture. Some of these new technologies have direct applications as medical interventions for human health, but the focus of the symposium was animal production, animal health and food safety. Five subject areas were explored in detail through scientific presentations and expert panel discussions: (i) alternatives to antibiotics, lessons from nature; (ii) immune modulation approaches to enhance disease resistance and treat animal diseases; (iii) the gut microbiome and immune development, health and diseases; (iv) alternatives to antibiotics for animal production; and (v) regulatory pathways to enable the licensure of alternatives to antibiotics. This presentation reviews promising technologies selected from the 110 scientific presentations included in the symposium. Importantly, challenges and recommendations for advancing the development and commercialisation of alternatives to antibiotics will be provided.
PHYTOBIOLOGICS: USING REDOXIGENIC PLANT IMMUNITY TO SUPPORT THE IMMUNE SYSTEM IN PIGS

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With pressure to reduce (and eventually eliminate) the use of antibiotic growth promoters in food animals, producers are investigating the use of alternative agents derived from the plant and other natural materials to promote digestive health of piglets. Phytobiologic agents can play a role in reducing the dependence on antimicrobial agents while introducing a mechanism of immune support derived from plant-based solutions. In living plants, polyphenols are central to the instigation of redoxigenic plant immunity (RPI), the natural biochemical mechanism that plants have evolved to defend against physical or microbial assault. When plant cells are ruptured, resident polyphenols mix with intracellular oxidants and enzymes, forming molecules that aggressively bind to proteins and other biopolymers to seal damaged tissues, stop proliferation of microbes, and neutralise virulence factors of pathogens.

Digestion of viable plant cells rich in polyphenols includes a rich source of reactive oxygen species (ROS), oxygen ions and peroxides produced and stored in plant cytoplasm. Phytobiologics deliver a stable, rich source of this polyphenol-ROS immune augmenting duo. In plant cells, production and presence of ROS has direct antimicrobial actions, such as strengthening host cell walls through cross-linking of glycoproteins, lipid peroxidation and membrane damage and inducing intracellular signalling pathways that mediate the activation of defense genes. Since the receptors on the plasma membrane of plants that recognise pathogens are similar to components found in the innate immune system of animals, there may be downstream signalling components common to both. Redoxigenic plant immunity can support the immune systems of growing pigs via four routes of activity, which may be present singly or work cooperatively:

- inhibition of toxic compounds;
- inhibition of microbial growth;
- disruption of inflammatory signal pathways; and/or
- wound healing/protection of tissue.

Inhibition of toxic compounds
Based upon the rapid resolution of scour/diarrhoea documented in both animal and human studies following the ingestion of phytobiologic solutions, binding of bacterial toxins appears to be central to the effect. Within the cell walls of Gram-negative bacteria resides a lipopolysaccharide (LPS) complex, termed ‘endotoxin’, which elicits an inflammatory response by the host. Since the major component of endotoxin is LPS, a phytobiologic agent interfering with the adhesion of LPS to target receptors could help modulate gut health and reduce gut damage. Recent research has noted that the binding of LPS increases as the concentration of a phytobiologic solution increases until levels of interference that would reduce availability of endotoxins in the system are achieved.

Inhibition of microbial growth
Redoxigenic plant immunity can also support the immune system by reducing the proliferation of bacteria and other pathogens. Polyphenols and other phytobiologic compounds have been noted to inhibit the proliferation of Gram-negative and Gram-positive bacteria with minimal inhibitory concentrations as low as 3.9 µl/ml. Such low inhibitory concentrations are due to increased bioactivity when polyphenols are coupled with ROS.
Disruption of inflammatory signal pathways.
Interference of the inflammatory cascade is a central role of many phytobiologic agents. For example, epigallocatechin gallate, the most abundant polyphenolic metabolite present in green tea, modifies the nuclear factor κB (NFκB) by inhibiting interleukin-1β proinflammatory signal transduction and interleukin-8 gene expression. In addition, research has reported that phytobiologics inhibit the production of the inflammatory mediators interleukin-8, nitric oxide, and prostaglandin E₂. Quorum sensing by bacteria is reduced substantially in the presence of several phytobiologics, which inhibit autoinducer-1 signalling, swarm motility, and biofilm formation of several bacterial pathogens. Blocking the production of these mediators may explain the rapid resolution of acute intestinal upset reported in both animal and human clinical studies where phytobiologic solutions have been consumed.

Wound healing/protection of tissue
In addition to disruption of activation of NFκB, research has noted that phytobiologic agents can block infiltration of CD8+ T cells into specific sites of inflammation.

Conclusions
Antimicrobial agents may eliminate pathogens, but over time some bacteria mutate and develop resistance to these antimicrobial agents. In contrast, phytobiologic agents eliminate bacteria by mechanical impairment. Such mechanism is difficult to be overcome by bacteria and is unlikely to be invoked or selected for expression relevant to antibiotic resistance. The data to date suggest that phytobiologic agents have the potential to limit infection and inflammation by blocking/remove toxins, inhibiting quorum sensing, curtailing microbial growth, disrupting inflammatory signal pathways, and augmenting wound healing, thus, reducing the digestive disturbances and promoting the intestinal homeostasis in both pre- and post-weaned piglets on commercial pig units. With ever-increasing restrictions on the use of antibiotics to improve piglet health and performance, alternative solutions derived from natural sources, phytobiologics, may contribute to gut health of pigs and sustainable efficiency in productivity of pig herds.
CAN MEDICATED FEED BE REPLACED BY PRE-PROBIOTICS?

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The overuse of antibiotics has created resistant strains of deadly bacteria (nosocomial problems). The World Health Organization [1] is dealing with antibiotic resistance genes (ARG). The main goal of WHO is to reduce the consumption of antibiotics without therapeutic prescription and also improve the monitoring of antibiotic resistance. The European Union (EU) territory banned the use of antibiotic growth promoters (AGP) in 2006. Avilamycin, avoparcin, bacitracin, flavomycin, spiramycin, tylosin and virginiamycin are no longer used in animal feeding in Europe as feed additive [2]. The ban of AGP led to a reduction in antibiotic consumption. No important consequences on the therapeutical use of antibiotics per animal have been detected in northern European countries except for piglets [3]. In other areas of Europe, no reports have been produced. However, it is also known that the consumption of medicated feed, especially in piglets, is important. For instance, in southern European countries, such as Spain, Italy and France, the volume of medicated feed reaches a percentage over the total production of feed higher than 4% [4].

Today, one of the main challenges of animal production is to reduce the use of antibiotics in medicated feed. However, there are many difficulties to assess the problem, because not all European countries have the same procedures. Therapeutical antibiotics through oral administration can be applied as medicated feed or into water or by top dressing/mixing at the farm. UK, France, Italy, Poland, Portugal and Spain use medicated feed produced in the feed manufacturing plant. In other countries, such as Germany, Belgium and Denmark, the most common route is top dressing/incorporation of ready-to-use products in feed and mixing into water. Thus, several types of applications are used today in the EU. The replacement of antibiotics as medicated feed is not the only route of administration to consider in a monitoring process.

An important task has been initiated to find new substances or combinations with functionality as alternatives to AGPs in practice, even before the ban of AGP. However, none of the non-antibiotic AGP alternatives has shown comparable effects as AGPs [5]. According to research by Niewold [6], the benefits of AGP are based on the reduction of energy cost produced by reduction of immune reaction and consequently a non-antimicrobial concept is also accepted as new mode of action for AGP. Research should focus on discovery of alternatives to growth promoters. Rostagno [7] stated that “All farms animals will experience some level of stress during lives”. This means animals will be under stressors that may influence animal welfare conditions. Therefore, new aspects or innovations involving the potential benefits provided by new substances or enzymes, direct feed microbial (probiotics) and prebiotics in animal feeding must be important to improve zootechnical performance as well animal welfare conditions.

This presentation will compare the potential use of probiotics or prebiotics as alternatives to the benefits obtained by antibiotic application. This comparison is based on the concept of using pro- or prebiotics to modulate the gut microbiota and enhance animal health and growth. This balance should be measured considering the increased energy and nutrient cost to support the gut bacteria that could affect the needs for animals [8]. It should be noted that probiotic effect is bacterial specific. According to Gong [9], the selection of a novel probiotic is not only science, but also an art requiring a sophisticated design for selection and experience for handling. It will also be discussed why prevention using alternative products might be used under good conditions.
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GROWTH-PROMOTING AND HEALTH BENEFIT EFFECTS BY REDUCING INFLAMMATION AND IMPROVING GUT INTEGRITY

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An important way to improve piglet intestinal health is with nutrition. In general, pig health is closely related to their nutritional status. Improving health with nutrition is becoming increasingly important, as the use of antibiotics is becoming more and more restricted. For example, in the European Union, antibacterial growth promoters were banned in 2006 and the reduction of antibiotic therapy is encouraged.

The surface of a pig’s intestine is formed by villi and microvilli, enabling the pig to digest and absorb valuable nutrients from its feed. However, this enormous surface can also be used by pathogenic microorganisms to adhere to and enter the pig’s body. The intestine has the very challenging task to absorb nutrients, but at the same time keep bacteria, viruses and toxins at bay. To keep pathogens out, the intestine is equipped with the largest immunological organ of the whole body: the gut-associated lymphoid tissue (GALT). Because of this, it is important to maintain the integrity of the intestinal wall. Antioxidants, such as vitamin E, protect intestinal cells against oxidative damage caused by immunological reactions against pathogens. Several alternatives for antibiotics have been developed in the past decades. Antibacterial growth promoters suppress pathogenic bacteria in the intestinal tract leaving more nutrients for the pigs to grow. In fact, most of the alternatives for antibiotics do the same. Undesired bacteria can be suppressed by preventing them from adhering to the intestinal wall. For example, if bacteria, such as E. coli cannot adhere to the intestine, they cannot multiply and will be flushed out of the intestinal tract. One way to achieve this is to block the bacteria's binding sites with which they bind to receptors on the intestinal wall. Bacteria need these receptors to adhere. The binding sites are located on the fimbriae of bacteria and are very specific. For example, specific antibodies that are present in spray-dried plasma can block them.

At first sight, it seems appropriate to maximise the immune response of the intestine. This can be done by several immunostimulants, such as peptidoglycans and zinc. However, triggering the immune system requires quite some energy and amino acids (to produce immune cells and immunoglobulin), and in a worst-case scenario it could lead to undesired inflammation. Also, cytokines can be released leading to a drop in feed intake. In some cases, it may be better to temper the immune system rather than to stimulate it. The immune system can be tempered by lowering the contact of pathogens to the intestinal wall and, for example, adding blood plasma to feed. The antibodies in the blood plasma bind to the bacteria and viruses preventing them from coming into contact with the intestine.

To control inflammation, omega-3 fatty acids from fish oil reduce inflammatory processes. Among the plant extract-based products, a patented combination (sanguinarine, magnolol and honokiol; brand name Powerjet) has been selected for its anti-inflammatory, anti-oxidant properties and for its gut motility influencing abilities. Trials have demonstrated the synergistic action between these active molecules. One described property of these plant extracts is the modulation of intestinal motility that may prevent diarrhoea disorders. Recently, a trial has been conducted at the Beauvais University, France, to assess the impact of the three plant extracts on both intestinal integrity and inflammation. Human colon cells have been cultivated and then have been stimulated with a severe model of inflammation. Each plant extract alone and the combination of the three plant extracts have
been tested to evaluate their impact on trans-epithelial resistance (TER) and interleukin-8 (IL-8) secretion. Trans-epithelial resistance is an indicator of intestinal integrity, where a high level accounts for well-preserved tight junctions allowing a good barrier effect against pathogens and a good absorption of nutrients. IL-8 is a pro-inflammatory marker and its production is reflecting the level of inflammation. The tests indicated a better intestinal integrity and a lower level of inflammation with the three plant extracts combination. Also, a trial was conducted with 77 sows and 624 of their piglets. Half of the sows received the plant extracts before farrowing and during lactation. Half of piglets received the plant extracts from 20 to 67 days of age. Results in maternity showed a reduction of dead piglets/sow between 24 h after birth and weaning in the group of sows receiving the plant extracts. After weaning, growth performance and feed conversion ratio were improved in the group of piglets fed with the plant extracts and originating from sows fed also with the plant extracts (+30.9% of ADG compared to negative control). These experiments show that Powerjet plant extracts can improve intestinal integrity, reduce inflammation and improve piglet’s growth performance and health.
Bacteriophages (phages) are naturally occurring predators of bacteria, ubiquitous in the environment, with high host specificity and capacity to evolve to overcome bacterial resistance. These features make phages appealing options for the control of pathogens occurring in animals. Despite the great advantage of using phages to control pathogens, the development of phage therapy is constrained by numerous obstacles of regulatory nature.

In this talk, advances and drawbacks of phage therapy in poultry production will be presented using as examples the in vivo trials that we have conducted aiming at assessing the effectiveness of phages against Salmonella enterica serovar Enteritidis, Campylobacter coli, Campylobacter jejuni and avian pathogenic Escherichia coli. We have isolated and characterised several phages infecting the above mentioned pathogens and tested their efficacy in different in vivo infection models. Our in vivo trials were firstly performed using artificially colonised chickens and demonstrated that phages administered orally and incorporated in food reduced by approximately 3 log and 2 log the numbers of Salmonella and Campylobacter, respectively. However the same efficacy was not achieved in large scale animal experiments in poultry farms with naturally colonised chickens. Conversely, attempts to control severe E. coli respiratory infections in chickens in confined rooms, using a phage a cocktail, failed. Though, when the cocktail was tested in real poultry farms the mortality decreased more than 70%. Overall, our results showed that the efficacy of phage therapy depends on the pathogen and infection model. Furthermore we demonstrated that a careful selection of the phages that compose the cocktail, timing, dose and mode of administration are key factors for the success of phage therapy in animal production.
FROM SMALLEST TO BIGGEST FEED ADDITIVES: ORGANIC ACIDS AND ENZYMES IN FEED HYGIENE AND GUT FLORA MANAGEMENT

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Key to animal performance is the health status of the gastro-intestinal tract (GIT), including its microbiota. The composition of compound feed and the nutrients therein have major impact on gut health. Multiple categories of feed additives are typically utilised to improve the nutritive value and quality of compound feed.

Organic acids, such as formic acid, exhibit multiple gut health and nutritional benefits in monogastric animals. Organic acids are effective against pathogenic microorganisms in feed as well as in the GIT and can furthermore improve digestion by lowering the gastric pH. This enhances dietary protein digestion and it reduces the proliferation of pathogenic bacteria that cause diarrhoea [1]. The nutritive effect is most pronounced in piglets but also in growing pigs formic acid has been shown to have a beneficial effect on daily weight gain and feed conversion [2]. Canibe et al. [3] reported that the presence of formic acid in the proximal segments of the GIT of growing pigs is a crucial factor contributing to reduction of number of enterobacteria along the GIT. Finally, organic acids are completely metabolised. It has been shown that organic acids can also promote healthy gut morphology. Studies in piglet and broiler have exhibited that butyric acid improves gut morphology leading to increased villi length and crypt depth [4,5]. Buffered non-corrosive products were introduced to make organic acids more user-friendly in terms of compound feed production as well as drinking water applications.

Feed enzymes contribute to gut health by different modes of action, e.g., by reducing viscosity of the digesta or release of nutrients. It has been shown that undigested protein as well as undigested viscous non-starch polysaccharides (NSP) may negatively influence the composition of microflora in the gut. Growth of Clostridium perfringens in the upper gut of broilers is associated with high viscosity of digesta [6]. The incidence of swine dysentery in pigs can be reduced by feeding diets that limit the amount of fermentable substrate entering the large intestine [7]. Carbohydrases partially digest soluble fibres so that viscosity of digesta is heavily reduced. Protein digestibility is improved by adding proteases and phytases to compound feed. Phytase releases protein from otherwise indigestible protein-phytate complexes. Combined application of organic acids and phytase further improves phytate digestion. This could be explained by higher phytate solubility and an increased availability of phytate to be cleaved by phytase. Furthermore, the digesta pH is shifted to more optimal conditions for the enzyme [8]. The above-mentioned enzymes enable more efficient use of nutrients as well as they improve gut health. There are only few in vivo studies on feed enzymes having antimicrobial properties. For instance, it has been shown that lysozyme improves small intestinal morphology in nursery pigs [9].

References


USE OF DIETARY QUORUM QUENCHING ENZYMES AS BACTERIAL DISEASE PREVENTION IN AQUACULTURE

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N-acylated homoserine (AHL) lactonases are capable of degrading signal molecules involved in bacterial quorum sensing and, therefore, represent a new approach to control bacterial infection. Here, we will summarise our successfully industrialised quorum quenching enzymes and discuss their application in bacterial disease prevention in aquaculture.
I HAVE DEVELOPED A GREAT PRODUCT, NOW WHAT? REGULATORY ISSUES!

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Alternatives to antibiotics obtain high attention in the feed industry. Antibiotics are normally veterinary products to prevent, treat or cure a disease, but due to resistance, residues and also the wish of consumers for low use of antibiotics in animal production, the market is looking for alternatives. In general, two type of products can be identified: products that have an effect on the gastro-intestinal environment and products that have an effect on the immune system. It depends on several criteria whether a new product is to be regarded as a veterinary product, a feed additive or a feed material. Main criteria for the position of the product are the (intrinsic) claim attributed to the product, the (intrinsic) function, the purity, the chemical definition and the manufacturing method.

Legislation has also made it possible to attribute claims to feed materials or feeds. Such a claim can be related to the health of the animal, but it cannot have a claim as a veterinary product. Usually, claims for feed materials or feeds are 'softer'. When a feed material or feeds are sold with a claim, a national authority can ask for proof and judge whether a claim is acceptable. A problem is that there is no overall acceptance of claims of feed materials or feeds in the European Union (EU). In specific cases, it may be an option to apply a feed as a dietetic feed, which approval has an EU status. In most cases, specific products to be used as alternative of antibiotics will be regarded as feed additive. Functions of feed additives include digestibility enhancers, gut flora stabilisers and products that favourably affect the environment. It also includes products that may support the health of animals. Not only enzymes, probiotics, organic acids and purified plant products but also products such as bacteriophages are regarded by the authorities as feed additives.

Feed additives need pre-market authorisation in the EU. The process of registration starts with a dossier that contains information on the identity, safety and efficacy of the product. There are regulations that describe the registration process and regulations that indicate the requirements of a dossier. The European Food Safety Authority (EFSA) performs a risk assessment on the information of the dossier, using scientists from all over Europe. This assessment ends in an opinion presented to a commission of the EU. This commission performs a risk management on EFSA's opinion. Finally, it results in an authorisation or rejection of the application.

Normally, studies are done during the development of a product. Companies tend to start with registration when the development of a product has been finished. To build a dossier for registration, studies are also necessary. It depends on the type of product and the function of an additive, which kind of studies are necessary. In several cases, it is possible to use studies conducted for the development of the product. If the right studies are performed in the right way, they will be accepted by EFSA. Therefore, it is advised to integrate the registration process with the development of a product; this may save costs and time to get a great product on the market.
BIOSECURITY AS A TOOL TOWARDS REDUCED ANTIMICROBIAL CONSUMPTION

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Biosecurity embraces all aspects of the prevention of pathogens entering (external biosecurity) and spreading (internal biosecurity) within a group of animals. It is assumed that higher levels of biosecurity lead to improved animal health and productivity, and to a reduction of the use of antimicrobials [1], which are important features of sustainable animal production. In the past, specific biosecurity or management measures have often been related to the prevention of specific disease. In these, the external biosecurity measures were often promoted in the framework of the prevention of epidemic diseases, such as classical swine fever or Aujeszky's disease, whereas specific internal biosecurity measures have been promoted in the framework of the control of endemic (e.g., enzootic pneumonia, streptococci, ...) or zoonotic diseases (e.g., Salmonella). Only recently interest has grown in the holistic approach of biosecurity as a tool to improve the total health status of the herd taking into account all potentially present clinical and subclinical diseases.

Since a number of years a risk-based weighted biosecurity scoring system (Biocheck.ugent®) has become available for pigs [2] and poultry (broilers) [3]. This methodology provides a handle to score biosecurity in pig herds in an objective and transparent manner and relate these scores, or the evolution in the scores, to the health status of the herd or the level of antimicrobial consumption. Using this weighted risk-based biosecurity score accounts for the fact that on different herds, depending on the specific herd situation, different measures are to be taken and that also limited changes in management and hygiene procedures may have important impacts. The Biocheck.ugent scoring system is freely available and is provided in already five different languages at www.biocheck.ugent.be. The biosecurity scoring system has been used extensively in pig and poultry herds in over 10 countries. Results invariably show huge range in the biosecurity levels indicating that despite the well-known importance of biosecurity, there is a lack of implementation of many biosecurity measures and room for improvement.

Using this scoring system, Laanen et al. [4] has studied the association between biosecurity scores and production factors and antimicrobial use in 95 pig herds in Belgium. The average external biosecurity score in these herds was 65 (range, 45-89) and the average internal score was 52 (range, 18-87). External scores were positively associated with herd size, while internal scores were negatively associated with both 'age of buildings' and 'years of experience of the farmer', indicating that biosecurity is generally better implemented in larger herds, in more modern facilities and by younger farmers. External and internal biosecurity scores were positively associated with daily weight gain and negatively associated with feed conversion ratio of fattening pigs. Internal scores were negatively associated with disease treatment incidence, suggesting that improved biosecurity might help in reducing the amount of antimicrobials used prophylactically.

In two recent projects (RED AB), pig (n=60) and poultry (n=19) herds in Belgium were advised towards a reduced antimicrobial use. This was done by visiting each of the participating herds and making an inventory of the current animal health management and biosecurity practices. Based on this each of the herds received an individually adapted action plan for improvement of the biosecurity and management and a subsequent reduction of preventive use of antimicrobials. On average 9 months later, herds were revisited and the situation was re-evaluated. In the pig herds both internal and external biosecurity scores
improved substantially by implementing changes such as implementation of an additional hygiene lock, improvement of hand hygiene, improvement of water quality, better separation of age groups, implementation of working lines,... In general, the animal health and production parameters either stayed constant or improved after implementation of the changes. The antimicrobial consumption, on the other hand, was reduced on average 48% during this period. In the broiler production again both internal and external biosecurity scores were improved and an average reduction of the antimicrobial consumption of 29% was achieved without any negative impact on health or production parameters.

All these results clearly show that biosecurity is of major importance in safeguarding animal health and reducing the need for preventive antimicrobial use. The freely available risk based scoring system Biocheck.ugent is a very valuable tool in this.

References
INTRODUCTION TO EPRUMA

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The European Platform for Responsible Use of Medicines in Animals (EPRUMA) is a multi-stakeholder platform linking best practice with animal and public health. Established in 2005, it works to promote the responsible use of medicines in animals in the European Union (EU) in order to maintain efficacy, and both prevent and minimise adverse reactions. EPRUMA’s objectives include:

- promoting animal health and welfare as well as human health through the responsible use of veterinary medicines;
- developing best-practice frameworks concerning the use of veterinary medicines. EPRUMA works on broad principles at EU level, which in turn can be tailored nationally to reflect local needs in EU Member States; and
- communicating with and engaging all parties concerned with the responsible use of veterinary medicines.

EPRUMA enables and promotes a co-ordinated and integrated approach and has achieved buy-in from all stakeholders, including European

- veterinarians;
- farmers and agri-cooperatives;
- manufacturers of animal medicines and diagnostics;
- feed manufacturers;
- professionals working in animal health, sanitary security and sustainable agriculture;

and

- pharmacists.

EPRUMA has built communication links with EU institutions, national organisations promoting the responsible use message, the food processing industry, retailers, consumer organisations, etc., through the quality of its advice and guidelines, an example being the ‘Best practice framework for the use of antimicrobials in food-producing animals’, which EPRUMA launched in 2008. The crux of EPRUMA’s position is that all medicines should be used responsibly with animal keepers following a holistic approach of minimising disease through the adoption of working practises, such as:

- biosecurity, a set of preventative measures aiming to keep groups of animals healthy or to limit the spread of diseases within an animal population;
- good housing and ventilation;
- good hygiene;
- appropriate nutrition;
- regular monitoring of health and welfare;
- herd health planning as a voluntary and flexible management tool tailored to record specific actions at individual farms; and
- vaccination.

When disease occurs, diagnosis and treatment under veterinary care should follow.
THE FARMER’S ROLE AND MANAGEMENT OPTIONS REGARDING BIOSECURITY, HOUSING AND NUTRITION

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This paper can be summarised in 13 words: “Antibiotics should be used as little as possible and as much as necessary.”

Responsible use of antibiotics does not start and finish with the veterinary diagnosis of disease and prescription to treat. The best way to use antibiotics responsibly is to minimise the need for them in the first place but to then use them responsibly when they are needed. Working on this basis the farmers’ primary goal is to have healthy animals through good husbandry and management. Animals on farm have a commercial value. Sick animals cost a business through increased veterinary bills, reduced yield potential, business and trade disruption, losses in feed conversion rates, increased infertility, etc. A farmer can reduce these losses by implementing good management practices such as maintaining good hygiene, providing appropriate feed and diet rations, working to high standards of husbandry and implementing good management routines. However, despite these measures, animals still get sick and will still need to be treated.

Many farms have implemented a team approach to managing the health of farm animals with their veterinary surgeon considered part of the farm team. Various health monitoring systems can be adopted to measure key performance indicators and when problems arise, management strategies are devised to minimise and resolve the problems.
THE VETERINARIANS’ ROLE AND OPTIONS REGARDING DISEASE DETECTION, DIAGNOSIS, TREATMENT AND PREVENTION

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The oath that we take as veterinarians on admission to the Royal College of Veterinary Surgeons states that “…my constant endeavour will be to ensure the health and welfare of animals committed to my care”. In order to achieve this aim, a variety of skills are required, from diagnosis of disease in an individual, or group of individuals, through to treatment, and if successful a return to good health and in the case of livestock productivity. Having arrived at a return to good health the aim is then to look to the future and prevent the recurrence of disease.

Often in the treatment of disease a range of medicinal products are utilised which are essential if the veterinarian is to adequately perform their role. Antimicrobial drugs are an essential part of the veterinary pharmacy without them responsive infection would go unchecked affecting the animals health and resulting in detrimental welfare impacts. Resistance to these drugs can be inherent within the bacterial populations that they are directed at, or it can be selected for by inappropriate or inaccurate usage. In human medicine the concerns surrounding resistance to these drugs has increased with time and is now profiled beyond national boundaries and is of global significance.

There is little if any direct evidence that veterinary use of antimicrobials is a driver of resistance in the human population; indeed, it is recognised that the main driver occurs within the interface between the medical profession, the patient and the drugs that are prescribed with inappropriate prescription and poor patient compliance being high on the causal list. There is broad recognition that the human and veterinary profession have a commonality of purpose in doing all they can to maintain an effective range of antimicrobials for future generations of clinicians to administer to their respective patients. The ‘One Health’ concept as it develops further will allow collaboration between the two professions to hopefully achieve this aim.

But what of the ‘here and now’, what can we as veterinarians do to ensure that the correct medicines are used responsibly? What tools and guidelines do we have that we can use and communicate to our clients to limit inappropriate use? Are there aids to diagnosis that would allow more targeted use of antimicrobial use and are they capable of rapid deployment so that welfare is not compromised whilst we await laboratory results? Indeed, are there situations where other forms of therapy and interventions would achieve similar successful outcomes? What of the future? Are there preventative measures we can put in place that will limit disease and therefore the need to use antimicrobials for treatment. This paper will discuss these pertinent issues with reference to common disease situations seen in practice.
PARTNER IN THE CHALLENGES POSED BY THE THREAT OF ANTIMICROBIAL RESISTANCE

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The European Manufacturers of Veterinary Diagnostics (EMVD) was founded in 2006 in Brussels, Belgium; the headquarters are based in Paris, France. EMVD is an association of medium-sized veterinary diagnostics companies and large companies with only a small veterinary activity. The main objective of EMVD is to represent and develop the activities of manufacturers of veterinary diagnostics. All the EMVD members operate at least under ISO 9001 and together the EMVD represents the majority of veterinary diagnostics producers in the world.

According to the Outcome Statement ‘Joining Forces for Future Health’ on 25-26 June 2014 in The Hague, the Netherlands, the battle against the increase of antimicrobial resistance (AMR) will require a ‘One Health’ approach. Human and animal health are closely related and should be considered as one. Most of new emerging diseases originate from animals; neglected zoonosis continues to threat human health. Now the challenges posed by the threat of AMR ask for a global action.

EMVD can be more than an association defending their own interest. EMVD is a biotechnology platform with key players in the life science market to provide ‘high-tech’ solutions. An example of the advantage of the EMVD platform is the open ‘Veterinary Diagnostics’ database. This database is developed and maintained by EMVD. In this database, all the veterinary diagnostics that are produced and marketed by all EMVD members are listed, including the countries where they have a registration. This platform is also useful to develop, produce and market diagnostic tools to combat AMR. However, the framework has to be clear. What will be the business model, the regulatory environment, and the application possibilities of these new diagnostics tools?
THE ANIMAL HEALTH INDUSTRY’S ROLE AND OPTIONS REGARDING VETERINARY MEDICINES AND OTHER TOOLS/SERVICES FOR TREATMENT AND PREVENTION

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The role and mission of the animal health industry is to fulfil the needs of animal owners and veterinarians in what regards the health of their animals with appropriate, innovative medicines and diagnostic tools. In doing this, the animal health industry also plays an important role in the ‘One Health’ concept, as underlined by the important role of veterinarians in public health.

In what regards anti-infective solutions, a number of options have come and will continue to flow from the animal health industry in terms of immunological products. For new antibiotics, the response is likely be more mixed as the overlap between human and animal antibiotics is important – in spite of the fact that some animal health only molecules exist. This shows that innovation is more critical than ever.

Many developments will flow from the application of diagnostic tools combined with data management on farms. This will allow using veterinary medicines on farms in a way that make them both more efficacious and more targeted. In all these aspects, the EPRUMA platform allows to define responsible use in a way that commits the whole chain of users of veterinary medicines, thus promoting best practices for all stakeholders in but also beyond the European Union.
GRSB’S APPROACH TO TECHNOLOGY AND INNOVATION

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The Global Roundtable for Sustainable Beef (GRSB) is a multi-stakeholder initiative drawing membership from the major beef producing, exporting and importing countries. The organisation involves members from all parts of the beef value chain from producers through to both supermarket and restaurant chains. The mission of GRSB is to advance continuous improvement in global beef value chain sustainability, through leadership, science, and multi-stakeholder engagement and collaboration.

Planet, People, Animals and Progress
We define sustainable beef as a socially responsible, environmentally sound and economically viable product that prioritises:

- Planet (relevant principles: natural resources, efficiency and innovation, people and the community);
- People (relevant principles: people and the community and food);
- Animals (relevant principles: animal health and welfare); and
- Progress (relevant principles: natural resources, people and the community, animal Health and welfare, food, efficiency and innovation).

As part of the process of developing principles and criteria, we have also developed guidance for regional roundtables to assist in their development of indicators. This includes guidance on the responsible use of antibiotics.
Veterinary use of antibiotics in livestock in the Netherlands has been reduced with 57.7% over the last 5 years. This reduction is the result of clear targets defined by the government, measures for prudent use initiated by private livestock sectors together with the veterinary association and transparency in use of antibiotics at farm level realized by founding an independent control institute (SDa).

Until 2009, the consumption of antibiotics in the Netherlands expressed in use per kg live weight produced was highest in comparison with other European countries [1]. In 2008, several initiatives were taken by the government together with the major livestock sectors, i.e. veal calves, pig, poultry and cattle sectors. The Minister of Agriculture installed a task force on antibiotic resistance in the above mentioned livestock sectors in 2008 and demanded their stakeholders, the Royal Dutch Veterinary Association (KNMvD) included, to sign a memorandum of understanding in which measures for prudent use of antibiotics were described. The first activity of the taskforce was to make use of antibiotics transparent. In 2012, it became mandatory for farmers to register all antibiotics supplied by veterinarians but the animal sectors already partly implemented this policy voluntarily earlier. Therefore, the Netherlands Veterinary Medicines Authority (SDa) was founded. The SDa is financed by the government, the four animal sectors mentioned above and the KNMvD (10% each). Reduction targets for antibiotic usage in livestock industry were set by the government at 20% reduction in 2011 and 50% reduction in 2013, and they were taken over by stakeholders. All these target values would be benchmarked against the use of antibiotics in 2009, based on sales data.

After Dutch scientists reported about NT-MRSA (2005) and ESBLs (2010) in food animals, the Netherlands Health Council advised a complete ban on usage of any new antibacterial drug in animals as well as a restriction of the use of 3rd and 4th generation cephalosporins in animals. The Health Council also advised to restrict the use of colistin, all beta-lactams, aminoglycosides and fluoroquinolones in food animals. The Antibiotics Policy Working Group (WVAB) of the KNMvD worked out a guideline in which drugs were classified as first, second and third choice drugs for inclusion in treatment plans on farms (http://wvab.knmvd.nl/wvab). Measures for prudent use, set up by stakeholders in 2009, included a mandatory treatment plan for each farm and a herd health plan. These plans have to be custom made by the veterinarian for each farm, based on treatment guidelines of the KNMvD (http://wvab.knmvd.nl/wvab/formularia/formularia). In 2013 the Dutch Animal Drug Law was changed, ruling that only first choice drugs are allowed to be present on farms for empiric treatment of infections based on a mandatory treatment plan for each farm.

The SDa has had an instrumental role in the reduction of antibiotics over the last years in different ways:

- Transparent reporting of use of antibiotics. Since 2011 use of antibiotics is being reported transparently per livestock sector, for the four major Dutch sectors (veal farms, cattle farms, poultry farms and pig farms).
- Benchmarking of livestock farms. In the beginning the signalling and action level benchmark values were based on the 50th and 75th percentile, respectively, of the distribution of ADDD/Y across livestock farms in a sector. Benchmarking has initially
been based on overall use of antibiotics on a farm. At present, there is a trend towards a more refined methodology and to benchmark for different animal age groups to overcome problems with heterogeneous animal populations leading to under- or overestimation of the use of antibiotics. In 2013, SDa set quantitative reduction targets for antibiotic use for fluoroquinolones and 3rd, and 4th generation cephalosporins at zero DDD/Y.

- Benchmarking of veterinarians. Since early 2014, the SDa introduced the Veterinary Benchmark Indicator (VBI). This indicator summarises the distribution of use of antibiotics of all the livestock farms in a particular sector a veterinarian is responsible for, by calculating the likelihood that farms have antibiotic usage above the action level of the benchmark. The VBI appeared to differ strongly between veterinarians and is thus indicative of clearly different prescription patterns.

So far, benchmark values have been based on pragmatically chosen parameters, obtained for strongly right skewed distributions. Over the last years, we have seen a clear reduction is usage of antibiotics. This change appeared to have been accompanied by a reduction of the number of resistant microorganisms that circulate in farm animals, with some distinct differences between different sectors. The SDa is planning a detailed analysis of these changes and in combination with a review of the open peer review literature to explore whether more 'science-based' benchmark values, with a direct relation with microbial resistance, can be derived. If this appears possible, the benchmarking system will be revised.

References
THE ALBERTA PLATFORM FOR THE RESPONSIBLE USE OF MEDICINES IN ANIMALS (APRUMA)

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The science of antimicrobial resistance is very complicated and the politics behind its management is complex. However, antimicrobial resistance is very real and presents a serious threat to the global population. Tradition has seen many stakeholders trying to assign the blame to someone other than themselves. However, the time has come to get past trying to assign responsibility for the cause and accept the fact that everyone who uses antimicrobials has ownership of the outcome and must participate in responsible use practices.

The Alberta Veterinary Medical Association (ABVMA) is the veterinary statutory body responsible for the practice of veterinary medicine in Alberta, Canada. As a self-governing body of veterinarians and veterinary technologists, we have accepted a firm commitment to insure that our members develop practice standards that help insure the integrity and available of antimicrobials for use in animals. We established mandatory guidelines for their use by veterinarians (Council Guidelines for Prescribing, Dispensing, Selling and Compounding Drugs). These guidelines require a veterinarian to:

- establish medical need before prescribing antimicrobials;
- dispense or oversee dispensing practices and procedures;
- oversee the use of dispensed medications;
- be available for follow up in case of treatment failure or adverse drug reaction; and
- maintain detailed records in regards to these activities.

It was soon recognised that these guidelines were a threat to the current culture of access to antibiotics on demand. Many livestock producers considered this an infringement of their traditional right to diagnose their own animals’ diseases and request treatment based on this diagnosis. Some veterinarians also felt that these guidelines were too restrictive and posed an interference to their business models. At the same time, veterinarians and the livestock industry were sensitive to the negative reports in trade publications and the popular press regarding what is reported as an overuse of antibiotics in agriculture. This messaging calls for limitations on access of antimicrobials in the area of animal health and production. It was clear that the animal industry needed to become engaged and that leadership was necessary. We needed to achieve compliance with best management practices at the veterinary and livestock producer level. To do this, we needed to educate a much wider audience than veterinarians alone. We established a discussion group that meets monthly via teleconference to discuss related issues. This group consists of veterinarians, government (federal and provincial), all livestock producer groups, academics, industry, etc. We identified a need for qualified and consistent messaging regarding antimicrobial use/resistance directed to all levels of interest.

With this as a goal, we obtained permission to adopt the European Platform for Responsible Use of Medicines in Animals (EPRUMA). With very little adaptation, this excellently worded document met our needs for an understandable message that could be used to stimulate discussion. The revised document was branded as Alberta Platform for the Responsible Use of Medicines in Animals (APRUMA) It was produced in print and digital versions and was widely distributed to practitioners, producers and the public. The ABVMA participated in many annual meetings of producer groups discussing the changing landscape of antimicrobial use.
and outlining anticipated changes in practices for the future. The APRUMA document served as a strong foundation for this discussion.

Our experience highlights the need for and efficiency of international cooperation in our efforts to establish responsible practices for the use of antibiotics in agriculture.
ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS (AMCRA) – THE BELGIAN APPROACH

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The Center of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA) is a Belgian initiative that was launched in January 2012. AMCRA aims to fight against the selection and spread of antimicrobial resistant bacteria by promoting reduced and responsible use of antibiotics in veterinary medicine in Belgium. This requires joint action through an industry-wide approach, together with the authorities and all relevant stakeholders: veterinary practitioners, agricultural organizations, the pharmaceutical industry, compound feed manufacturers and the scientific world. In order to accomplish this mission, several strategic objectives were achieved from 2012 onwards and more objectives are planned in the coming years.

In Belgium, national sales data on farm and companion animals are annually reported from 2007 onwards. They consist of all veterinary antibiotics sold to a veterinarian or pharmacist and of antibacterial premixes incorporated in medicated feed intended to be used in Belgium [1]. Compared to 2011, set as the year of reference, an overall reduction (in terms of mg per kg of biomass produced) of 12.7 % was recorded in 2013. The achieved reduction is in line with the recently set objective by AMCRA of 50% reduction in antibiotic usage in animals by 2020, one of the 10 ambitious objectives that are fully supported by all partners of AMCRA (www.amcra.be/sites/default/files/bestanden/AMCRA%202020%20finaal_EN_0.pdf).

Equally, the tone has been set in view of a reduction of 75 % in antibiotics of critical importance for public health by 2020, namely the quinolones and the 3rd and 4th generation cephalosporins. Compared with 2011, the use of the group of ‘red’ antibiotics in the AMCRA guidelines for responsible antibiotic use fell dramatically in 2013, with 17.4 % less being used.

Furthermore, at country level, reliable usage data per animal species are needed, because a country overall is an inaccurate indication of true differences of exposure per species [2]. Thereto, a first and crucial objective achieved by AMCRA involved drafting a study report on the establishment of an electronic database on antimicrobial consumption per animal sector and category at the veterinarian and farmer level. In this respect, a Belgian swine-farming quality system initiated in January 2014 a data collection programme for providers of antibiotics in the swine farming industry covering approximately 50% of the swine farms in Belgium. An independent unit within AMCRA is currently responsible for safeguarding quality of data input, analysing and reporting herd specific data, as the latter are the basis for herd specific recommendations [3]. Combined with a farm’s health plan and the plan of approach, another objective for 2020, the veterinarian responsible for guidance might lead farmers towards a sustainable reduced usage. Using the data collection systems specific to each species, boundary values will be defined for the use of antibiotics by farm and veterinarian. Further data collection systems ought to be planned for the poultry, calves and beef cattle industries. A global data collection system should be operational by 2016.

Following the AMCRA report on the possibility of using ZnO at pharmacological doses in swine feed as an alternative to antibiotic use, several temporary registrations have led to the use of medicinal ZnO in feed from September 2013 onwards. This might partially have led to the 18.3 % fall in colistin use in 2013 [1]. Dosing schedules have been established to reduce the environmental Zn burden. Yet, the search for alternatives to both antibiotics and heavy
metals should be continued, as resistance to Zn might occur in bacteria and Zn is a potential selector for methicillin-resistant *Staphylococcus aureus*.

Since the foundation of AMCRA, working committees per animal species have worked on the establishment of national guidelines on the prudent and rational use of antibiotics in production and companion animals. Species specific information with specific therapeutic recommendations depending on the disorder has been developed. Moreover, other challenging aspects were dealt with, for example storage of medicines by veterinarians and farmers, which led to drafting an opinion on the need to hold a stock of antibacterial agents and the conditions for doing so. Proposals to broaden legislation on the prescription and use of medicated feed in view of centralised electronic data collection are currently in process. Also, guidance documents for production animals are planned concerning the implementation of alternatives that could reduce the use of antibiotics, with special attention to vaccines and biosecurity measures. Furthermore, it is and will remain essential to continue encouraging the different animal sectors and quality labels to provide specifications concerning the implementation of self-regulating measures, and the use of animal health guidelines and formularies. Next to informing veterinarians, farmers and animal owners through local campaigns, collaboration and exchanging results with similar organisations in other countries of the European Union are needed, as well as a continued contact with policy makers at the regional, federal and European level.

**References**

VETRESPONSABLE: SPANISH INITIATIVE FOR THE PROMOTION OF RESPONSIBLE USE OF VETERINARY MEDICINES

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Since its creation in 2008, the Spanish Technology Platform for Animal Health, Vet+i, has become the interdisciplinary forum in Spain gathering all relevant stakeholders interested in animal health, from academia, research, farmers, veterinarians, industry, regulators, etc. Currently, there are more than 500 members from more than 300 organisations. It has the full support of the Ministries of Health, Agriculture, Industry and Economy. Vet+i is the Spanish ‘mirror group’ of the European Technology Platform for Global Animal Health (ETPGAH), and has proven to be an efficient instrument to improve research, development and innovation in the field of animal health in Spain. Its main goal is to facilitate networking in order to enable the efficient transfer of research developed in Spain and accelerate the development and delivery of innovative products and technologies for controlling important animal diseases. Vet+i is also committed to ensure that these products once they reach the market, are used in a responsible way in order to maintain their benefits.

Vet+i has developed a national initiative to ensure best practice through the responsible use of veterinary medicines in the prevention and control of animal diseases. The initiative is called ‘Vetresponsable’ and it consists of the development and publication of ‘Guidelines on the Responsible Use of Veterinary Medicines’ in all animal species of importance in Spain, including companion animals, food-producing animals and wildlife. A specific website has also been launched (www.vetresponsable.es) that includes the guidelines as well as information related to the concept of responsible use of veterinary medicines. The principles contained in these guidelines are based on the recommendations agreed by a team of experts from all areas related to animal health: representatives from veterinary associations, associations of producers, the animal health industry and the competent authorities, such as the Spanish Medicines Agency and the Ministry of Agriculture. These framework documents are mainly targeted at the veterinary profession for its relevant role in the diagnosis of diseases and the prescription and use of veterinary medicines. These guidelines have become a reference document for the veterinarians in their daily practice, contributing to maintaining the benefits of the veterinary medicines.

Vet+i intends to promote responsible use of veterinary medicines based on a holistic approach including biosecurity, good housing, good hygiene, appropriate nutrition, regular monitoring of health and welfare, herd health planning and proper vaccination strategies. This is why these guidelines have a very comprehensive approach that covers issues related to veterinary medicine and regulation; previous elements in responsible use, such as preventive and biosecurity measures, diagnosis, veterinary prescription, including exceptional prescription; design, monitoring and evaluation of treatments; the type of veterinary medicine used; storage and conservation; good management practices on record keeping; and the obligation of veterinarians under the veterinary pharmacovigilance system and specific issues on antibiotics, among others.

Communication is an essential part of the process. This is why we have also developed a specific website on the responsible use of veterinary medicines that includes basic information on how to use the medicines targeted to vets, including students, farmers and pet owners (www.vetresponsable.es). The website also includes the guidelines. Apart from developing the material, ‘Vetresponsable’ has set up a communication targeted to vets and
students of veterinary medicines in order to raise awareness of this initiative and to ensure responsible use of the veterinary medicines.

Vetresponsable has been officially presented at the 5th Annual Conference of Vet+i in May 2013; an event attended by more than 200 experts and authorities related to the animal health sector. We have also participated in specific conferences and technical seminars targeted to veterinarians, etc. We believe that veterinary students are a key audience. For that, we have signed a collaboration agreement with the board of Deans of all the Veterinary Faculties existing in Spain and the Association of the Veterinary University Hospitals in order to organise information campaigns targeted to students, so that they could obtain a deeper understanding of the responsible use of medicines and veterinary pharmacovigilance. So far, it has been presented to the Universities of Córdoba, Madrid and Valencia with very positive results and will be presented to the rest of the Faculties in the following months.

As mentioned before, Vetresponsable has been developed with the support and the participation of the key authorities, such as the Spanish Medicines Agency and the Ministry of Agriculture. Furthermore, this initiative will play an important role in the implementation of the Spanish National Plan to minimise the risk of selection and dissemination of antimicrobial resistance, which is now being developed by the authorities. We are also maintaining a close contact and coordination with other European initiatives of responsible use of veterinary medicines. In this context, Vet+i supported the publication and translation into Spanish of the EPRUMA ‘Best-practice framework for the use of antimicrobials in food-producing animals’, which was led by Veterindustria with the support of the Spanish Medicines Agency, the Ministry of Agriculture and the Veterinary College Council, among other stakeholders. In addition, Vetresponsable has been designated as an associate partner in the European Platform for the Responsible Use of Medicines in Animals (EPRUMA).
RESPONSIBLE USE OF MEDICINES IN AGRICULTURE

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The need for responsible use of antibiotics, and all other medicines, in agriculture was seen in the UK in 1997 when a group of interested parties got together to set up the Responsible Use of Medicines in Agriculture (RUMA) Alliance. This is a unique alliance of organisations with the aim of promoting responsible use of medicines. RUMA is unique because most livestock issues are considered on a species basis to cater for the different challenges when farming cattle, pigs, poultry, fish, etc. Responsible use of antibiotics applies across all species and so RUMA is the only alliance in the UK that covers all livestock species. Membership is wide ranging and includes representatives of farmers, veterinarians, pharmacists, medicine manufacturers, quality assurance schemes, animal welfare groups and human medicine with observers from the UK Government. This broad church of interests is united in supporting and promoting responsible use.

Responsible use means using medicines ‘as little as possible and as much as necessary’. Farmers and veterinarians are encouraged to work together to reduce the risk of disease challenge on farm which in turn will minimise the need to use medicines other than preventive medicines, such as vaccines. But animals do get sick and then the farmer, in conjunction with the veterinarian, should use the right medicine, at the right time, in the right dose and for the full course of treatment. Antibiotics should be used only after diagnosis and prescription by the veterinarian responsible for the animals. Farmers should buy the antibiotics prescribed by their veterinary surgeon from legitimate sources and follow the instructions on the product, and from their veterinarian, when administering the antibiotic to their animals.

RUMA is a lean organisation funded annually by members’ fees totalling around £20k. Many of our resources are provided in kind by members who freely give their time for RUMA activities. RUMA’s primary role is to provide up to date guidance to farmers and veterinarians on the responsible use of antibiotics (and other medicines) on farm. This advice is available through species specific guidelines that are free to download from the RUMA website (www.ruma.org.uk). Each guideline has two versions, a shorter one for farmers and a longer more technical one for veterinarians. RUMA encourages farmers and veterinarians to discuss the guidelines together and to work to responsible use principles.

RUMA publishes an annual business plan setting out the focus of our work. For 2014, our main focus will be on implementing the UK Department of Health’s 5 year Antimicrobial Resistance Strategy published in 2013. This is a One Health strategy which includes actions for both human and animal medicines. RUMA has welcomed the strategy and developed an action plan to help the livestock sector to implement it. The plan is available on the RUMA website and we will regularly update the plan to record progress on actions. RUMA is also involved in preparing for changes to EC veterinary medicines and medicated feeds legislation and we are providing evidence to the All Party Parliamentary Group on pigs, eggs and poultry’s enquiry into welfare and antibiotics. To enhance the training available for farmers in responsible use RUMA will be preparing guidance and a toolkit for trainers on the content of responsible use training. We are also developing a new RUMA website for launch on the European Antibiotic Awareness Day 2014 and continuing to work on keeping RUMA guidelines up to date and to make them more user friendly.
Antimicrobial resistance is a global concern both for animal and human health. Programmes to monitor antimicrobial susceptibility among veterinary pathogens as well as zoonotic and commensal bacteria are therefore essential. Various European countries have national monitoring programmes in place for foodborne pathogens and commensal bacteria. The European Food Safety Authority (EFSA) provides technical guidance and compiles the data from the Member States on antimicrobial resistance in zoonotic Salmonella spp., Campylobacter spp. and indicator Escherichia coli and Enterococcus spp. from food-producing animals and retail meats. Further EU-wide harmonisation of sampling, testing methodology and data interpretation would facilitate data comparisons between countries. Only a few national surveillance programmes monitor antimicrobial susceptibility of target pathogens from farm and companion animals. The Executive Animal Health Study Center (CEESA), an international association with scientific purpose, attempts to fill these gaps.

The resistance monitoring programmes of CEESA have been for more than a decade a collaboration of various multinational veterinary pharmaceutical companies which have set up several microbial culture collections throughout Europe. These unique collections have enabled CEESA to test the susceptibility of these organisms against numerous antibiotics, depending on the project, commonly used in human medicine or specific to the veterinary field. They have also given their sponsors access to a wide range of well-defined zoonotic, commensal and veterinary organisms, which can be used by the participating companies for individual regulatory requirements and for scientific purposes. CEESA makes the data generated by these collections publically available through peer-reviewed scientific conference communications as well as through more extensive publications in established peer-reviewed journals.

These culture collections include two different projects: the European Antimicrobial Susceptibility Surveillance in Animals (EASSA) programme, which collects since 1999 foodborne bacteria at slaughter from healthy animals and the pathogen programmes, which collect first-intention target pathogens from acutely diseased animals. The latter consists of three different sub-programmes: VetPath, MycoPath and ComPath. VetPath is since 2002 an ongoing resistance monitoring programme in 11 European Union (EU) countries for veterinary pathogens from respiratory tract infections, mastitis, PPDS (MMA) and digestive diseases isolated from diseased antimicrobial untreated cattle, pigs and poultry. ComPath collects isolates from skin/wounds/ears, urinary tract and respiratory tract infections of untreated dogs and cats in 11 EU countries and has started in 2008. MycoPath was initiated in 2010 and exclusively addresses the recovery of mycoplasma organisms from cattle, pigs and poultry in six EU countries.

All CEESA projects include uniform sample collection and bacterial identification to species level in various EU Member States. A central laboratory for each sub-programme conducts quantitative antimicrobial susceptibility testing (minimum inhibitory concentrations (MICs)) to a range of antimicrobial agents either important in human medicine (EASSA) or commonly used in veterinary medicine (VetPath, MycoPath, ComPath). Data are interpreted using either CLSI (Clinical and Laboratory Standards Institute) or EUCAST (European Committee...
on Antimicrobial Susceptibility Testing) interpretive criteria, as appropriate. Conducting MIC determination in a single central laboratory has a number of advantages including eliminating any interlaboratory variation and interpretation of results using identical interpretive criteria. These standardised procedures allow for easy comparisons between different EU Member States and make these longstanding veterinary pharmaceutical industry sponsored resistance monitoring programmes robust and valuable to address food safety and in vitro efficacy of antibiotics.

References
EFSA'S ACTIVITIES ON ANTIMICROBIAL RESISTANCE IN THE FOOD CHAIN: RISK ASSESSMENT AND DATA COLLECTION

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Antimicrobial resistance (AMR) in bacteria causes increased morbidity and mortality in humans. Food is a transmission vehicle; its relative importance compared to other sources (direct contact with animals, environment, human-to-human transmission) is currently very challenging to estimate in a quantitative way. Since AMR is a complex multi-factorial issue, control of all the routes by which AMR bacteria can arise in the human patient requires a response from all stakeholders. Lack of data makes it difficult to determine the extent of human exposure to AMR bacteria/genes via food. Nevertheless, the high prevalence of resistance to fluoroquinolones in enteric pathogens (e.g. *Salmonella, Campylobacter*) may pose a significant health threat. The emergence of resistance to cephalosporins and to carbapenems is the latest concern. These are considered as critically or highly important medicines by WHO and OIE.

Scientific opinions provided by the European Food Safety Authority (EFSA) have addressed the problem of AMR giving advice as the bases for policy planning, some relevant examples on 'hot issues' such as MRSA, ESBLs, and carbapenemases. In these documents EFSA concluded that the main risks factors for resistance to cephalosporins in animals are: (i) the use of antimicrobials; (ii) the extensive trade of animals in the European Union (EU); and (iii) the spread from the top of some production pyramids (e.g. poultry breeding). Recommended control options for resistance to cephalosporins in animals are: (i) to stop or restrict all uses of cephalosporins; (ii) to control off-label usage; (iii) to decrease the total antimicrobial use in animal production (due to co-resistance and co-selection); and (iv) to implement measures to control dissemination (farm biosecurity, controls on animal trade, improve hygiene throughout the food chain). In more general terms (for all antimicrobials), there is an urgent need to promote prudent use in animals and to educate veterinarians and farmers on strategies to minimise AMR. It is now time to act and EFSA has given advice on potential control options. Risk managers are the best placed to decide on the most appropriate strategies to apply.

AMR is commonly found among bacteria from food and animals. Resistance to antimicrobials recognised as critically important to human medicine (for example, fluoroquinolones, cephalosporins) is also detected. There are large differences concerning levels of AMR in animals and foods in the EU, and in the occurrence of resistance over time between the Member States (MSs). The AMR levels observed in most indicator bacteria tend to be higher in the Western and Southern MSs when compared to other parts of Europe as observed in the annual EU Summary Report on AMR. It is extremely important to improve and harmonise the data collection systems both for occurrence of resistance and consumption of antimicrobials in animals and humans. With this information, it would be easier to quantitatively assess the risk posed by AMR. EFSA has recently produced proposals to improve the harmonisation of monitoring and reporting of AMR in animals and food. Furthermore, the integration of AMR occurrence data and antimicrobial consumption data in animals is ongoing (EFSA monitoring activities and ESVAC project (European Surveillance of Veterinary Antimicrobial Consumption)), and a joint EFSA/EMA/ECDC report will be produced soon.
EFFORT: JOINING FORCES AGAINST ANTIMICROBIAL RESISTANCE

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Historically, there are few European countries acting as pioneers in the reduction of veterinary antimicrobial use. The effect of current policy measures to reduce the development of antimicrobial resistance, however, are poorly understood and not fully documented. To study and to control antimicrobial resistance (AMR), there is a need for a European approach because of the strong inter-relatedness of the food producing industries, the common internal market, and the free movement of people, animals and goods. Within Europe, there are clear differences in agricultural practices, industry structure and dietary preferences of consumers with effect on the epidemiology of AMR. There is a need to investigate the current on-farm situation of antimicrobial use and antimicrobial resistance in different European countries in relation to farm management, animal welfare and economics. Also the effects and feasibility of interventions to control AMR should be assessed. Additionally, an estimation of the relative contribution from different sources on AMR bacteria in humans will allow to estimate the effect of reduction of antimicrobial usage on human exposure.

The European EFFORT (Ecology from Farm to Fork Of microbial drug Resistance and Transmission) project started December 2013 and will study these topics in the upcoming 5 years. EFFORT will study the complex epidemiology and ecology of antimicrobial resistance and the interactions between bacterial communities, commensals and pathogens, in animals, the food chain and the environment. This will be conducted by a combination of epidemiological and ecological studies using newly developed molecular and bio-informatics technologies. EFFORT will include an exposure assessment of humans to AMR bacteria from animal/environmental sources. The ecological studies on isolates will be verified by in vitro and in vivo studies. Moreover, real-life intervention studies will be conducted aiming at reducing the use of antimicrobials in farm animals. The research planned by EFFORT is closely linked to the needs of policy makers, food industry and public health services. Focus will be on understanding the eco-epidemiology of antimicrobial resistance from animal origin and based on this, predicting and limiting the future evolution and exposure to humans of the most clinically important resistance by synthesising different sources of information in the prediction models.

Some of the important innovative aspects of EFFORT are:

- The characterisation of the resistome of production animals as determined by metagenomics and assessing the added value of genomic analysis of isolates and metagenomic analysis of bacterial communities in comparison with the conventional used method for European Union (EU)- based surveillance of antimicrobial resistance using indicator organisms.
- The comprehensive and multinational/multispecies datasets that will be collected and built will allow determination of the complex associations between risk factors including antimicrobial usage, and the occurrence of resistance (resistome and conventional data).
- An estimation of the relative contribution of different sources and various transmission routes on antimicrobial resistance in humans in the general population as well as in selected occupational risk groups. This will also allow for an estimation of the effect of reduced antimicrobial use and other specific interventions on human exposure.
• The determination of genetic characteristics involved in success of high-risk clones and mobile genetic elements in the epidemiology of AMR and the estimation of the relative impact on human infection risks caused by transfer of antimicrobial resistance determinants between commensals and pathogenic organisms.

• The implementation of on-farm interventions (e.g. restricted usage of antimicrobials) in multiple European countries and animal species following a common approach, including an analysis of the economic effects, animal welfare consequences and resistance levels.

• The use of novel statistical analytical approaches for rich meta-genomic data to obtain a ‘fingerprint’ of resistance patterns for different populations (humans, animals) and the environment. Simultaneously these fingerprint patterns will be associated to determinants of antimicrobial resistance of relevance for human and animal health.

The EFFORT Consortium includes a diverse group of partners that include both academic, industrial and over-arching organisations. It consists of 20 partners from 10 European countries: Belgium, Bulgaria, Denmark, France, Germany, Italy, The Netherlands, Poland, Spain and Switzerland. There are 6 SMEs involved. The plans and results of the project are reviewed by an External Review Board comprising scientists and stakeholders from policy and industry. Interaction between scientists and policy makers will be promoted using policy round tables sessions. Through its results, EFFORT will provide scientific evidence and high quality data that will inform decision makers, the scientific community and other stakeholders about the consequences of AMR in the food chain and its relationship with animal health and welfare, food safety and economic aspects. These results can be used to support political decisions and to prioritize risk management options along the food chain to establish a sustainable animal production with minimal risks for public health.
RELATIONSHIPS BETWEEN ANTIBIOTIC USE IN ANIMALS AND INCREASED ANTIBIOTIC RESISTANCE IN AQUATIC AND SOIL ENVIRONMENTS

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Antibiotic resistance (AR) is the ability of microorganisms to defend themselves against the negative effects of antibiotics and antimicrobial agents. Although AR is a natural phenomenon, AR in clinically important microorganisms has increased dramatically in recent years, especially after the mass production of antibiotics expanded in the 1950s. Initially, antibiotics for medical use were obtained from natural sources, but as antibiotic use extended to other applications, target microorganisms progressively gained resistance to ‘old’ antibiotics and production of new antimicrobial agents became essential. Unfortunately, as antibiotic use has continued and environmental pollution has broadened, even new antimicrobials are becoming ineffective and multi-drug resistance is common around the world.

This presentation will summarise the role of pollution and the natural environment in increased levels of clinically relevant AR in soil and water environments; work presented as a series of case studies. Examples will include studies in the Netherlands that suggest relative ARG levels in agricultural soils have increased by one to two orders of magnitude since industrialisation of antibiotic manufacture; studies from the USA that show how different antibiotic use strategies in large animal agriculture differentially impact AR gene (ARG) abundances in downstream waters; and recent work on Danish soils (collected between 1920 and 2010) that show cattle and swine manure (vs. inorganic) fertiliser applications significantly correlates with increased extended spectrum β-lactamase (ESBL) ARG levels in exposed soils. This work further shows that the appearance of different, increasing potent ESBL ARGs in the manured soils almost exactly correlates (in time) with the first appearance of the same ARGs in hospital settings. The presentation suggests that medical and agricultural AR are linked, possibly bridged by AR dissemination through soil and water environments, although directional cause-and-effects on AR transmission are unclear.
TO WHICH EXTENT CAN WE EXPLAIN ANTIMICROBIAL RESISTANCE PATTERNS IN ESCHERICHIA COLI FROM ANIMAL DERIVED FOODS BY ANTIMICROBIAL USAGE PATTERNS IN LIVESTOCK?

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In the years 2009 to 2012, around 8,800 Escherichia coli isolates were collected in a systematic monitoring approach from primary production, slaughterhouses and retail stores. Minimum inhibitory concentration (MIC) was determined by the broth microdilution method according to CLSI guidelines (M07-A8) and using the plate format EUMVS (TREK Diagnostics Ltd., UK). Results were evaluated on the basis of the epidemiological cut-off values as fixed in Commission Decision 2007/407/EC or by EUCAST. Overall resistance rates differed significantly between isolates from the different populations of fattening animals considered. The highest resistance rates were detected in isolates from broilers and fattening turkeys, followed by fattening pigs and veal calves. The same situation was observed in food samples. In fattened bovines, resistance rates decreased with age of animals. This ranking reflects very much the magnitude of antimicrobial usage (calculated as used daily doses) in the respective livestock populations.

Even more worrying, most of the isolates were resistant to several antimicrobial classes. Resistance to the commonly used antimicrobial classes was frequently observed. Resistance rates to tetracyclines ranged between 30 and 85% in poultry, calves and pigs and products thereof, whereas in beef cattle and beef tetracycline resistance rates were below 20%. Whereas in poultry and poultry meat, quite similar resistance rates were observed, resistance rates decreased in the bovine and porcine production chain, showing highest resistance rates in young animals at primary production and lower rates at slaughter and in fresh meat. These patterns were quite similar for aminopenicillins, the second most frequently sold antimicrobial class in Germany. In contrast to tetracycline resistance, ampicillin resistance rates in broilers and chicken meat were much higher. Resistance rates to (fluoro)chinolones above 30% of the isolates were observed in the poultry production chains and veal calves at farm level. In contrast, ciprofloxacin resistance was present at a low level in E. coli isolates from pigs and pork. Again, this pattern reflects very much the usage patterns in livestock.

In contrast to these data, the spread of cephalosporin resistance in the poultry production chain cannot be explained by selective pressure due to antimicrobial usage only. There, other influencing factors, as for example vertical spread of bacteria carrying genetic determinants for resistance have to be considered too.

Results demonstrate the benefit from continuous monitoring of antimicrobial resistance and antimicrobial usage, which supports that management strategies can be continuously assessed and adapted.
A QUALITATIVE APPROACH TO EXPLORE MOTIVATIONS FOR ANTIMICROBIAL PRESCRIBING BY VETERINARY SURGEONS IN UK PIG PRACTICE

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Increasing levels of antimicrobial resistance in human and veterinary medicine have raised concerns over the issue of overprescribing and the indiscriminate use of antimicrobials. Their use in food producing animals is under scrutiny due to the treatment and prophylaxis of large numbers of animals, and the perceived risk from the zoonotic transfer of resistant pathogens from animals to humans. In the UK, the greatest amount of single species antimicrobial products sold for use in farm animals are for pigs; the majority of these products are for administration through medicated feedstuffs.

Qualitative research methods have been used increasingly in human medicine to investigate prescribing behaviours. This study used focus groups and in-depth interviews to explore the drivers and motivators behind prescribing patterns in veterinary surgeons in pig practice in the UK. A series of two focus groups and twenty one semi-structured interviews were completed with veterinary surgeons working in pig practice. Purposive sampling aimed to incorporate individuals from different areas of pig density, mixed species and specialist pig practices, both junior and senior veterinary surgeons with a distribution of age and gender. The focus groups elicited the motivations and behaviours behind prescribing practices within a group discussion setting and provided a framework for gaining further detailed insight across a wider population of pig veterinary surgeons.

Thematic analysis of transcriptions of the focus groups and in-depth interviews revealed eight common themes including ‘agricultural factors’, ‘drug-related factors’, ‘disease epidemiology and outcomes’, ‘responsibility’, ‘economic factors’, ‘external pressures’, ‘vet-client relationship’ and ‘knowledge base’ that were considered to influence antimicrobial use. In the focus groups ‘external pressures’, such as pressure from clients, legislation and public perception, were considered to influence prescribing behaviour commonly, whereas ‘agricultural factors’, relating to housing, and the management of systems, were deliberated regularly through the interviews.

Gaining in-depth insight and understanding into the influences behind prescribing decisions can identify behaviours associated with over or inappropriate use. Such qualitative studies have been used in human medicine to identify potential interventions and assess their efficacy on promoting prudent use. It is hoped that by understanding prescribing practices in veterinary medicine better, similar interventions may be developed to promote the judicious use of antimicrobials.
ANTIBIOTIC RESIDUE ANALYSIS IN NON-INVASIVE ANIMAL MATRICES IN THE FIGHT AGAINST BACTERIAL RESISTANCE.

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The excessive use of antibiotics in animal breeding is likely one of the main causes of the current widespread antimicrobial resistance. In the combat against emerging bacterial resistance, a main measure is the reduction of antibiotic usage in animal husbandry and the requirement to clearly administrate any antibiotics used on the farm. It is agreed that antibiotic residues might have an effect on the persistence and dissemination of antimicrobial resistance, however it is not clear what residue levels still have an effect in this. To understand the relation between antimicrobial resistance and antibiotic residues robust data are needed from both fields of expertise.

Two main challenges are discussed. First, the development of methods to determine antibiotic residues compatible with matrices that are routinely applied to determine antimicrobial resistance. Second, the development of an approach to be able to check farmers’ administrations or monitor unintended use, for example due to cross-contamination (from previous use or recirculation in the environment) of antibiotics. For both challenges it is of importance to select non-invasive sample matrices and to select matrices in which antibiotic residues are persistent.

We show that residue analysis of manure is an effective approach to accomplish both tasks. A multi-antibiotic method, monitoring over 50 antibiotics within one run, was developed and validated. Using this method, over 500 pig and calf manure samples, taken in the slaughterhouse phase, originating from 40 different farms were sampled and analysed. The data give good insight in the antibiotics used at Dutch pig and cattle farms and are valuable for comparison with antimicrobial resistance data. A second success is the use of chicken feathers as a tool to check farmers’ administrations. Our results show that antibiotics can be highly persistent in/on chicken feathers and it is suggested that based on the analysis of segmented feather the type and time of administration can be determined.
HOW THE REPRESENTATION OF ANTIMICROBIAL CONSUMPTION USING DIFFERENT INDICATORS CAN PROVIDE USEFUL INFORMATION ABOUT TREATMENT STRATEGIES AT FARM LEVEL?

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Antimicrobial usage in livestock can be measured by several indicators using different parameters in their numerator and denominator. However, it is not always clear how these indicators are related and which treatment practices they emphasize. In this study, we selected three indicators and conducted an in-depth comparison to evaluate: (i) which treatment practices are emphasized by these indicators, and (ii) if pair-wise comparison of antimicrobial usage between different indicators could provide useful information about the farmers’ treatment strategies. This study was part of the MINAPIG Consortium activities, which aim to reduce antimicrobial usage in the European pig industry (www.minapig.eu).

We conducted a cross sectional study in 60 randomly sampled French farrow-to-finish pig herds. Farm records and a questionnaire were used to collect data about antimicrobial treatments administered to the oldest batch produced at the moment of the visit and to sows over the past year. Data collected included product and dosage used, number of animals treated, number of animals and period at risk to be treated (i.e., duration of each production stage, e.g., suckling period), treatment route and length. Each individual treatment was calculated in terms of (i) treatment incidence (TI), (ii) number of daily doses per animal (nDD/animal) and (iii) number of course doses per animal (nCD/animal), corresponding respectively to (i) the number of animals per 1000 receiving a daily dose of antimicrobials, (ii) the number of days of treatment per animal, and (iii) the number of full treatments per animal. Individual treatments were then combined to obtain a single value per indicator and per farm.

The representation of nDD/animal as a function of TI emphasised the animal categories treated. In particular, farmers mostly treating animals with a high period at risk to be treated (i.e., sows and fatteners) were discriminated against those mostly treating animals with a short period at risk to be treated (i.e., sucklers and weaners). Additionally, the representation of nDD/animal as a function of nCD/animal differentiated farmers by their treatment length. Thus, farmers mostly administrating long treatments (e.g., medicated feed) had a higher nDD/animal than those using short treatments, such as parenteral treatments.

In conclusion, the representation of antimicrobial usage based on pair-wise comparison of three indicators provided useful insights to better understand the link between the amounts of antimicrobial measured and the farmers’ treatment strategies. This approach could also be used to monitor changes in antimicrobial treatment practices over time.
ANTIMICROBIAL REDUCTION IN PIGS FROM BIRTH TILL SLAUGHTER (-48%) AND IN BREEDING ANIMALS (-19%): A TEAM EFFORT WITHOUT JEOPARDISING PRODUCTION PARAMETERS

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Reducing antimicrobial usage in food producing animals should be the route to slow down antimicrobial resistance selection. A coach from Ghent University, in collaboration with the herd veterinarian and other relevant advisors, guided pig farmers in prudent antimicrobial usage.

Sixty-five herds representative for Flemish pig production voluntarily applied for participation. Three visits per herd were performed to gather data on antimicrobial usage (www.ABcheck.UGent.be), herd management, biosecurity status (www.Biocheck.UGent.be) and production parameters, to establish a herd-specific intervention plan and to evaluate proposed interventions and progress made. A risk factor analysis for antimicrobial usage was performed using a multivariable general linear model. Evolution data from 40 herds were evaluated by paired samples t-test.

For sows the average prophylactic treatment incidence (TI) per 1000 pig days at the first visit was 46.4 (TI_sows,prophylactic; 0 – 259.8), for curative treatments 37.2 (TI_sows,curative; 0-156). For finishers from birth till slaughter, this was 115.1 (TI_birth-slaughter,prophylactic; 0-492.8) and 107.2 (TI_birth-slaughter,curative; 0.2-1051.7), respectively. Penicillins, polymyxins and tetracyclines were most often used. Ceftiofur was the third most used for prophylactic treatment in piglets. External biosecurity scores were on average 64.8% (43-95%), internal 50.1% (25-84%). Proposed interventions were on biosecurity improvements, adjusting vaccination, increasing diagnostics and prudent/reduced usage of antimicrobials. Weaning (19-28 days) at a younger age was associated with higher prophylactic treatment in weaned piglets (p=0.03, β=-46.5), while a higher internal biosecurity was related to a lower TI (p=0.02, β=-9.9). After the interventions, average external biosecurity increased with 4.7% (p<0.01), internal biosecurity with 13.8% (p<0.01). Weaned piglets/sows/year increased with 3.1% (+0.8 piglet, p< 0.01). Feed conversion ratio, mortality finishers and growth all evolved positively, however non-significant. Mortality till weaning slightly increased non-significantly from 12.4 to 12.5%. TI_sows,prophylactic decreased with 55.3% (TI=- 25.6, p<0.01), while TI_sows,curative increased non-significantly with 56.9% (TI=+12.4, p=0.331). TI_birth-slaughter,prophylactic decreased with 32.6% (TI=- 37.6, p=0.107) and TI_birth-slaughter,curative with 62.6% (TI=- 73.7, p=0.0156). Totaling prophylactic and curative treatments showed 48% reduction in finishers from birth till slaughter and 19% in sows. Critically important antimicrobial classes were less used. Standard ceftiofur treatment in piglets was reduced by 62.3% (TI_prophylactic,before=6.34, TI_prophylactic,after=2.39).

In conclusion, coaching pig farmers in herd management, biosecurity and prudent antimicrobial usage can lead to an important reduction in antimicrobial usage and less use of critically important antibiotics without jeopardising production parameters.
AN ESTIMATION OF THE USE OF ANTIBIOTICS IN THE DUTCH SMALL RUMINANT INDUSTRY

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The aim of this study was to estimate the amount of antibiotics and groups of antibiotics used in the small ruminant industry in the Netherlands in 2011 and 2012. Twelve large veterinary practices that were randomly located throughout the Netherlands were selected for this study. All small ruminant farms associated with these practices that had complete recordings of antibiotic use were included. The veterinary practices provided data on all antibiotics prescribed and the animal defined daily dose of antibiotic use per year (ADDD/Y) was calculated for each farm. The median ADDD/Y in small ruminant farms in the study was zero in both years (mean 0.60 in 2011, and 0.62 in 2012). Most antibiotics were used in the professional goat industry (herds of ≥32 goats). In this subtype, the median ADDD/Y was 1.22 in 2011 and 0.73 in 2012. In the professional sheep industry (flocks of ≥32 sheep), the median ADDD/Y was 0 in 2011 and 0.10 in 2012. In the small scale industry (flocks or herds of <32 sheep or goats), the median ADDD/Y never exceeded 0 (Table 1). The most frequently used antibiotics in the small scale industry and professional sheep farms belonged to the penicillin group. In professional goat farms, antibiotics of the aminoglycoside group were most frequently used.

Table 1. The percentage of farms in this study for which antibiotics were prescribed, and the animal defined daily dose of antibiotic use per year in 2011 and 2012 for farms with antibiotic use and all farms with small ruminants in the Netherlands, per subtype of small ruminant farms.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>2011 Farms for which antibiotics were prescribed</th>
<th>Median (mean) ADDD/Y on farms with antibiotic use</th>
<th>Median (mean) ADDD/Y on all small ruminant farms</th>
<th>2012 Farms for which antibiotics were prescribed</th>
<th>Median (mean) ADDD/Y on farms with antibiotic use</th>
<th>Median (mean) ADDD/Y on all small ruminant farms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional goat farms</td>
<td>85%</td>
<td>1.57 (16.84)</td>
<td>1.22 (14.27)</td>
<td>85%</td>
<td>1.27 (8.00)</td>
<td>0.73 (6.81)</td>
</tr>
<tr>
<td>(≥32 goats)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Professional sheep farms</td>
<td>47%</td>
<td>0.60 (0.96)</td>
<td>0 (0.45)</td>
<td>57%</td>
<td>0.59 (1.10)</td>
<td>0.10 (0.63)</td>
</tr>
<tr>
<td>(≥32 sheep)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small scale goat farms</td>
<td>8%</td>
<td>1.52 (2.13)</td>
<td>0 (0.18)</td>
<td>8%</td>
<td>1.47 (5.48)</td>
<td>0 (0.44)</td>
</tr>
<tr>
<td>(&lt;32 goats)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small scale sheep farms</td>
<td>10%</td>
<td>1.61 (3.55)</td>
<td>0 (0.37)</td>
<td>12%</td>
<td>1.19 (3.20)</td>
<td>0 (0.39)</td>
</tr>
<tr>
<td>(&lt;32 sheep)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*ADDD/Y, animal defined daily dose of antibiotic use per year.
This study provided a first impression of antibiotic use in the small ruminant industry. Given that they have a comparable attitude towards antibiotic use, these results might be valid for small ruminant populations in other north-western European countries as well. The antibiotic use in the small ruminant industry appeared to be low, and is therefore expected to play a minor role in the development of antibiotic resistance. Nevertheless, several major zoonotic pathogens are associated with the small ruminant industry, and it remains important that antibiotics are used in a prudent way.
EXPERIENCE IN PRACTICE: HOMEOPATHY IN ANIMAL HUSBANDRY

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Homeopathy is a serious option in animal husbandry to reduce the use of antibiotics in animals. It is cheap, animal friendly and leaves no residues. But it is not an easy method. Knowledge of animals, animal diseases and homeopathic remedies are necessary. In the European Union (EU), homeopathic remedies are recognised as medicines for animals. Within organic farming in the EU, homeopathy (and phytotherapy) is the first choice in treating sick animals. Only if not sufficient, chemically synthesised allopathic products, including antibiotics, can be used. To support farmers and veterinarians in the future, it would be helpful if formulares are available for treating the most common diseases in pigs, (dairy) cows, veal and chicken with homeopathy.

In the Netherlands, courses have been given since 2001 by Liesbeth Ellinger, a homeopathic veterinarian and former president of the International Association for Veterinary Homeopathy (IAVH), to (mainly) dairy farmers to learn how to use homeopathic remedies on their own farms. A number of those farmers have been successful in using these methods to cure their animals and prevent certain diseases. An analysis of all the results shows that treatment of diarrhoea, acute mastitis, pneumonia, cough, infertility is successful, as well as problems around birthing (weak uterus contractions, labour pains, difficult breathing of the newborn). More chronic problems, such as chronic mastitis, need more skills in homeopathy. Because the Dutch government takes the reduction in the use of antibiotics in farm animals very seriously, farmers put more emphasis on the use of homeopathy. A number of them now hardly use antibiotics on their farm anymore. This has also led to a method to dry off cows with homeopathy instead of antibiotics.

Homeopathy is a method developed by Dr. Samuel Hahnemann (1755-1843), a German physician and doctor. It is based on the principle that ‘like cures like’. It means that any substance that can produce symptoms in a healthy person can cure, when diluted, similar symptoms in a person who is sick. This idea is referred to as the ‘Law of Similars’, and was already understood by Aristotle and Hippocrates. It was Hahnemann who turned it into a science of healing. In contrast to conventional medicine, the appropriate remedy/medicine is chosen on the basis of the totality of symptoms, a holistic view. Apart from the physical problem (for example, diarrhoea), the choice for a certain remedy depends on individual subjective symptoms to differentiate between different homeopathic remedies. If the right remedy is given, major changes in the animal and astonishingly quick recoveries can be seen. In epidemics, homeopathy can be also useful. Often one or two remedies can cure most of the patients. As diseases on commercial farms can be of an epidemic character, it is easier to treat the group as a whole, which makes it easier to use homeopathy on farms.

From well performed clinical studies in animals and in humans, there is more than sufficient scientific proof of the effectiveness of homeopathy. There is also proof on cellular level of the action of homeopathic remedies. The only thing that is difficult to prove is how homeopathy is working exactly. In the future, the explanation for the mechanism of action will probably come from a different scientific field of research: dealing with physics on particles and electromagnetic waves.

In this presentation, the results of a randomized clinical trial (RTC) to prevent Escherichia coli neonatal diarrhoea in piglets by means of a homeopathic treatment will be presented. The
homeopathic agent Coli 30K significantly diminished (p=0.0024) the occurrence of neonatal E. coli diarrhoea in piglets.

References

Links on homeopathy in animals and science
www.iavh.org
www.homeopathiestichting.nl/wetenschap (in Dutch)
www.homeopathicvet.org/veterinary_research_into_homeopathy
www.carstens-stiftung.de
MULTIDRUG-RESISTANT BACTERIA IN MEAT PRODUCTS: HOW CAN WE CONTROL THIS POTENTIAL THREAT TO PUBLIC HEALTH?

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The zoonotic risk
The occurrence of antimicrobial resistant bacteria in meat products is generally regarded as a threat to public health. The human health risks associated with foodborne transmission of resistant bacteria is highly dependent on the bacterial species and the type of resistance involved. Historically, the risks of zoonotic transmission of antimicrobial resistance have been associated with foodborne pathogens, such as Salmonella and Campylobacter. However, the public health burden attributable to antimicrobial resistance in these species is limited, since infections are generally self-limiting and, in most cases, managed without antimicrobial therapy. Of higher concern is the recent emergence in livestock of extended-spectrum β-lactamase (ESBL)-producing Escherichia coli and livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA). These multidrug-resistant bacteria are, by definition, resistant to cephalosporins, which are first-line agents in the therapy of severe E. coli and S. aureus infections, and therefore have a considerable impact on morbidity, mortality and healthcare costs. Notably, the risk that ESBL-producing E. coli are transmitted by food is higher than for LA-MRSA, since this route of transmission is unusual and largely unknown for S. aureus. Moreover, while LA-MRSA are animal-adapted clones with limited ability to colonize the human body and transfer the methicillin resistance, ESBL-encoding genes spread by horizontal transfer of plasmids that can readily be exchanged between animals and humans without host barriers. Thus, foodborne transmission of ESBL-producing E. coli is more insidious and difficult to assess and control compared to LA-MRSA. The actual burden of human infections attributable to ESBL-producing E. coli of animal origin remains poorly assessed. However, the level of acceptable risk is likely close to zero when human life is put at risk by resistant bacteria present in food.

Core topic: how to control this potential threat?
Foodborne transmission of antimicrobial resistance can be controlled in two ways: by reducing antimicrobial use or by preventing transmission of resistant bacteria from livestock to humans. Antimicrobial use can be reduced by a variety of interventions, including bans or restrictions of specific drugs, legal interventions limiting the profit of veterinary antibiotic prescription or penalizing antibiotic overuse, and any measures preventing bacterial disease or promoting rational antimicrobial use in livestock. Prevention of animal-to-human transmission comprises pre-harvest measures to control transmission within and between herds, and post-harvest interventions to prevent meat contamination and human exposure to bacterial contaminants in meat. Measures reducing antimicrobial use have been demonstrated to be effective in several circumstances in Nordic countries. However, antimicrobial use is not the only driving force promoting spread of resistant bacteria in meat products, as clearly indicated by the recent spread of ESBL-producing E. coli in broiler meat, which is driven by vertical transmission of strains introduced into broiler flocks from the top of the production pyramid without any apparent antimicrobial selective pressure. Moreover, interventions reducing antimicrobial use require variable time to decrease the prevalence of resistant bacteria in meat products. Thus, especially in situations where the occurrence of resistant bacteria is not directly related to the use of specific antimicrobial classes, the most rapid and effective way to prevent transmission to consumers would be to employ post-harvest interventions, such as improving hygiene standards during slaughtering and meat
processing. Besides technological innovations for generic reduction of the bacterial load in meat, post-harvest interventions comprise regulatory measures setting thresholds for the acceptable level of resistant bacteria. However, no food safety standards exist today to control trade of food products carrying resistant bacteria of zoonotic concern. Under these circumstances, it is impossible to control dissemination on a global scale and any national efforts to reduce occurrence of these bacteria in animals and foodstuffs are likely to be scarcely effective.

What is next?
There is no doubt that antimicrobial use selects for the occurrence of resistant bacteria in livestock and consequently in food products of animal origin. Nevertheless, control of antimicrobial use alone might not always lead to conclusive results, since the spread and persistence of multidrug-resistant bacteria, such as ESBL-producing *E. coli* in animal populations, is favoured by complex mechanisms of co-selection. As such, it is necessary to have a holistic approach that goes beyond the control of antimicrobial use and involves research aimed at developing pre-harvest and post-harvest solutions to control zoonotic transmission (e.g., vaccines, alternative treatment strategies, evidence-based diagnostic protocols, clinically effective dosage regimes, and new technologies to reduce the risk of meat contamination). Last, but not least, it is time to redirect the historical debate about antimicrobial use in animals to a different set of questions. Would consumers accept paying a higher price for livestock products obtained using lower stocking densities and fewer antimicrobials? Would such a radical change in industrial livestock production be economically sustainable on a global scale? There is a concrete risk that this debate will continue without coming to any rational conclusion if these questions remain unanswered.
FOSTERING COOPERATION TO ADDRESS THE THREAT TO HUMAN AND ANIMAL HEALTH – WHAT NEW APPROACHES SHOULD BE TRIED?

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Fleming alerted the world to the adverse consequences of overuse of antibiotics in the 1940s but inexorably, ever since the introduction of the sulphonamides and every antimicrobial agent since, the threat to human and animal health from antimicrobial resistance has increased progressively to reach the crisis described by Neu in 1992 [1] and the supracrisis of today. How true were the words of Goethe when he wrote “knowing is not enough; we must apply; willing is not enough; we must do.”

The knowledge hierarchy includes data, information, knowledge, understanding, and wisdom. There is no shortage of data from which information has been extracted, knowledge gained and understanding developed. But what about wisdom and what about the actions that must arise to avert disaster? A common element in success and failure in responding to other crises is the human factor. Even in the face of knowledge of the potential for harm decisions on antibiotic use are frequently made for counterfactual reasons in medical [2] and veterinary [3] practice. How can human behaviour be changed to help solve the problem rather than making it worse? Is there guidance provided by experiences in other fields [4,5]? If cooperation cannot be fostered then the post antibiotic era is inevitable.

References
“ALONE WE CAN DO SO LITTLE; TOGETHER WE CAN DO SO MUCH” – Helen Keller

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One Health is a collaborative effort of multiple disciplines working locally, nationally, and globally to attain sustainable optimal health for the ecosystem. It is a cultural and behavioural concept with socioeconomic elements and impact. One Health is driven by agents of change that include, but are not limited to: population growth; nutritional, agricultural, and trade practices; globalisation; shift in land use; accelerated urbanisation; deforestation, encroachment on wildlife; and climate change. This presentation will frame the issue of antibiotic use in animals as a One Health issue.

The role of trust will be explored. Trust is one thing that is common to every individual, relationship, team, family, organisation, nation, economy, and civilisation throughout the world, and if removed will destroy the most successful relationships, but if developed and leveraged it has the potential to create unparalleled success. Trust is a pragmatic, tangible, actionable asset that you can create.

The art and science of negotiation and utilising it to find win-win situations when parties are trying to find a mutually acceptable solution to a complex conflict will be explored. Negotiation is a process between individuals, within groups, and between groups to address the conflict of needs and desires between two or more parties. Negotiation is largely a voluntary process and is voluntary with the premises that parties believe they can get a better deal by negotiating than by simply accepting what the other side will voluntarily give them or let them have.
The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) with the aim to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. Currently, 50 IMI projects are up and running, covering diverse disease areas including infectious diseases, neurodegenerative diseases, oncology, diabetes, and inflammatory disorders. Many of the projects deal with biomarker research, knowledge management, standardisation of tools and methodologies. Key to every IMI project is the collaboration between scientists from the academic world with scientists from the private sector, both large industry and small- and medium-sized industries. Many of the more recent IMI project focus on later stages in the value chain of drug development and address key threats to public health, and therefore involve important stakeholders, such as regulatory agencies, public health bodies, reimbursement agencies and payers. All projects aim to involve patients as much as possible.

**IMI’s New Drugs for Bad Bugs (ND4BB) programme**

The ND4BB programme aims to speed up the discovery and development of new antibiotics for human use, by addressing challenges related to antibiotic drug discovery and development. Currently, seven projects are either up and running or in the planning stage under the ND4BB programme.

One of the challenges in antibiotic drug development is that clinical trials with new antibiotics are long, costly and often inefficient because of the need to include a large number of clinical centres from different countries that often do not work according to standardised protocols. Four projects under ND4BB aim at facilitating the clinical development of proprietary assets, thereby decreasing risk and investment for the pharmaceutical industry sponsor (COMBACTE, COMBACTE-CARE, ND4BB Topics 6 & 7). The project COMBACTE is creating self-sustainable clinical investigator and laboratory networks throughout Europe that will increase the efficiency of clinical trials. Clinical trials conducted in the four projects are using the networks and contributing to the extension of the networks where needed. In addition, epidemiology studies are carried out with the goal to inform future drug development.

Inherent scientific challenges exist for antibiotic drug discovery and development. For example, the double membrane structure of Gram-negative bacteria makes it particularly difficult for a drug to penetrate. In TRANSLOCATION, academic and industry experts join forces at an unprecedented level and share their experience, expertise and knowledge to advance our understanding of efflux mechanisms and penetration barriers in Gram-negative bacteria. In addition, Translocation is creating a ND4BB Information Centre where antibacterial R&D information and data (including legacy data from pharmaceutical companies) is shared. Analysis of the shared knowledge will lead to learnings and best practices that will help future antibiotic drug discovery and development efforts.

Another major challenge in antibiotic R&D is to turn newly discovered molecules with antibiotic activity into development candidates. Novel molecules that are discovered in...
university teams or by SME’s are not necessarily good development candidates, and owners of those compounds do not necessarily understand what it takes for a molecule to become a good candidate for clinical development. The project ENABLE represents a unique model of collaboration in the field of competitive drug discovery. At a scale never seen before, pharmaceutical industry antibiotic R&D experts join forces with owners of promising new molecules from universities and SMEs and with the best experts from academia to work on the most promising novel molecules and to jointly progress them towards early clinical stages. The ENABLE model of collaboration is based on an innovative intellectual property agreement reflecting collaborative work on competitive assets. The ENABLE model could prove inspirational for R&D collaborations in other disease areas.

The return on investment that a pharmaceutical company can expect from a new antibiotic is often too low to justify investment from a for-profit perspective. Antibiotics do not generate as much revenue as drugs for chronic conditions would do. There is a misalignment between the need of a pharmaceutical company to generate revenue and the public health need to use antibiotics as sparingly as possible to avoid resistance. The project DRIVE-AB will propose options for a new economic model of antibiotic R&D and responsible use of antibiotics. Key for success will be the engagement of stakeholders (patients, clinical societies, SME’s, large pharmaceutical companies, healthcare payers, public health officials, government officials).

In summary, IMI offers a neutral platform for researchers and stakeholders from different fields to work collaboratively in innovative partnerships to address current public health needs and threats.
Therapeutic use of antimicrobials to treat unavoidable disease and one-off metaphylactic use to prevent disease clearly benefit animal welfare. However, routine use of antimicrobials – be it prophylactic, metaphylactic or therapeutic – tends to lock animals in to low welfare industrial systems. In such cases, antimicrobial use undermines welfare as it facilitates – and indeed perpetuates – the continuing use of systems and practices that are inherently detrimental to good health and welfare. Recurrent diseases should be prevented, not by regular antimicrobial use but by improving production conditions, animal husbandry and management. If farmers find they regularly have to administer antimicrobials to each batch of animals at a certain stage of production (e.g., weaning of pigs), they should change their systems and practices. Prophylactic and metaphylactic use of antimicrobials should never be used as a substitute for good housing, hygiene and management practices.

A number of measures would contribute to reducing susceptibility to disease, so lessening dependence on antimicrobials; these measures would at the same time enhance animal welfare. A key factor in improving animal health is reduction in animal population density as high density – which is common in the European Union (EU) pig and poultry sectors – has been identified as a major risk factor in the emergence and spread of infections. The routine use of antimicrobials allows animals to be kept in stressful conditions which reduce immune competence and impoverish welfare. If regular antimicrobial use were ended, farmers would have to reduce stress in order to strengthen animals' natural immunity, for example by avoiding overcrowding, mixing and large herds/flocks as well as providing the opportunity for animals to perform natural behaviours. Early weaning (at 3-4 weeks of age) in the pig sector would not be possible without regular antimicrobial use. Early weaning contributes to intestinal and immune system dysfunctions. Treating or preventing diarrhoea at weaning is one of the main uses of antimicrobials in pig production. Good weaning practice, in which pigs were not weaned until they had gained immunological and nutritional independence from their mother, would improve welfare and enable regular antimicrobial use to be reduced. Animals that are given full access to the outdoors, in conditions which are not overly intensive, tend to require far fewer antimicrobials than those farmed entirely indoors. Well-designed and well-managed free range systems also have the potential to provide better welfare than intensive indoor systems. Selection for greater productivity often means that breeding for disease resistance and general health can be neglected. Animals selected for high production levels appear to be at increased risk of immunological problems and pathologies and so are more likely to require antimicrobial treatments. The European Food Safety Authority (EFSA) has concluded that genetic selection for high milk yield is the major factor causing poor welfare, in particular health problems, in dairy cows and that the genetic component underlying milk yield has been found to be positively correlated with the incidence of lameness, mastitis, reproductive disorders and metabolic disorders. High yielding dairy cows are vulnerable to poor welfare and serious health problems, which are often dealt with by using antimicrobials for prevention and for treatment.

It is clear that, in facilitating the use of systems that compromise the welfare of the animals involved, regular prophylactic and metaphylactic antimicrobial use has an adverse impact on the well-being of animals. Routine antimicrobial use is a sure sign that something is wrong with the system.
If our twin objectives are to substantially reduce antimicrobial use and to improve animal welfare, major changes in housing and management practices are needed to promote ‘positive health’ in animals: stocking density and herd/flock sizes should be reduced, stress factors, such as mixing and inability to perform natural behaviours should be addressed, good air quality should be maintained in housing, early weaning of pigs should be ended and selection for high productivity should be avoided when this harms animal health and welfare. Costs will be involved in introducing these changes but the long-term costs to society of reduced antimicrobial efficacy in human medicine (to which the livestock sector’s over-reliance on antimicrobials contributes) are likely to far outweigh the costs incurred in introducing better farming practices. Moreover, certain economic benefits will arise from improving health. Healthier animals need less veterinary attention and medicines and have lower mortality. In addition, they may have improved growth rates and better feed conversion. Ultimately, however, it is society and in particular consumers who must decide whether they are prepared to pay for the extra costs involved in producing meat and dairy products from animals reared with low antimicrobial use and high welfare standards. The livestock sector could aid this process by greater openness and transparency about how today’s intensively animals are farmed.
ANTIBIOTIC USE IN LIVESTOCK FARMING THROUGH THE EYES OF CONSUMERS

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The goal of the study was to explore – together with consumers – the prospects for communication about antibiotic use in Dutch livestock farming. To this end, a qualitative study was carried out with 24 participants. The study primarily involved questions about associations and impressions of antibiotic use. A quantitative study was then performed among a representative sample of 519 Dutch respondents who eat meat, dairy or eggs. A third of these consumers eat at least 15% organic dairy, meat or eggs.

The studies revealed that the use of antibiotics in livestock farming is not really seen as important by consumers; there were few strong views on this theme. The overall view of both the utility and the risks of antibiotic use for farmers, the environment, consumers’ own health, animal welfare, others and public health is not positive. Consumers find antibiotics a difficult subject. They know little about the relationship between antibiotic use and taste, and the relationship between antibiotic use and the quality of the meat. Many people think that antibiotics are still in the meat sold in supermarkets. Additionally, little is known about terms, such as curative and preventive antibiotic use. Consumers themselves say that they do not know everything about this subject and that they have trouble judging to what extent antibiotics are used, and what for. The use of antibiotics is primarily associated with meat; antibiotics are linked to eggs and milk to a lesser extent. People also have the idea that antibiotics are used more in conventionally produced meat, eggs and milk than in the environmentally friendly or animal friendly varieties. Consumers believe that antibiotics are used the least in organic meat, eggs and fish. Consumers express a clear preference for exclusively curative antibiotic use. They do not want to see preventive use. Consumers want only sick animals to be treated. A large group of respondents also believes that illnesses in animals should be allowed to run their course and, if that fails, that the animals should be destroyed. They would prefer no antibiotic use at all. At the same time, their willingness to pay for an antibiotic-free product is limited.

Consumers have a great confidence in the government and the supermarkets when it comes to checks and food safety. Most have confidence that things are ‘as they should be’. There appears to be insufficient scope for different segments in the market. Consumers say they want to be able to choose more consciously in favour of or against antibiotic use when they are in the supermarket, but there are no large differences between groups of consumers. In this study, consumers were classified according to a large number of variables, but no major differences were observed. Only consumers who ate organic products were prepared to pay more (15%) for an antibiotic-free product. Consumers therefore have a lot of confidence in the products in the supermarket. At the same time, they have less faith in the information they receive from supermarkets. They primarily trust what non-governmental organisations (NGOs), the Netherlands Nutrition Centre, universities and research institutes tell them.
Continuous reports in the media on meat associated scandals and on residues of antibiotics in meat products create an environment of uncertainty amongst the consumers. This is enforced by reports on livestock-associated resistances of bacteria that may have an impact on human health. Trends can be summarised as a high societal pressure on livestock producers and on the actors in the meat supply chain regarding the responsible use of antibiotics and their reduction to regain consumer’s trust. Besides the legislative bodies in the individual countries, the retailers and the food service providers plus the food processors are the drivers that react with improvements, enforcements and solutions on this societal pressure. In addition to the legal framework, private standards that integrate specific requirements on the prudent use of antibiotics are the tool to regain consumers’ trust. These may go beyond legal requirements. The standard setters operate and react quickly on new challenges and create customised solutions. The additional requirements on the use of antibiotics in food producing animals are integrated in existing standards or implemented in voluntary add-on modules that become part of the producers’ certifications.

Reducing the risks by proper documentation for traceability, sophisticated reporting and annual auditing of the supply chain operators assist to regain consumers’ confidence. The Sustainable Meat Initiative of the Dutch retail for pork production (SMI) is an example of how the industry may take initiative. Pig producers, slaughterhouses, meat processors, food service providers and retailers jointly with consumer representatives and non-governmental organisations (NGOs) were involved to agree on additional requirements for all pork meat that will be on the shelves of Dutch supermarkets starting by 2015. Three modules of voluntary add-ons were agreed amongst the partners of the pork supply chain. Module 1: Animal Health and Responsible Use of Antibiotics; Module 2: Animal Welfare; and Module 3: Environment and Sustainability. The implementation of a chain of custody tool is part of the programme. It will safeguard the avoidance of mixing of SMI certified with non-certified pork. The certification of SMI criteria is performed on top of GLOBALG.A.P.’s Integrated Farm Assurance Standard (IFA) and of the Dutch IKB System that is benchmarked to GLOBALG.A.P. IFA. Independent certification bodies (CB) will audit annually compliance with the requirements at the participating farms. The Certification Integrity Program (CIPRO) of GLOBALG.A.P. is part of the initiative and will verify the CB’s decisions by additional controls.

The effects on primary production are associated with improvement of livestock management and the responsible and prudent use of antibiotics leading to a reduction of the use at farm level. The role assigned to the contracted veterinarian is crucial. He/she has to set up jointly with the livestock producer a veterinary health plan and an antibiotic reduction plan and review it annually. The selection of the appropriate antibiotic for therapy by the contracted veterinary surgeon shall be underlined by resistograms. Nevertheless, in an urgent case of disease the attending veterinarian has to make the immediate decision on the selection and application of the appropriate antibiotic to avoid further suffering of the animals and the spread and progression of the bacterial disease. The prophylactic use of antibiotics shall be prohibited, whereas the metaphylactic and therapeutic uses are promoted. Oral medication is in growing livestock herds, especially in poultry and pigs, the method of choice for application. Whether the medication shall preferably be done via compound feed or via water
shall depend on the production system. There is a clear trend for the latter to be the method of choice. Normative rules, technical approval and regular calibration for automated devices for dosage of antibiotics via drinking water are necessary.

Recording and reporting of the antibiotic treatments to databases are required followed by an annual benchmarking. The benchmarking within the country of production and amongst countries shall be performed with the data of the specific species and not with the overall use of antibiotics in livestock production, since there are differences amongst the countries regarding the composition of the livestock species. Improved husbandry systems for good animal welfare, regularly updated management systems and best stockmanship plus the prudent use of antibiotics are the founder for sustainable intensification of livestock production. The implementation of the related criteria must be verified annually by independent third party certification to safeguard the compliance with the societal challenges and to keep the consumers’ trust in livestock products.
POSTERS

P1 Multidrug resistance in *Escherichia coli* isolated from one-day old Leghorn chickens and its persistence throughout chicken lifespan
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P2 Mapping the global consumption of antimicrobial in livestock
Thomas Van Boeckel
Princeton University, USA

P3 Antimicrobial resistance of *Escherichia coli* in piglets in Australian commercial pig herds
Lechelle van Breda, M. Ward and O. Dhungyel
Faculty of Veterinary Science, The University of Sydney, Australia

P4 Reduced somatic cell counts in response to a standardised high activity proprietary garlic powder administered to lactating cows – a pilot trial
Lynette Chew1, P. De Costa1 and J Zonderland2
1InQpharm Group Sdn Bhd, Malaysia and 2Veterinary Health Research, New Zealand

P5 Improved faecal consistency in calves administered with standardised high activity proprietary garlic powder
M. Musthapa1, P. De Costa1 and J.J.C. van Hattum2
1InQpharm Group Sdn. Bhd, Malaysia and 2Farma Research Animal Health BV, the Netherlands

P6 Optimisation and implementation of an analytical methodology for the detection of tetracycline, oxytetracycline and chlortetracycline residues and their metabolites in feathers by liquid chromatography tandem mass spectrometry
Javiera Cornejo1, E. Pokrant1, L. Lapierre1, A. Maddaleno2, C. Araya2, H. Hidalgo3 and B. San Martín2
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P7 Implementation of an analytical methodology for the detection of oxytetracycline and epi-oxytetracycline in chicken claws by liquid chromatography tandem mass spectrometry
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P8 Reduction of antibiotic usage in animals: the effect on antimicrobial resistance in indicator *E. coli* derived from livestock
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P9  Can livestock-associated MRSA levels in veal calf farms be modulated by reducing antimicrobial use and by applying a cleaning and disinfecting programme? Experiences from an intervention study
Alejandro Dorado-Garcia¹,², H. Graveland², M.E.H. Bos¹, K.M. Verstappen², J.A. Wagenaar¹,³ and D.J.J. Heederik¹
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P10  Evaluation of a project to stimulate vets and farmers to collect milk samples for diagnostic testing
Monique Driesse¹ and I. Botvliet²
¹Boehringer Ingelheim bv and ²Brabants Veterinair Laboratorium, the Netherlands

P11  Welfare (findings at slaughter) consequences following a reduction in antibiotic use
Nana Dupont and H. Stege
Department of Large Animal Sciences, University of Copenhagen, Denmark

P12  Rosen’s test to objectively evaluate B SAFE feed additive in poultry and swine
G. Benzoni, M.L. le Ray and Thomas Dumont
Neovia, France

P13  Antibacterial effect of selected Australian essential oils and associated compounds on E. coli O149:K88 from pig gut
Zoey Durmic¹, M. Heudelot², P. Hutton¹,³ and J. Pluske³
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P14  The application of biochip array technology to the broad detection of antibiotic residues in different matrices from food producing animals
B. Bell, M. Clarke, J. Mahoney, N. O’Loan, L. Farry, A. McBride, M.C. McGarrity, J. Porter, David Ferguson, M.E. Benchikh, R.I. McConnell and S.P. FitzGerald
Randox Food Diagnostics, UK

P15  Detection and quantification of selected veterinary antimicrobials in poultry manure
Brecht Gorissen¹,², T. Reyns¹, M. Devreese², P. De Backer², J. Van Loco¹ and S. Croubels²
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P16  A study of the efficacy of Orego-Stim®, compared with virginiamycin, Zn bacitracin and salinomycin
Emma N. Graystone, L.J. Broom and L. Falconer
Meriden Animal Health, UK

P17  Use of ‘highest priority critically important antimicrobials’ in the Austrian poultry production
W. Obritzhauser¹, K. Fuchs², J. Raith¹ and Josef Köfer¹
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P18 Use of ‘highest priority critically important antimicrobials’ in Austrian dairy cattle
W. Obritzhauser\textsuperscript{1}, J. Raith\textsuperscript{1}, K. Fuchs\textsuperscript{2}, M. Trauffer\textsuperscript{1} and Josef Köfer\textsuperscript{1}
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P19 Antimicrobial susceptibility of Campylobacter jejuni isolates from animal production and meat in Chile
Lisette Lapierre, C. Vergara, J. Cornejo, C. Araya and B. San Martín
Faculty of Veterinary Sciences, University of Chile, Chile

P20 The antibiotic carbadox reduces bacterial richness and abundance of the swine gut microbiota
Torey Looft, H.K. Allen, T.A. Casey and T.B. Stanton
National Animal Disease Center, Agricultural Research Service, US Department of Agriculture, USA

P21 Quantification of antimicrobial usage in different animal species in Switzerland
L.P. Carmo\textsuperscript{1}, G. Schüpbach-Regula\textsuperscript{1}, C. Müntener\textsuperscript{2}, A. Chevance\textsuperscript{3}, G. Moulin\textsuperscript{3} and Ioannis Magouras\textsuperscript{1}
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P22 Surveillance and characterisation of antimicrobial resistance-encoding determinants in Escherichia coli cultured from diseased food-producing animals
Marta Martins\textsuperscript{1}, B. Martins Alves\textsuperscript{1}, F. El Garch\textsuperscript{2}, F. Woehrle\textsuperscript{2} and S. Fanning\textsuperscript{1}
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P23 CAMPYBRO EU project: control of Campylobacter in poultry without the use of antibiotics
Á. Martín\textsuperscript{1}, J. Mayot\textsuperscript{1}, M. den Hartog\textsuperscript{3}, Y. Carre\textsuperscript{4}, G. Molnar\textsuperscript{5}, F. Sánchez\textsuperscript{6}, A. Fernández\textsuperscript{7}, M. Tenk\textsuperscript{8}, M. Chemaly\textsuperscript{9}, D. Dory\textsuperscript{9} and Pedro Medel\textsuperscript{10}
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P24 Antibiotic resistance transfer during food production and preservation
Eva Van Meervenne\textsuperscript{1,2,3}, E. Van Coillie\textsuperscript{1}, N. Boon\textsuperscript{2}, F. Devlieghere\textsuperscript{3} and L. Herman\textsuperscript{1}
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P25 An evaluation of antibiotic use in cats and dogs in Switzerland
Cedric R. Muentener\textsuperscript{1}, A.C. Schönenerberger\textsuperscript{2} and K. Torriani\textsuperscript{3}
\textsuperscript{1}Institute of Veterinary Pharmacology, University of Zurich and \textsuperscript{2}Institute of Parasitology, University of Zurich and \textsuperscript{3}Federal Office of Food Safety and Veterinary Affairs, Switzerland
P26 Antimicrobial use in meat poultry production in Finland 2007-2012
Hannele Nauholz¹, E. Kaukonen², S. Nykäsenoja³ and P. Yli-Soini⁴
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P27 Danish experience regarding management of the risk associated with use of antimicrobials in pigs – effect of the Yellow Card Scheme
Elisabeth O. Nielsen¹, A.B. Kruse² and L. Alban¹
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P28 A mixture of capsicum and turmeric oleoresins improves performance of vaccinated broilers challenged or not with coccidiosis
Clementine Oguey¹, A. Casarin², M. Forat² and D. Zandstra¹
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P29 A protected blend of phytonutrients permits similar performance and better animal health compared to monensin in feedlot cattle
Clementine Oguey¹, F.M. Hagg², L.J. Erasmus³, R.H. van der Veen², E. Haasbroek³ and D. Zandstra¹
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P30 A protected blend of phytonutrients improves homogeneity and health of calves
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P31 Effect of the phage-derived endolysin PlyPl23 in controlling Paenibacillus larvae spread in apiaries – in vitro studies
Ana Oliveira, M. Leite, L. Melo, D.R. Luís, S.B. Santos and J. Azeredo Centre of Biological Engineering (CEB), Universidade do Minho, Portugal

P32 Antimicrobial resistance profile and rnd efflux pump expression of Acinetobacter baumannii clinical isolates
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P33 Antibiotic residue control program at Vion
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P34 Activities towards responsible use of veterinary antimicrobials in Czech Republic
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P35 Biosecurity and hygiene as an opportunity in reduction of antibiotic use
Esther Schonewille and I. Bräunig Lohmann Animal Health GmbH, Germany
P36  **Widespread distribution of antimicrobial resistance of *Salmonella* isolated from retail pork and humans in Northeastern Thailand**  
Nuananong Sinwat¹, Sunpetch Angkititrakul² and Rungrup Chuanchuen¹  
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P37  **Opinions of Dutch veterinarians on antimicrobial use in farm animals**  
David C. Speksnijder¹, D. Jaarsma³, T. Verheij⁴ and J.A. Wagenaar¹,⁵  
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P38  **Increase in resistance of *salmonella* from food to fluoroquinolones and cephalosporins – an overview over 10 years**  
Bernd-Alois Tenhagen, A. Schroeter, I. Szabo, C. Dorn, B. Appel, R. Helmuth and A. Käsbohrer  
Department Biological Safety, Federal Institute for Risk Assessment, Germany

P39  **MRSA in cattle in Germany**  
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Federal Institute for Risk Assessment, Department Biological Safety, Germany

P40  **The use of the ‘highest priority critically important antimicrobials’ in Austrian pig farms**  
Martine Trauffler⁴, W. Obritzhauser¹, J. Raith¹, K. Fuchs² and J. Köfer¹  
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P41  **GERMAP, the German report on antimicrobial use and resistance – why all these data?**  
Juergen Wallmann¹, H. Kaspar¹, W.V. Kern² and M. Kresken³  
¹Federal Office for Consumer Protection and Food Safety (BVL), Germany, ²Division of Infectious Diseases, University Hospital Freiburg, Germany and ³Antiinfectives Intelligence GmbH, Germany

P42  **The German national resistance monitoring (GERM-Vet) – resistance data over a period of 13 years on the example of *E. coli***  
H. Kaspar, U. Steinacker, K. Heidemanns, A. Roemer and Juergen Wallmann  
Federal Office for Consumer Protection and Food Safety (BVL), Germany

P43  **Oral vaccination against *Lawsonia intracellularis* shows similar growth performance as antibiotic medication**  
M. Schlepers¹, M. Steenaert², Nico Wertenbroek², H. van Beers-Schreurs¹ and M. Nielen¹  
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MULTIDRUG RESISTANCE IN ESCHERICHIA COLI ISOLATED FROM ONE-DAY OLD LEGHORN CHICKENS AND ITS PERSISTENCE THROUGHOUT CHICKEN LIFESPAN

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Increasing levels of bacterial resistance have been associated primarily with the inappropriate and excessive use of antimicrobials in animal production; however, factors influencing its rapid spread have not been thoroughly studied. In this regard, it is important to acknowledge that there is a continuous flow of resistant bacteria and resistance genes between different ecosystems (humans, animals, aquatic and terrestrial environment). The objective of this study was to assess the presence of multidrug resistance in strains of E. coli, a commensal bacterium of the intestinal microbiota, isolated from one-day old Leghorn chickens from two chicken farms, and the persistence of this resistance over the productive lifespan of birds. 25 one-day old white Leghorn chickens were used. Bacterial isolation was carried out using cloacal swabs analysed within 24 h from sampling. The first sampling was performed at the chicken house, 12 h after hatching. In addition, feeders, drinkers and chicken bedding were sampled. After the first sampling, the chickens were transferred to an experimental unit and the following samples were taken at 1, 2, 5, 6, 16, 25, 27, 28 and 29 weeks of age. Throughout the experimental period, the chickens received no antibiotic therapy. At each sampling time, two strains were isolated and susceptibility studies were performed using the plate dilution method (CLSI, 2012). Of all isolated strains, 46% showed multiple resistance to two or more antimicrobials. 15.3% showed resistance to tetracyclines and quinolones, 14% to tetracycline, quinolones and aminoglycosides, and 8.7% to aminoglycosides, quinolones, sulfonamides and chloramphenicol. These resistance profiles were also observed in strains isolated from the farm environment. There were no significant differences in the resistance profiles found in strains isolated until 29 weeks of age. Our results address the spread of bacterial multidrug resistance within a farm, particularly considering that intestinal E. coli acts as a reservoir of resistance genes and is constantly eliminated through faeces to the environment, effectively colonising newly arrived chickens. In this regard, the World Health Organization (WHO) notes that the rapid spread of bacterial resistance should be seen as an environmental problem and, moreover, resistance can persist during the productive life of animals, even in the absence of selection pressure exerted by antimicrobial therapy. These findings suggest that lowering the current levels of antimicrobial resistance is a long-term task, given the high persistence of resistance.
P2
MAPPING THE GLOBAL CONSUMPTION OF ANTIMICROBIAL IN LIVESTOCK

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In the United States, 80% of antimicrobials sales are for animal use. This figure is estimated to be double the amount of human prescription at the global scale. Variations in antimicrobial resistance levels across countries are attributable, in part, to differential patterns of antibiotic consumption but also to farming practices and to the level of intensification of the livestock production sector. Understanding these variations in consumption is essential to monitor the rise of resistance levels in both animals and humans. In this context, maps are essential tools for implementing rational-use policies, targeting surveillance efforts and providing a baseline for the future assessment of antimicrobial reduction objectives set by government, companies and international organizations. Here, using fine scale maps of the distribution of poultry, cattle and pigs, we estimated the global burden of antimicrobial use in livestock in 2010, predicted its geographical distribution and identified regional hotspots of antimicrobial consumption. We further projected the potential consumption and geographic distribution of antimicrobial use in Asia by 2030 as growth will drive an unprecedented development of the livestock production sector. The cornerstone of our methodology is to estimate the consumption of antimicrobial in milligrams per population correction units (PCU): a standardised livestock weight unit allowing comparison of antimicrobial consumption between different types of livestock. The number of milligram per PCU is derived from estimates of antimicrobial use in twenty one OECD countries using regression methods. These estimates are subsequently adjusted for each country in the world according to the farm size distribution as well as socio-economic indicators to reflect the level of intensification of the livestock production sector.
The Australian pig industry commonly uses antimicrobials to fight diseases, such as pathogenic Escherichia coli (E. coli) disease, that causes severe diarrhoea in weaner and suckling piglets. Piglet diarrhoea is a cause for substantial concern as significant production losses are experienced, including reduced growth rates, high medication costs and high levels of mortality and morbidity [1]. Antimicrobial resistance (AMR) limits the effectiveness of antimicrobials used to combat bacterial diseases in pigs as well as impacting human health. AMR genes can be transferred from pigs to humans, directly via cross transmission or indirectly via transfer of mobile genetic elements [2]. Increasing and indiscriminate use of antimicrobials can induce drug resistance and reliance on newer drugs (similar to higher importance drugs used for human health), and can lead to possible emergence of resistance clones with additional virulence factors, which would require immediate investigation [3]. The aim of this pilot study was to identify and determine virulence genes and AMR patterns of E. coli disease in South-eastern Australian pig herds. Faecal samples were collected off the floor from 6 farrow-to-finish farms over a 3-month period (August-October 2013) to determine pathogenic E. coli virulence genes and AMR patterns. From each farm 50 samples were collected, 10 from pre-weaned and 40 from post-weaned piglets. Selective culture for haemolytic and non-haemolytic E. coli was performed on Sheep blood agar and also by selective enrichment in Buffered-peptone water. DNA extractions were performed using the boiling technique and PCR were performed on 16S gene for E. coli isolate confirmation. Twenty-five isolates were randomly selected to test for common virulence genes, fimbriae genes (F4, F18) and entertoxin genes (STb, STA and LT) and AMR was performed using MIC testing. All isolates were 100% resistant to clindamycin and tilmicosin, with strong evidence of emerging resistance to penicillin, sulphaemethoxamine, apramycin and florfenicol across all 6 farms. All isolates were 100% susceptible to enrofloxacin and gentamicin. The most prevalent virulence genes were F18 and STb, which were present in 3 out of the 6 farms. There was also an indication of higher AMR patterns in farms where there was a presence of more virulence genes. AMR E.coli strains were present at farms displaying both clinical and sub-clinical cases of diarrhoea and in both pre and post-weaned piglets. Survival of these strains in the environment could possibly lead to further spread of infection and emergence of more virulent clones, warranting further investigation.

References
P4
REDUCED SOMATIC CELL COUNTS IN RESPONSE TO A STANDARDISED HIGH ACTIVITY PROPRIETARY GARLIC POWDER ADMINISTERED TO LACTATING COWS – A PILOT TRIAL

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Elevated somatic cell counts (SCC) during lactation could only be treated at the end of lactation with long acting intramammary preparations, usually with a host of antibiotics. Any attempt to treat the cow during lactation would mean discarding the milk. A herd with a persistently high SCC results in poor quality milk and lower returns for the farmer. In view of these issues, natural alternatives are constantly sought to better the health of cows and increase returns to the farmer. A standardised high activity proprietary garlic powder (IQP-AS-106-1) was administered in different concentrations to lactating cows in a research farm in New Zealand to assess its efficacy in lowering SCC in milk. Eighty cows with composite SCC over 300,000 cells/ml were selected and a random, stratified method was used to allocate them into 4 groups of 20 cows each. All groups at start of study had equal means. Quarters on these cows that were over 300,000 cells/ml were observed throughout the study. Group 1 was the control and was given water. Each cow in groups 2, 3 and 4 received 150, 300 and 450 ml, respectively of IQP-AS-106-1 dissolved in water. All cows were dosed for 5 days. SCC analyses were performed from the milk samples of all cows until 28 days after the last day of dosing. The efficacy of the dosing was evaluated by calculating the geometric means of the SCC in the observed quarters before and after dosing. Group 3 showed the best response with a 61% reduction of SCC after the last day of dosing versus 46 and 54% reduction in groups 2 and 4, respectively. Meanwhile, the control group had only 41% reduction of SCC. After just 3 days of dosing, groups 3 and 4 had their SCC reduced to below 300,000 cells/ml. No adverse events were reported during the study. This study showed that at 300 ml, IQP-AS-106-1 (a component in Vetrinol) was able to lower high SCC in cows during lactation to less than half of their starting SCC. Thus, further investigations in a larger study seem to be warranted to show herd-wide effects.
P5
IMPROVED FAECAL CONSISTENCY IN CALVES ADMINISTERED WITH STANDARDISED HIGH ACTIVITY PROPRIETARY GARLIC POWDER

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Neonatal calf diarrhoea is a major cause of economic loss in the dairy industry. Common practice on farms is to start treatment with oral rehydration solutions (ORS). Antibiotics are used when calves have elevated temperatures, an indication of viral or bacterial infection. Consistent use of antibiotics for treatment could potentially contribute to resistance and may alter ruminal and gut flora. Therefore, the objective of this study was to assess the efficacy of a standardised high activity proprietary garlic powder, IQP-AS-106-2 (a component in Vetrinol), as a natural alternative for the treatment of diarrhoea. Twenty-two male Holstein-Friesian calves, aged from 2 to 6 weeks, were randomised into 3 groups within 24 h of the first onset of diarrhoea: control group (CON), treatment group (VET) and oral antibiotic group (OAG). A daily dose of 20 ml IQP-AS-106-2 was administered orally to VET group for 5 days. All calves received their normal supply of ORS. Throughout the study, calves were weighed and rectal temperature was recorded. Calves appearance and faecal consistency were scored. Faecal samples that were normal (semi-formed or pasty), fluid (some solid) or watery (no solids) were assigned 1, 2 or 3, respectively. Faecal samples were collected and tested for E.coli K99, Cryptosporidium spp., rotavirus and coronavirus using Bovidiar, an on-site immunoassay test kit. There were no notable differences in body weight, rectal temperature nor appearance of calves in all groups over the 8 days. In faecal consistency score, 91% of the calves in the VET group recovered to normal consistency (score=1) compared to only 67% in the antibiotic group on day 8. Results also showed that there was more elimination of rotavirus in the VET group compared to the OAG group. There were no adverse events reported in the trial. The trial has identified clinically important findings, which warrant further research into the effects of IQP-AS-106-2 in calf diarrhoea.
OPTIMISATION AND IMPLEMENTATION OF AN ANALYTICAL METHODOLOGY FOR THE DETECTION OF TETRACYCLINE, OXYTETRACYCLINE AND CHLORTETRACYCLINE RESIDUES AND THEIR METABOLITES IN FEATHERS BY LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY

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Antimicrobials are currently widely used in poultry production to treat infectious diseases of bacterial origin. The introduction of these antimicrobial agents in production systems has created favourable conditions for the selection, propagation and persistence of antimicrobial resistant zoonotic bacteria. The available scientific information shows the importance of poultry production as a source of these resistant microorganisms, emphasizing the need to monitor and oversee this problem in a comprehensive way. For broiler chickens edible tissues there is enough information showing that the antimicrobials, after therapy completion may remain in tissues for varying times, and that respecting withdrawal times decreases the risk that concentrations of these drugs remain in food over admissible levels. However for sub products derived from poultry production as feathers there is few information in the literature. And in the form of feathers meal they can be used as additive in feeds of other species for being low cost alternative protein source. The objectives of this study were to optimise and implement an analytical methodology for the detection of six analytes, i.e. tetracycline (TC), oxytetracycline (OTC), chlortetracycline (CTC) and the metabolites 4-epi TC, 4-epi OTC and 4-epi CTC, in broiler chicken feathers by LC-MS/MS. Feathers free of residues where used. Blank samples were spiked at five level concentrations (20-40-60-80-100 µg/kg) with certified analytical standards; tetracycline-d6 was used as internal standard. Methodology developed by Berendsen et al. (2013) was taken as a reference. Two different extraction solvents were tested, EDTA-McIlvain buffer and EDTA-McIlvain buffer plus acetone (1:1). For sample clean-up, two SPE columns were compared, reverse phase hydrophilic-lipophilic balance cartridges (HLB OASIS™) and silica based cartridges (Sep-pack C18). Instrumental analysis was performed by HPLC-MS/MS (API 4000, AB Sciei), in Farmavet Laboratory, University of Chile. The analytical methodology showing best performance was the extraction with solvent EDTA-McIlvain buffer/acetone, and the clean-up with HLB OASIS™ cartridges. This sample treatment showed an average recovery of 101%. All the calibration curves in a range of 20-100 µg/kg showed a correlation coefficient (r) greater than 0.98. This recovery and linearity show that the method is suitable to detect three TCs antibiotics and their metabolites (six analytes) in feathers. In conclusion, the implemented methodology allows the recovery and detection of TC, OTC, CTC, 4-epi TC, 4-epi OTC and 4-epi CTC residues in chicken feathers in a range of 20-100 µg/kg. Therefore, it can be used for validation studies and other further studies in this matrix.

Acknowledgements
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IMPLEMENTATION OF AN ANALYTICAL METHODOLOGY FOR THE DETECTION OF OXYTETRACYCLINE AND EPI-OXYTETRACYCLINE IN CHICKEN CLAWS BY LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY

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The use of antimicrobials to treat bacterial infections has increased production by lowering incidence of infectious diseases and mortality, enabling consumers purchase products (meat and eggs) at reasonable price, good quality and safe. However, if these drugs are not properly used during production, residues may persist. In the case of edible tissues of broiler chickens, muscle and liver, there is information showing that antimicrobials after therapy completion remain in tissues for varying times depending on drug elimination kinetics and pharmaceutical formulation. In case of sub products derived from poultry production incorporated into the food chain as feed ingredient or consumed directly as chicken claws, there is little information. In the case of chicken claws, their structure favours the persistence of certain antibiotics as tetracyclines (TCs) at higher concentrations for longer times than the edible tissues, being potential sources of antimicrobial re-entry into the food chain, which represents a risk to public health. The objective of this study was to optimise and implement an analytical methodology for the detection and quantification of OTC and its metabolite 4-epi OTC in broiler chicken claws by LC-MS/MS. Claws free of residues were used as blank samples spiked at five concentrations (20-160 µg/kg) with certified analytical standards; tetracycline-d6 was used as internal standard. Six different modifications in the methodology were compared. Drug extraction applying or not, hydrolysis reagent tris(2-carboxyethyl)fosfin hydrochloride (TCEP) was assessed. Four different clean-up techniques were studied: defatting with hexane, centrifuging at 0°C, reverse phase hydrophilic-lipophilic balance cartridges (HLB OASISTM) and silica-based cartridges (Sep-pack C18). EDTA/McIlvaine buffer was used for residues extraction and 0.01 M oxalic acid in methanol was used as eluting solution. Instrumental analysis was performed by HPLC-MS/MS (API 4000, AB Sciex) in Farmavet Laboratory. Samples showing the best results were those centrifuged at 0°C and eluted in silica cartridges with an average recovery of 115.7% for spiked samples, and a correlation coefficient (r) over 0.98 for calibration curves. The use of hydrolysis reagent TCEP in sample extraction did not improve any average recovery (111.9%) and calibration curves correlation coefficients were below acceptable linearity (r= 0.8883). In conclusion, the methodology for detection of OTC and 4-epi OTC in chicken claws using SPE silica cartridges and centrifuging at 0°C allows recovery and quantification of these residues. Therefore, this method can be used for further studies of these residues in this matrix.

Acknowledgements

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REDUCTION OF ANTIBIOTIC USAGE IN ANIMALS: THE EFFECT ON ANTIMICROBIAL RESISTANCE IN INDICATOR E. COLI DERIVED FROM LIVESTOCK

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In 2008, a memorandum of understanding was signed by national authorities, private parties involved in animal production and the Dutch Royal Veterinary Association to accomplish a decrease in antimicrobial use in the major livestock producing sectors. In 2013, compared to 2007, a decrease of 63% in total sales of antibiotics licensed for therapeutic use was accomplished. This study focused on the resistance rates of commensal indicator E. coli from the gastro-intestinal tract for critically important antibiotics comprising 3rd generation cephalosporins and fluoroquinolones in relation to this marked decrease in antibiotic usage in animals in the Netherlands. Since 1998, a national monitoring programme on antibiotic resistance in animals has been implemented in the Netherlands involving broilers, slaughter pigs, veal calves and dairy cattle. The monitoring includes not only the indicator bacteria E. coli (this study), but also enterococci and foodborne pathogens (Salmonella and Campylobacter). Each year, E. coli isolates are cultured from faecal samples on MacConkey agar. One randomly selected isolate per sample is tested for antimicrobial susceptibility with broth microdilution according to ISO 20776-1: 2006. Proportions of acquired resistance are determined using epidemiological cut-off values as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Each E. coli isolate represents one flock of animals. In the period 2004-2010, the resistance rates against 3rd generation cephalosporins (cefotaxime) in broilers were high (9.7-20.9%), but remarkably decreased from 18.3% in 2010 to 2.7% in 2013. In slaughter pigs, veal calves and dairy cows, resistance against 3rd generation cephalosporins was continuously low in the last five years (0-4.6%). In contrast, resistance against fluoroquinolones (ciprofloxacin) did not decrease recently. In broilers, resistance against ciprofloxacin remained stable at a high level (50-60%). In veal calves, resistance decreased from 23.5% in 2011 to 5.6% in 2012, but increased again in 2013 to 8.5%. In both slaughter pigs and dairy cows, resistance levels against ciprofloxacin remained low in the last 4 years (0-1.7%). Furthermore, an overall decrease in resistance for most antibiotics in broilers, slaughter pigs and veal calves was observed. In conclusion, the decrease in consumption of antibiotics in food-producing animals in the Netherlands was probably the main reason for the overall decline in resistance rates in all animal species. However, resistance against fluoroquinolones is still undesirable high in some animal species, particularly broilers.
CAN LIVESTOCK-ASSOCIATED MRSA LEVELS IN VEAL CALF FARMS BE MODULATED BY REDUCING ANTIMICROBIAL USE AND BY APPLYING A CLEANING AND DISINFECTING PROGRAMME? EXPERIENCES FROM AN INTERVENTION STUDY

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To tackle the emergence of resistant bacteria, such as livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA), the Dutch government has been promoting a nationwide reduction in antimicrobial use (AMU) in food-producing animals since 2010. In this context, an intervention study was undertaken from 2010 to 2012. Fifty-one veal calf farms were followed up over 2 consecutive production cycles and assigned to one of 3 study arms: RAB farms reducing antimicrobials by protocol; RAB-CD farms reducing antimicrobials by protocol and applying a cleaning and disinfection program between cycles; and control farms without interventions. Nasal swabs were collected from farmers, family members and employees and from veal calves to assess MRSA carriage in week 0 and week 12 of the 2 cycles. A marked downward trend in AMU (daily dosages per animal per cycle (DDDA/C)) was observed over 4 pre-study production cycles and the 2 study cycles. This trend was comparable to the national AMU trends. Comparison of AMU before and during the study, showed 35% AMU reduction in RAB-CD farms, 24% in RAB farms and 15% in control farms. MRSA in calves increased considerably from week 0 to week 12, but more marked in control farms and RAB-CD farms than in RAB farms. MRSA steadily decreased over the 4 sampling moments in humans, not paralleling animal dynamics. Human MRSA carriage probability was 81% lower in RAB farms compared to control farms (OR=0.19, Wald p=0.001) while the difference between RAB-CD and control arms was not statistically significant. RAB-CD farms complied with the cleaning and disinfection programme but MRSA air loads evaluated through passive samplers were, surprisingly, twice as high compared to RAB and control farms. AMU was positively associated with MRSA in animals and humans during the study across study arms. A 2.2% increase in MRSA animal prevalence (β=0.22, p=0.17) and a 26% higher probability in the human study population for being MRSA positive (OR=1.26, p=0.065) per 10 DDDA/C increase were observed using mixed models. This work shows that reduced AMU is associated with a reduced MRSA carriage likelihood in veal calves and people working and/or living on veal calf farms. Longer follow up is needed to explore the effect of intervention measures such as AMU reduction. Cleaning and disinfection did not show to be an effective approach for reducing MRSA carriage in veal calf farms.
EVALUATION OF A PROJECT TO STIMULATE VETS AND FARMERS TO COLLECT MILK SAMPLES FOR DIAGNOSTIC TESTING

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The main objective of this project was to stimulate vets and farmers in the Netherlands to collect milk samples for determination of mastitis causing pathogens and antimicrobial susceptibility testing. With more and more focus on prudent use of antibiotics, diagnostic testing will become more important. Boxes (245) with materials for milk sample collection and shipment were provided through vet clinics to farmers. Samples from both clinical mastitis and subclinical cases were accepted. Bacteriological culture of the samples was performed according standard procedures of the laboratory. After identification of the mastitis causing pathogen, antimicrobial susceptibility testing was performed (according CLSI in 2012 and EUCAST in 2013). Mastitis pathogens were tested against first and second choice antibiotics according the Dutch formularium. The antibiotics (panel) tested depended on the pathogen. The susceptibility for cefalexin+kanamycin combination was only tested in case of Escherichia coli, Staphylococcus aureus, Streptococcus uberis, Streptococcus dysgalactiae and coagulase negative staphylococci (CNS). 52 veterinary practices submitted 792 samples from 167 dairy herds. 69% of the boxes were submitted for diagnostic testing. E. coli, S. aureus, S. uberis, S. dysgalactiae were found in 50% (393/792) of the milk samples. The overall susceptibility for all pathogens to 1st and/ or 2nd choice antibiotics was good in general (94-100%). Only in case of penicillin high resistance was found in CNS (38%) and S. aureus (16%), and in case of ampicillin there was some level of resistance for E. coli (19%). The cefalexin+kanamycin susceptibility of E. coli, S. aureus, S. uberis, S. dysgalactiae and CNS was 93, 98, 94, 100 and 98%, respectively. The submission rate of milk samples in this project was high and shows that there is an interest of veterinary practices to send in milk samples for diagnostic testing when offered the opportunity. Some mastitis pathogens show high levels of resistance against 1st choice antibiotics, which supports the growing importance of diagnostic testing to judiciously use antibiotics.
WELFARE (FINDINGS AT SLAUGHTER) CONSEQUENCES FOLLOWING A REDUCTION IN ANTIBIOTIC USE

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During 2010, the Danish authorities introduced legislation subjecting pig herds with high antibiotic (AB) usage to fines and regulation. The following year overall use of AB dropped by ~25%. Hence, the aim of this project was to determine if this decrease had affected animal welfare in finishers, measured as prevalence of pathological findings and dispersion of lean mean percent (LMP). This would reflect higher variation in growth rate which may indicate a higher prevalence of disease. Herds with an AB consumption of >3.5 kg active compound in the year before June 2010 and a reduction in AB consumption of >10% the following year were randomly selected from the national database, Vetstat. Organic and outdoor herds, herds that had suffered severe disease outbreaks, performed eradication programs or made any other major changes during the study period were excluded. AB consumption was calculated as gram active compound AB/pen places and as average number of daily doses given per 100 animals per day (ADD/100 animals/day). Data on number of animals produced, pathological findings and LMP at slaughter were collected. Multi-level models for binary outcome were performed to test for differences (significance level 95%) (PROC GLIMMIX, SAS Enterprise Guide 4.3). The 65 participating herds averagely sent 11201 finishers to slaughter (std dev 5569). AB consumption decreased 55% in the year following June 2010 regardless of calculation method (g/pen place: 12.1 to 4.9; ADD/100 animals/day: 5.8 to 2.3). In the year following June 2010, a significant increase was observed in the proportion of finishers at slaughter with abscesses (2.9% to 4.4%; p<0.001) and with osteomyelitis (0.3% to 0.5%; p<0.001). There was no significant difference between LMP before and after June 2010 (60.2 to 60.3%; p=0.36) or between standard deviation of LMP within each herd (2.4; 2.5; p=0.68). In a similar study in 53 weaner herds (7-30 kg pigs) a significant 25% increase in mortality was observed (2.4% to 4.0%; p<0.001). Herds with a consumption ≥25ADD/100 animals/day in the year before June 2010 had a significantly higher increase in mortality compared to herds with a lower AB consumption (p=0.04). In conclusion, the 52 and 67% significant increase in the proportion of pigs with abscesses and osteomyelitis, suggest that a reduction in AB consumption may affect animal welfare.
P12
ROSEN’S TEST TO OBJECTIVELY EVALUATE B SAFE FEED ADDITIVE IN POULTRY AND SWINE

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Number and diversity of growth promoting feed additives available for animal feed have intensely increased during last decades. In the meantime, improvement of technical and economical performances remains a major objective for farmers. Therefore, it is necessary to define which additive is reliable and evaluate objectively its benefits on zootechnical performances and economical return on investment. One impartial solution is submitting the feed additive results to the Rosen evaluation (Rosen, 2004). Indeed, the model contains 7 criteria to determinate if a growth promoting product can be considered as an efficient feed additive. The 7 criteria evaluate the reliability of the data, performance improvement and reproducibility of the effects. B-SAFE is a natural growth promoter based on patented technology: activated copper exchanged on specific clay. Thus, B-SAFE secures digestive process and allows daily weight gain (DWG) and feed conversion ratio (FCR) improvement. For poultry, B-SAFE achieves 6 out of the 7 Rosen’s criteria and leads to an increase of +2.9% on DWG and a decrease of -1.8% on FCR. Globally, B-SAFE improves zootechnical performances in 74% of case (36 R&D and field trials carried out). For swine, B-SAFE achieves 5 out of the 7 Rosen’s criteria and allows an increase of +5.0% on DWG and a decrease of -1.9% on FCR. In average, B-SAFE improves zootechnical performances in 78% of case (27 R&D and field trials carried out). Thanks to the Rosen’s analysis, B-SAFE proved that it is an efficient and reliable natural growth promoter feed additive. The large number of trials set up all over the world demonstrates also that B-SAFE is a cost effective solution in broad spectrum of situations.
Enteric colibacillosis is a common disease in weaning pigs caused by pathogenic *Escherichia coli*. The control relies on antibiotics, but due to elevated antibiotic resistance in bacteria from food animals some safer and natural alternatives are pursued, including the use of bioactive plants [1]. Several Australian plant essential oils (EO) were found to be active against pathogenic gut microbes common to humans [2] and ruminants [3] but have not been tested on *E. coli* from pigs. Seven EO and five associated essential oil compounds (EOC, Table 1) were examined against pathogenic (O149:K88, pE. *coli*) and saprophytic (sE. *coli*) strains using an agar dilution method [2]. Briefly, a dilution series ranging from 0.5-20 mg/ml was prepared in melted agar, poured and allowed to solidify prior to inoculation. Minimum inhibitory concentration (MIC) was defined as the lowest concentration of EO/EOC that prevented visible growth of bacteria. Five EO and two EOC were active at concentrations of 5 mg/ml, while two EOC had a MIC of 1 mg/ml (Table 1). There was no selective effect of any of the treatments towards pE. *coli* only. In conclusion, five Australian EO and associated EOC inhibited pathogenic *E. coli* from pig gut, but the effect was not selective under the conditions tested. The potency of EO was similar to that in observed previously in the ruminant *E. coli* [3], and part of the activity was linked to their major EOC. Plant derivatives reported here have potential to assist or replace antibiotics in the prevention/therapy of enteric colibacillosis in pigs. Further study will determine appropriate doses, selectivity, application and potential toxicity in vivo.

<table>
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<th>Treatment</th>
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<td>Geraniol</td>
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* Plant imported to Australia.

References
P14

THE APPLICATION OF BIOCHIP ARRAY TECHNOLOGY TO THE BROAD DETECTION OF ANTIBiotic RESIDUES IN DIFFERENT MATRICES FROM FOOD PRODUCING ANIMALS

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Though antibiotics contribute to animal health and welfare, the use of veterinary drug residues in food producing animals is globally restricted and an important topic in food safety. The emergence of problems, such as antibiotic resistance, has led to growing concerns for public health. High levels of food imports have increased the need for reliable, efficient and user-friendly screening methods. Biochip array technology allows the simultaneous screening of multiple veterinary drug residues from a single sample. This consolidates testing and reduces the quantity of samples to be assessed by confirmatory analysis. This study reports the applicability of biochip arrays to the multiplex screening of antibiotic residues in different matrices from food producing animals. For the determination of residues, simultaneous chemiluminescent competitive immunoassays are employed for each biochip array. The biochip represents the platform where the capture molecules define microarrays of discrete test regions (DTRs). The biochip is also the vessel where the reactions take place. The reactions are detected by chemiluminescence and the light emitted in each DTR is simultaneously detected and quantified using digital imaging technology. The immunoassays were applied to the semi-automated bench-top biochip analyser Evidence Investigator. The system incorporates dedicated software to process and archive the multiple data generated. The beta-lactam antibiotics array detected penicillins and cephalosporins in milk with a limit of detection (LOD) value of 0.6 ppb for ampicillin. Four antimicrobial biochip arrays detected respectively: (i) sulphonamides and trimethoprim (LOD range: 1.6-10.0 ppb in tissue, 1.6-20.0 ppb in honey, 0.5-2.5 ppb in milk); (ii) ceftiofur, quinolones, streptomycin, tetracyclines, thiamphenicol, tylosin (LOD range: 0.9-14.0 ppb in tissue, 1.0-5.0 ppb in honey, 0.5-2.5 ppb in milk, 0.5-7.0 ppb in urine); (iii) nitrofurans (AHD, AMOZ, AOZ, SEM) chloramphenicol and chloramphenicol glucuronide (LOD range: 0.06-0.2 ppb in prawn/shrimp, 0.06-0.4 ppb in beef/pork/poultry, 0.08-0.5 ppb in honey); and (iv) aminoglycosides, lincosamides, macrolides, polymyxins and streptogramins (LOD range: 1.0-8.0 ppb in honey). The intra-assay precision values of all the immunoassays, expressed as %CV were typically <12%. In conclusion, different biochip arrays enable multiplex screening of residues from a single sample and are applicable to different matrices. Biochip array technology is applicable to the simultaneous screening of multiple veterinary drug residues on one platform. This methodology enhances the scope of tests and the test result output.
P15
DETECTION AND QUANTIFICATION OF SELECTED VETERINARY ANTIMICROBIALS IN POULTRY MANURE

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The most important source of Salmonella infection in humans is through consumption of contaminated poultry products. Due to the risk of resistance development, the Belgian legislation introduced the Royal decision concerning the eradication of Salmonella (C – 2007/22784), which prohibits treatment of poultry with antimicrobials against zoonotic Salmonella. Nowadays, illegal use of these antimicrobials is determined through analysis of tissue samples of sacrificed animals. An analytical method using UPLC-MS/MS for the quantitative and reliable determination of antimicrobial residues in non-invasive samples of poultry manure was developed including beta-lactams (amoxicillin, phenoxymethylpenicillin), fluoroquinolones (enrofloxacin, difloxacin, flumequine), sulfonamides in combination with trimethoprim (sulfachloropyridazine, sulfadiazine, sulfadiazine) and tetracyclines (chlortetracycline, doxycycline). Extraction of samples was carried out by means of ultrasonication and vortex mixing using a combination of acetonitrile and McIlvaine buffer as the extraction solution, followed by centrifugation and filtration for subsequent analysis. Structurally related internal standards were used to correct for compound losses and matrix interferences during extraction and analysis. Samples were analysed on a Waters Xevo™ TQ-S triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA). During validation the performance characteristics of the developed method were determined in terms of limit of quantification, limit of detection, precision, trueness, linearity, specificity and matrix effect. All results fell within the acceptance criteria mentioned in Commission Decision 2002/657/EC.

An animal experiment with twelve laying hens was conducted to gain preliminary insight into faecal excretion of the selected compounds. For each antimicrobial class, one active compound was selected and administered by route of drinking water during five subsequent days, with dosages calculated according to prescriptions. Manure samples were collected every twelve hours before, during and after treatment. The developed method was applied in the determination of target compounds in these samples, with quantification of concentrations up to 41.78 µg/g (difloxacin), 19.5 µg/g (sulfachloropyridazine), 3.23 µg/g (trimethoprim), 25.05 µg/g (doxycycline) and 2.72 µg/g (amoxicillin). Further analysis and animal experiments will be carried out to determine the stability of the compounds in manure as well as the post-administration period within which it is possible to accurately detect the antimicrobial residues. This will eventually lead to recommendations concerning the ideal circumstances for sampling and sample storage to the concerned authorities, and a possible implementation of the developed method in the national Salmonella control programme.
A STUDY OF THE EFFICACY OF OREGO-STIM®, COMPARED WITH VIRGINIAMYCIN, Zn BACITRACIN AND SALINOMYCIN

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There is an increased demand for meat and animal-related products as a result of a growing and more prosperous world population. In addition to this, animal producers must have viable businesses. These factors contribute to the need to increase productivity, whilst improving the efficiency with which this is achieved. Historically, even within the European Union (EU), the use of antibiotics as growth promoters (AGPs) has been an established method for overcoming this challenge. However, due to increasing concern over the resistance to antibiotics, the use of AGPs has been/is under very serious scrutiny. AGPs were finally banned within the EU in 2006 and their use in various other countries of the world is currently under serious review or in the process of being prohibited. It is, therefore, clear that alternative methods of consistently improving productivity and efficiency are required.

Interest in the use of essential oils to improve the health and productivity of farmed animals continues to increase. The objective of this study was to compare the effectiveness of an oregano-based essential oil product (Orego-Stim®) with an AGP and coccidiostat combination in broilers. A total of 1,710 day old broiler chicks (farm’s own strain) were randomly divided into 19 pen replicates with 90 chicks per pen. Birds were fed standard wheat-soy diets formulated to meet their nutritional requirements and were allocated 750 g feed per bird of the starter diet and thereafter, fed the grower diet through to the end of the trial. There were two treatment groups. Nine replicates were fed the basal diet supplemented with virginiamycin (20/15 mg/kg; starter/grower), Zn bacitracin (50 mg/kg) and salinomycin (60 mg/kg). Ten replicates were fed the basal diet plus Orego-Stim® (300 mg/kg in both the starter and grower diet), which contained no AGPs or coccidiostats. Water was available ad libitum throughout the trial. Performance, including mortality, was monitored throughout the 37 day trial period. Data were subject to statistical analysis via a one-way ANOVA test. Final broiler live weight, FCR and mortality were not different between control and Orego-Stim® supplemented birds (p>0.05), confirming that Orego-Stim® was equally as effective as the AGP/coccidiostat combination. With the use of antibiotics as growth promoters subject to ever-increasing scrutiny and prohibition, the essential oil based product, Orego-Stim®, offers the potential to maintain broiler health and performance as well as producer profitability.
P17
USE OF ‘HIGHEST PRIORITY CRITICALLY IMPORTANT ANTIMICROBIALS’ IN THE AUSTRIAN POULTRY PRODUCTION

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The use of antibiotics in livestock is under growing criticism in the context of human health risks caused by multi-resistant bacteria. The World Health Organization classified macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptide antibacterials as ‘highest priority critically important antimicrobials’ (HPCIA). These substances are considered essential for the treatment of specific human infections with a high absolute number of people affected, for which no or only few therapeutic alternatives exist. The usage of HPCIA in farm animals must be minimised in order to save their efficacy for treatment in humans. There is insufficient information about the use of HPCIA in poultry production. To calculate the consumption of HPCIA in the Austrian poultry production data from the Austrian ‘Poultry Health Database’, in which diagnoses as well as the quantity of drugs prescribed in member farms of the ‘Poultry Health Service’ were recorded by the attending veterinarian, were used. The dataset provided medication records of antimicrobials of 1,994 poultry farms within the period from 2008 to 2011. The production of poultry (in total), broilers and turkeys was 84,025 tons, 47,754 tons and 10,643 tons per year, respectively. The antimicrobial consumption was specified using the ‘number of product-related daily dose per kg biomass’ (nPrDD/kg) as the unit of measurement. The PrDD was defined for each veterinary pharmaceutical product as the maximum dose recommended by the manufacturer and adjusted by a factor of 0.8. The number of PrDDs was referred to the produced biomass per year (nPrDD/kg/year). The total consumption of antimicrobials in poultry production (in total), broilers and turkeys was 1.62, 1.58 and 3.85 PrDD/kg/year, respectively. The HPCIA (macrolides and fluoroquinolones; cephalosporins must not be applied to poultry in Austria) summed up to 0.71 PrDD/kg/year in broilers and 1.22 PrDD/kg/year in turkeys. A proportion of 38% of the total number of PrDDs in poultry production was related to HPCIA. The main indications specified in the prescriptions of HPCIA were general bacterial infections and infections caused by clostridia. The results of this study emphasise the need for drug consumption data at an on-farm, sector and diagnostic level in poultry production. Valid data of the use of antibiotics allow further investigations about the impact of HPCIA consumption on the development of antimicrobial resistance.
P18

USE OF ‘HIGHEST PRIORITY CRITICALLY IMPORTANT ANTIMICROBIALS’ IN AUSTRIAN DAIRY CATTLE

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The use of antibiotics in farm animals triggers the public debate concerning the growing threat of antimicrobial resistance. Macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptide antibacterials, which are declared as 'highest priority critically important antimicrobials' (HPClAs) by the World Health Organization, are essential for the treatment of severe human infections, in which no or only few therapeutic alternatives exist. Thus the usage of HPClAs in livestock must be minimised in order to save their efficacy in human medicine. In dairy cattle, 3rd and 4th generation cephalosporins are frequently used due to their broad antimicrobial effect and their poor penetration into milk, which leads to short withdrawal periods for raw milk. The study at hand should fill the information gap regarding the amount and frequency of use of HPClAs in dairy cattle in Austria. Within a project for the modelling of antimicrobial consumption in farm animals in Austria 8,027 prescription data of 465 dairy herds were provided by 11 veterinary practices during 2008 to 2010 to estimate the use of antimicrobials in the Austrian dairy cattle population. The number of cattle kept by treated herds equated to 17,267 livestock units (LU). The antimicrobial consumption was expressed as the 'number of product-related daily dose per LU' (nPPrDD_{LU}). To derive a PrDD_{LU} value for each veterinary pharmaceutical product, the maximum dose according to the SPC was considered and adjusted by a factor of 0.8. The PrDD_{LU} for intramammary preparations was derived according to the manufacturers recommended dosage without any correction. The nPrDD_{LU} was related to the livestock units kept in the study population per year (nPPrDD_{LU}/LU/year) and finally corrected by the proportion of untreated herds. The variation of nPrDD_{LU}/LU/year was quantified by calculating the lower and upper quartiles by Monte Carlo simulation techniques. The total consumption of antimicrobials for systemic use in the study population was 1.27 PrDD_{LU}/LU/year (median). Part thereof, namely 0.31 PrDD_{LU}/LU/year (25%) were categorised as HPClAs, primarily 3rd and 4th generation cephalosporins (0.22 PrDD_{LU}/LU/year), which were most frequently used for the therapy of udder diseases (69%) and diseases of claws and legs (20%). Monitoring the antimicrobial consumption in association with diagnostic data on an on-herd level gives valuable information about prudent use of HPClAs and serves as a basis for further research on the impact of use of antibiotics on antimicrobial resistance.
P19

ANTIMICROBIAL SUSCEPTIBILITY OF CAMPYLOBACTER JEJUNI ISOLATES FROM ANIMAL PRODUCTION AND MEAT IN CHILE

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The responsible use of antibiotics in animal production should be aimed to improve sanitary status of the flock ensuring that the food products intended for human consumption are safe, looking after environmental sustainability. The main consequences of introducing antimicrobial agents in productive systems are the favourable conditions for selection, propagation and persistence of antimicrobial resistant zoonotic bacteria that can be transferred to man and into the environment. Risk increases when these resistant strains are foodborne pathogens causing severe gastroenteritis in humans, such as Campylobacter jejuni. The objective of this study was to isolate C. jejuni strains from food-producing animals’ faeces (chickens, turkeys and cattle) and their edible tissues to assess their susceptibility to five antimicrobials used for the treatment of infections in human patients. Strains were isolated following the recommendations of World Organization for Animal Health (OIE); for meat samples, the Bacteriological Analytical Manual (BAM, FDA) protocols where used. All the isolated strains were analysed by the minimal inhibitory concentration technique (MIC) described by the Clinical and Laboratory Standards Institute (CLSI) for the following antibiotics: ciprofloxacin, erythromycin, gentamicin, nalidix acid, and tetracycline. 65 chicken, 64 turkey and 56 cattle strains were isolated from faeces. In meat samples, the number of strains isolated for poultry, turkey and beef were 25, 29 and 17, respectively. For these isolated strains, the percentages of resistance were respectively: ciprofloxacin 68.4, 67.2 and 5.3% (faeces), 12, 24.1 and 0% (meat); erythromycin 77.7, 21 and 1.6% (faeces), 12, 41.3 and 0% (meat); nalidix acid 52, 78 and 18.5% (faeces), 25, 86.2 and 11.7% (meat). None of the isolated strains was resistant to gentamicin. These results show high percentages of antibiotic-resistant strains, particularly in chicken and turkey samples, probably to high selection pressure because of the density of the populations in the productive systems. The lower percentages observed in meat can be attributed to the slaughter and food process. In conclusion, the results obtained show the importance of responsible and sustainable use of antibiotics in food-producing animals to reduce the resistance to antibiotics used in both veterinary and human medicine, especially in zoonotic foodborne pathogens, such as C. jejuni.

Acknowledgements
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P20
THE ANTIBIOTIC CARBADOX REDUCES BACTERIAL RICHNESS AND ABUNDANCE OF THE SWINE GUT MICROBIOTA

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A variety of antibiotics are used prophylactically and therapeutically in food animal production, and their widespread use has raised concerns about the spread of antimicrobial resistance. Although prohibited in the European Union (EU), carbadox is one of the most commonly used antibiotics in the US swine industry, employed for both disease prevention and improving feed efficiency. The objective of this study was to characterise changes in the intestinal microbiota due to carbadox and following its withdrawal in swine. Starting at three weeks of age, six pigs received feed containing carbadox (50 g/ton) and six received unamended feed. After three weeks of continuous carbadox administration, all pigs were switched to a maintenance diet without carbadox. Faecal DNA was extracted (n=142) from samples before, during, and six weeks after withdrawing carbadox treatment. Phylotype analysis targeting 16S rRNA gene sequences showed that feeding carbadox had immediate effects, with significant alterations in both community structure and bacterial membership, notably a large relative increase in Prevotella populations in medicated pigs. Digital PCR analyses, however, demonstrated that the absolute abundance of Prevotella was unchanged between the medicated and non-mediated pigs, an indication that differences were due to a reduction in total bacteria rather than increases in absolute numbers of Prevotella. Bacterial species richness was significantly reduced after four days of continuous carbadox administration, confirming that the bacterial load was reduced albeit temporarily. Carbadox therefore caused a reduction other gut bacteria but did not affect the absolute abundance of Prevotella. After both pig groups were switched to a maintenance diet, E. coli viable populations bloomed in non-mediated pigs but not in pigs previously fed carbadox, suggesting that carbadox pretreatment prevented an increase of E. coli populations. We are currently evaluating the effects of alternative non-antibiotic feed additives on swine growth performance and microbiota composition using similar analyses. These results demonstrate that the swine gut microbiota was initially disturbed by carbadox, but the overall microbial community structure recovered despite the continued presence of carbadox. Defining how in-feed antibiotics shape gut bacterial communities will lead to an understanding of microbial changes associated with improved production efficiency, which could identify potential targets for modulation to promote animal health.
P21
QUANTIFICATION OF ANTIMICROBIAL USAGE IN DIFFERENT ANIMAL SPECIES IN SWITZERLAND

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Veterinary antimicrobial (AM) usage has often been considered to contribute to the emergence of antimicrobial resistance, which may be transferred to humans. However, evidence on this link is limited. A fundamental piece to evaluate this association is to measure AM usage per animal species and relate it to the development of AM resistance in each species. Only a few countries have established a prescription based monitoring, which enables such usage stratification. In most European countries, Switzerland included, solely statistics on total sales per AM class are available, without any information on the animal species. With this in mind, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) highlighted in their last reflection statement the need to detail AM sales data with respect to animal species within the next few years. To achieve this aim new approaches are required. In Switzerland, sales data on a package level are available from 2006 onwards. Products licensed for a single species are easily attributed. For the ones which can be used in multiple species, five different repartition methods will be applied and the results compared. For the first approach, the number of different animal species to which a certain product is licensed will be determined using the Swiss Veterinary Drug Compendium. The amount of product sold will then be equally distributed between the different species. The second model aims to partition the AM used based on the total body mass of the different animal species. For the third model, Marketing Authorization Holders (MAH) will be consulted to provide an estimate of the product distribution per species. In case these data are not possible to access, Periodic Safety Update Reports (PSUR’s) will be used to design the fourth approach, since these reports contain an estimate made by the MAH about the sales distribution per species. Finally, for the last approach, a Bayesian method will be implemented. The distribution of each product sales per animal species will be based on prescription data from a previous field study (2004-2005). The results of this study might provide new options to quantify veterinary AM usage per animal species. Furthermore, in Switzerland, a surveillance programme on AM resistant bacteria in food animals is implemented since 2005. Combining the results from these models with surveillance data, will make it possible to analyse temporal trends of AM resistance with respect to AM usage in different animal species and for specific bacteria.
Multi-drug resistant (MDR) bacteria pose a major threat to public health. Some antimicrobial compounds widely used in animal therapy belong to the same chemical families that are used for human treatment. Surveillance studies from different countries generally report an increase in the level of resistance to the major classes of antibiotics used for the treatment of livestock and companion animals. In this study, 150 *Escherichia coli* strains were isolated from adult bovines, which have not been treated by antibiotics 3 weeks before sampling and these were sourced in two countries, France and Germany during 2004, 2007 and 2010. The isolates were all obtained from sick animals presenting with either diarrhoea or mastitic infections. Antimicrobial susceptibility tests (AST) were performed using 17 different antibiotics (representing 9 different classes) used in animal and human medicine. These included: amoxicillin, amoxicillin/clavulanic acid (penicillins and penicillins combinations); cephalothin, cefoxitin, cefotaxime, cefepime (cephalosporins); ertapenem, meropenem, imipenem (carbapenems); marbofloxacin, ciprofloxacin, nalidixic acid ((fluoro)quinolones); gentamicin (aminoglycosides); tetracycline (tetracyclines); colistin (polypeptides); florfenicol (phenicols) and trimethoprim/sulphamethoxazole (sulfonamides). AST results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (M31-A3 and M100-S23) when possible. 

*E. coli* ATCC 25922 was also included as a control strain for quality control purposes. Resistance to amoxicillin (44.7%; n=67) and tetracycline (43.3%; n=65) was prevalent. No resistance to cefepime or any of the carbapenems (meropenem, imipenem, ertapenem) was detected. These data highlighted that resistance to trimethoprim/sulphamethoxazole was the third most prevalent (n=33; 22%), followed by the (fluoro)quinolones, nalidixic acid (n=24; 16%), ciprofloxacin (n=16; 10.7%) and marbofloxacin (n=15; 10%). AST profiles were further analysed and compared using the BioNumerics Character data module (version 7.1: Applied Math, Belgium). A major cluster was noted and this was related with cultures taken from diarrhoea cases. These showed an increased profile of resistance when compared with those isolates from the mastitis cases. When analysing the samples sourced from France or Germany no major differences were observed. Similarly the year-on-year trends showed no clear differences. Some 47 bacterial isolates, were defined with a multidrug resistant phenotype, wherein these showed resistance to more than 3 different classes of antibiotics. Monitoring the development and emergence of antibiotic resistance among bacteria of food-producing animal origin is important. Extending our understanding of the factors that contribute to the development of resistance in animals and uncovering transmission routes is essential to protect veterinary public health.
P23
CAMPYBRO EU PROJECT: CONTROL OF CAMPYLOBACTER IN POULTRY WITHOUT THE USE OF ANTIBIOTICS


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Campylobacteriosis is the most important zoonosis in the European Union (EU) [1], with 214,268 cases reported in 2012, and an average of 55.5 cases per 100,000 inhabitants. The actual incidence is estimated 9 million cases and a cost of 2,400 million €/year in the EU. 20-30 % of human cases of campylobacteriosis can be contributed to (bad) preparation and/or consuming of chicken meat, while 50-80% of the human cases of campylobacteriosis can be contributed to the chicken reservoir as a whole. Campylobacteriosis is produced by Campylobacter spp. The most important species are C. jejuni and C. coli. The European Commission had launched a workshop among Member States (MSs) and stakeholders to assess the possibility of introducing a microbiological criterion in chicken meat. Because the poultry sector wants to produce the best possible products, it is necessary to develop efficient tools to control these bacteria, which is present in 71% of broilers batches as average in the EU [2]. The sector wants to use the least possible amount of antibiotics. Controlling campylobacter with antibiotic therapy does not seem advisable: in Europe (average of 10 MSs), the rates of strains resistant to ciprofloxacin, erythromycin, gentamycin, nalidixic acid and tetracycline were 44.1, 0.4, 0.7, 41.4 and 34.1% for C. jejuni, and 78.4, 11.2, 4.1, 75.7 and 73.1% for C. coli, respectively. In Spain, the resistance rate for ciprofloxacin was 96.9 and 96.3% for C. jejuni and C. coli, respectively. In this context, the project ‘Control of Campylobacter infection in broiler flocks through two-steps strategy: nutrition and vaccination’ (CAMPYBRO; http://campybro.eu) has established two paths to try to decrease the level of infection without the use of antibiotics: a long-term strategy based in a vaccine development through reverse vaccinology, and a short-term strategy based on nutrition. The nutritional strategy is based in detecting the best combinations of additives that decrease the caecal counts in vivo with the most adverse feed form for the bacteria (playing with cereal type, level of fibre, whole grains, mash vs. pellet form). CAMPYBRO has been funded by the 7th Framework Programme of the EU (FP7-SME-2013-605835). The partners are the associations of chickens in Spain (Propollo), France (FIA and CIDEF), the Netherlands (NEPLUVI) and Hungary (BTT), a producer of poultry (Explotaciones Avícolas Redondo), a specialised vaccine laboratory (CZ Veterinary), an analysis laboratory (Mikrolab), and two research centers (ANSES in France and Imasde Agroalimentaria S.L. in Spain), and will be developed between 2013 and 2016. The project will be coordinated by Imasde Agroalimentaria S.L.

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ANTIBIOTIC RESISTANCE TRANSFER DURING FOOD PRODUCTION AND PRESERVATION

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Antibiotic resistance is a worldwide public health problem. There are strong indications that the use of antibiotics in primary production contributes to human infections with antibiotic resistant bacteria. Food serves hereby as an important vector. The contribution of food production and preservation to antibiotic resistance transfer by plasmids was studied in biofilms and during preservation by low temperature and modified atmosphere packaging (MAP). Biofilms can represent a persistent source of contamination in the food industry. Moreover, these structures are considered as hotspots for plasmid transfer, whereby they can contribute to the dissemination of antibiotic resistance. In this study, the transfer of a multiresistance plasmid was examined in biofilm models, representative for the food industry. Two flow configurations, two inoculation strategies and three attachment materials were applied. Pseudomonas putida served as donor and Escherichia coli as recipient. High transfer ratios (number of transconjugants per total cell number) were obtained, which could reach an order of magnitude of $10^{-1}$. The effect of two preservation techniques, low temperature and MAP was studied in a Gram-positive model with Lactobacillus sakei subsp. sakei as donor and Listeria monocytogenes as recipient. Transfer of plasmids containing antibiotic resistance genes was observed in a temperature range between 10 and 37°C. However, the lower limit could be decreased by extending the incubation period. To examine the effect of modified atmosphere three gas compositions (air, 50% CO₂/50% N₂ and 100% N₂) were applied. When high inoculum densities were used, plasmid transfer was observed under each condition, both on agar plates and on slices of cooked ham. To simulate a more realistic situation, plasmid transfer was also analysed on cooked ham with low inoculum densities. Transfer was observed only under one condition (100% N₂) after ten days. In the MAP experiments, the transfer ratio (number of transconjugants per number of recipients) was of the order of magnitude of $10^{-4}$-$10^{-6}$. It should be noted though that transfer was only observed with donor and recipient densities which exceeded the food safety criteria or guidelines. In this work, it became clear that biofilms are not only a source of contamination in the food industry, but the risk of antibiotic resistance dissemination by plasmid transfer in biofilms should also be acknowledged. Furthermore, two commonly used preservation techniques which prevent bacterial growth in the food industry, do not necessarily seem to prevent plasmid transfer.
AN EVALUATION OF ANTIBIOTIC USE IN CATS AND DOGS IN SWITZERLAND

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Sales data of veterinary antimicrobials are a valuable tool to identify trends over time but do take neither potency of the active ingredients nor duration of therapy into account. Therefore, they do not directly reflect data on actual use and are difficult to correlate with monitored bacterial resistances. As no data on actual usage is available in Switzerland, we extrapolated sales to number of potential treatments, using Animal Course Dose (ACD; ANSES, France) as a technical unit expressing the total amount of antimicrobials applied to an animal during one complete therapeutic course. ACD is obtained by multiplying the highest daily dose with the longest therapy duration taken from the marketing authorisation of each product. The concept was applied to products for oral use with additional data on injectable critically important antimicrobials whenever possible.

In the year 2013, 733.2 kg of betalactams and 28.7 kg of fluoroquinolones authorised for companion animals only were sold for oral use, corresponding to 252,689 and 80,677 potential treatments, respectively. The quantities of active ingredients taken together account for 88.7% of the total sales of all antimicrobial products for use in companion animals. To evaluate the accuracy of our extrapolations, we compared those data to a study on prescribing behaviour in small animal practice done during the year 2011 with an online survey and open answers to four clinical scenarios: pyodermia, uncomplicated diarrhoea and septic arthritis in dogs and a case of cat flu. Among 97 answering practitioners, 52, 8, 78 and 94% would have prescribed antibiotics in the respective scenarios. The most frequently mentioned antimicrobials were cephalexin for pyoderma, amoxicillin/clavulanic acid or fluoroquinolones for septic arthritis and amoxicillin/clavulanic acid or doxycycline for cat flu. Except fluoroquinolones, critically important antimicrobials were rarely mentioned in the survey. However, using ACD, we can extrapolate that besides the already mentioned oral treatments, more than 18,000 dogs and some 157,000 cats (representing more than 10% of the cat population) received at least one injection with a critically important antimicrobial during the year 2013. These results emphasise the importance of the prudent use guidelines in companion animals. The latter has been identified as a central point by the responsible Federal Office of Food Safety and Veterinary Affairs and is currently envisaged in the context of a national strategy against antimicrobial resistance in Switzerland.
The Health situation of meat poultry is good in Finland. There are no serious viral diseases causing secondary bacterial infections. For responsible use of antibiotics, the focus is set on management, housing conditions and biosecurity. The National Working Group for Meat Poultry Health Care has, since 2007, collected data about antimicrobial use for meat poultry (Table 1). The main reasons for the antimicrobial medications were tenosynovitis of broiler grandparent (GP) and parent (P) flocks and necrotic enteritis of meat turkeys. Amoxicillin and penicillin have been the most used antibiotics. Indicator bacteria are isolated according to the FINRES-Vet monitoring program from broilers every third year. In 2008 and 2011 antimicrobial resistance levels in indicator Escherichia coli in broilers were overall low, only streptomycin resistance exceeded 10% in both years. Ampicillin resistance in E. coli has declined during the last decade and was 3.8% in 2011. Highest resistance levels were seen in enterococci, the most common resistances were against narasin, erythromycin, bacitracin, and tetracycline. Campylobacter jejuni is isolated from broilers yearly in the national Campylobacter monitoring program. Antimicrobial resistance levels have been mainly low throughout the years 2007-2012. Ampicillin susceptibility in C. jejuni was tested only in 2007 and 2008, and resistance was moderate (15.9% and 12.3%, respectively). Salmonella findings in poultry are mostly sporadic and antimicrobial resistance is rarely seen in domestic isolates. Preventive treatment as mass medication is not allowed in Finland. Antibiotic medication of poultry must be based on bacteriological diagnosis and antibiotic susceptibility testing. Recommendations of the Finnish Food Safety Authority for the Use of Antimicrobials against the Most Common Infectious Diseases of Animals have to be followed. A narrow spectrum antibiotic has to be chosen when possible, as well as a right dosage for a sufficient time. Only few antimicrobial agents are available for poultry use in Finland, e.g., cephalosporins have never been allowed.

Table 1. Antimicrobial medicated meat poultry flocks in Finland 2007-2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Chicken</th>
<th></th>
<th>Turkey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flocks/year</td>
<td>Medicated flocks %</td>
<td>Flocks/year</td>
</tr>
<tr>
<td>Commercials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>2,357</td>
<td>0.04</td>
<td>264</td>
</tr>
<tr>
<td>2008</td>
<td>3,169</td>
<td>0.06</td>
<td>325</td>
</tr>
<tr>
<td>2009</td>
<td>2,949</td>
<td>0.37</td>
<td>337</td>
</tr>
<tr>
<td>2010</td>
<td>3,185</td>
<td>0</td>
<td>342</td>
</tr>
<tr>
<td>2011</td>
<td>3,349</td>
<td>0</td>
<td>306</td>
</tr>
<tr>
<td>2012</td>
<td>3,449</td>
<td>0</td>
<td>282</td>
</tr>
<tr>
<td>P/GP* Rearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>68</td>
<td>2.9</td>
<td>28</td>
</tr>
<tr>
<td>2008</td>
<td>104</td>
<td>1.9</td>
<td>29</td>
</tr>
<tr>
<td>2009</td>
<td>102</td>
<td>12.8</td>
<td>24</td>
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<tr>
<td>2010</td>
<td>103</td>
<td>9.7</td>
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<td>2011</td>
<td>100</td>
<td>17.0</td>
<td>12</td>
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<tr>
<td>2012</td>
<td>117</td>
<td>17.1</td>
<td>16</td>
</tr>
<tr>
<td>P/GP* Laying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>99</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>2008</td>
<td>148</td>
<td>2.7</td>
<td>37</td>
</tr>
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<td>5.2</td>
<td>24</td>
</tr>
<tr>
<td>2011</td>
<td>157</td>
<td>1.9</td>
<td>18</td>
</tr>
<tr>
<td>2012</td>
<td>195</td>
<td>0.5</td>
<td>24</td>
</tr>
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</table>
Several initiatives have been put in place in Denmark to minimise the risk associated with use of antimicrobials in pigs. These include no use of antimicrobials as growth promoters and a ban or restrictions on use of fluoroquinolones and cephalosporins, respectively. Furthermore, the DANMAP surveillance is tracking occurrence of antimicrobial resistance in bacteria from animals, food and humans. Since 1995, Danish vets are not allowed to sell antimicrobials. Instead, they can prescribe antimicrobials and offer advisory service on contracts, which legalise the producer to initiate treatment on his own animals. In 2000, a national database called Vetstat was set up. It records all medicine prescribed for livestock. For pigs, each prescription is registered according to age group and indication. Despite of the actions taken, the consumption of antimicrobials in pigs was increasing, resulting in political pressure on the Danish authorities. In response, the Yellow Card Scheme was adapted in 2010. The goal was a 10% reduction. This scheme imposes restrictions on pig farmers, using more antimicrobials than twice the average in an age group. Actions related to a Yellow Card include restrictions on prescriptions, development of an action plan by the vet and tightened supervision by the authorities – all at the expense of the farmer. A 13% reduction in use of antimicrobials was achieved. However, in the last two years a slight increase has been seen. One explanation given by the vets is that vaccines as an alternative were less cost-effective. Another explanation is that the maximum limits indicated by the Yellow Card Scheme gradually are becoming acceptable limits for some farmers. As a result, the limits were lowered again both in June 2013 and March 2014. Danish livestock production is among the lowest users of antimicrobials in Europe. There can be several explanations for this: the pig vet focus more on advisory service than treatment, the unique Danish SPF health management system, and also the farmers being well-educated and providing a high level of herd management in general. The Yellow Card has acted as an incentive to lower the consumption, because farmers become more aware of their antimicrobial consumption, and they are inclined to talk with their vet about alternative treatment and prevention to avoid a Yellow Card. It requires monitoring of use by species and age group in each herd. The impact on health and production will be presented.
A MIXTURE OF CAPSICUM AND TURMERIC OLEORESINS IMPROVES PERFORMANCE OF VACCINATED BROILERS CHALLENGED OR NOT WITH COCCIDIOSIS

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Plant extracts are known for their beneficial effects on the modulation of innate immunity in broilers. At the opposite, vaccines stimulate the development of acquired immunity. Therefore these extracts should improve immunity induced by vaccination in animals infected with coccidiosis. The objective of the present study was to evaluate the effect of a mixture of capsicum and turmeric oleoresins (XT, XTRACT® Nature, Pancosma) on performance of vaccinated broilers challenged with coccidiosis, and shame non-vaccinated birds, and raised in a commercial context. Day 1 broilers were allotted to the following treatments (48 birds * 10 cages/treatment): (i) T1a = nicarbazin + bacitracin from day 1 to 28, nicarbazin + bacitracin + roxarsone from day 29 to 52; (ii) T1b = T1a + challenge to *Eimeria* spp. at day 14; (iii) T2a = 50 ppm XT from day 1 to 42, 100 ppm XT from day 42 to 52; and (iv) T2b = T2a + coccidiosis vaccine at day 1 + challenge to *Eimeria* spp. at day 14. Before and after challenge, BW, BWG and FCR were recorded. Data were analysed using GLM procedure of SAS. Pre-challenge, T2a and b performed better (p<0.01) than T1a and b for BWG (+8.2%), FCR (-5.5%) and BW at day 14 (+6.9%), showing the benefits of immune modulation on performance. After day 14, T2a and T2b exhibited the same BWG, FCR and final BW (p>0.7), as well as T1a and T1b (p>0.5). So, XT and vaccination can maintain performance of challenged birds at the same level as non-challenged birds. Finally, BW at day 42 in T2a and T2b was 3.7% higher than in T1a and T1b (p<0.03). These results suggest that a typical rotation programme with antibiotics and anticoccidials can be replaced by XT combined to coccidiosis vaccination without negatively altering broiler performance.
A PROTECTED BLEND OF PHYTONUTRIENTS PERMITS SIMILAR PERFORMANCE AND BETTER ANIMAL HEALTH COMPARED TO MONENSIN IN FEEDLOT CATTLE

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The use of ionophore antibiotics (MON, monensin) has proven to be a very successful approach to improving production efficiency of beef animals, but as been highly criticised, and banned in the European Union (EU). Among possible alternatives, a standardised protected blend of cinnamaldehyde, eugenol and capsicum oleoresin (XT, XTRACT® 7065, Pancosma) was shown to improve feed efficiency of beef cattle fed high concentrate diets. Therefore, the objective of this study was to evaluate the effect of replacing MON by XT on performance and health in commercial feedlot cattle. In trial 1 (experimental trial), 120 recently weaned male beef cattle (± 225 kg) were randomly allocated to one of two treatments for 119 days (6 pens of 10 animals each per treatment): (i) MON: basal diet + MON (21-33 mg/kg DM; and (ii) XT: basal diet + XT at 1.0-1.2 g/head/day. In trial 2, (commercial trial), 780 recently weaned male beef cattle (± 225 kg) were used in a similar design, but for each treatment 3 pens, with 130 cattle per pen, were randomly allocated, with a trial period of 115 days. Beef performance (ADG, DMI, FCR) and health parameters (rumen health, number of pulls and reasons) were recorded per pen. Results were statistically analysed using the Mixed Model with repeated measure. In trial 1 there were no differences (p>0.05) in DMI, FCR or ADG between treatments. In trial 2, XT increased ADG compared to MON (respectively 1.77 and 1.70 kg/d, p<0.05). XT tended to increase DMI (10.05 and 8.96 kg/day, respectively, p=0.09). FCR was similar between the two treatments (p=0.26). Percentage of healthy rumens was improved (p<0.01) when XT (76.3%) replaced MON (27.1%). Finally, XT reduced the proportion of treated animals, and more specifically minimised the respiratory disorders (p<0.05). Results suggest that XT can be a good alternative to MON in commercial beef feedlot diets without any negative effect on animal performance, and to improve rumen health (453.7 and 472.9 g/day, respectively, p=0.01) and G:F (784.8 and 800.0 g/kg, respectively, p=0.02).
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A PROTECTED BLEND OF PHYTONUTRIENTS IMPROVES HOMOGENEITY AND HEALTH OF CALVES

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In the first months of life, young calves are very prone to different kinds of stress and diseases, explaining the heavy use of antibiotics for curative and preventive purposes. This led to the development of antibiotic resistance of bacteria and thereby a declining health status of livestock. Among alternatives, a protected standardised blend of phytonutrients (XT; XTRACT® Instant, Pancosma) demonstrated beneficial effects on performance and resistance to disease in monogastric animals. Therefore, the objective of the present trial was to evaluate the effect of the addition of XTRACT® Instant in milk replacer on performance and health of calves. A total of 50 bull dairy calves (10 to 14 days of age; 48.7 kg BW) were individually housed for 8 weeks and randomly allocated to 2 treatments according to body weight: (i) CT: basal feeding program; and (ii) XT: CT + 200 g/t powder of XT in milk replacer. Performance data (BWG, G:F) were recorded every 2 weeks, health (number of veterinary treatments) parameters and solid feed intake were assessed weekly. Data were statistically analysed by analysis of variance, initial body weight being considered as a covariable then, Fisher’s test was performed to compare the variability in both treatments. Results showed that solid FI and BWG were not significantly affected by XT. In addition, calves fed XT exhibited a higher G:F compared to calves fed CT (+5.1%, p=0.02). However, variance in solid FI, ADG and G:F was reduced in XT compared to CT (p≤0.08). This suggests that XT increased the homogeneity of calves. Finally, XT reduced the number of veterinary treatments compared to CT (1.67 vs. 2.21 treatments/sick calf, p=0.2). These results show that XT improves homogeneity and performance of calves, and minimised the usage of veterinary treatments.
Honeybees are constantly exposed to numerous threats, such as pests and parasites, viruses, fungi and bacteria. One of the most widespread and destructive bacterial diseases of the honeybee brood is the American foulbrood (AFB), caused by the Gram-positive bacterium Paenibacillus larvae. This bacterium forms spores, which constitutes the infectious form. Generally, P. larvae are highly virulent and after infection can kill the bee colony. In some countries, antibiotics (such as oxytetracycline) are commonly used, either at relatively high doses to treat AFB, or at sub therapeutic doses as ‘growth promoters’, leading to the rising of antibiotic resistant bacteria. Besides, the extensive use of antibiotics leads to an accumulation of residues in honey decreasing the quality and hampering marketing. The present European Union (EU) regulation does not allow the treatment of honeybees with antibiotics and the trading of honey containing antibiotic residues. Therefore, it became urgent the development of alternative methods to control this disease. In this work, the in silico analysis of the P. larvae bacteriophage phiIBB_Pl23 (Siphoviridae) enabled the identification of its endolysin, the PlyPl23. This endolysin, with a molecular weight of 25.8 kDa and an isoelectric point of 6.08, was predicted to present an N-acetylmuramoyl-L-alanine amidase catalytic domain in the N-terminus and no identifiable cell-wall binding domain at the C-terminus. Activity tests were performed at 37°C to mimic the hive temperature and revealed that the endolysin presents a broad-spectrum for P. larvae with an optimal reactivity pH between 3 and 4, which matches the pH levels of honey, nectar, pollen, and royal jelly. Additionally, high antimicrobial activity was observed at pH between 5 and 7, which includes the intestinal pH of bee larvae (6.8) and adult bees (5.6-6.3). Indeed, at pH 7, a concentration of 0.2 μM of endolysin was able to lyse 10^5 cfu/ml in less than 2 h. Furthermore, simulated challenging field conditions, such as the incorporation of endolysin in larvae fluids (including gut content) or in highly concentrated sucrose solutions, showed no activity decrease. Moreover, the endolysin incorporation in royal jelly enabled an increase in the activity. These results are encouraging indicators of the endolysin in vivo effectiveness suggesting the endolysin as an interesting and efficient tool to control AFB. In conclusion, the present work describes, to our knowledge, the first characterisation of an endolysin from a P. larvae phage, which seems to present high potential to integrate a commercial product to control the problematic AFB.
Acinetobacter baumannii is one of the most common causes of nosocomial infections. The pathogen is infamously known for high resistance to various antimicrobials and prevalence of multidrug-resistant (MDR) A. baumannii in humans has been increasing worldwide. A. baumannii exhibits resistance to antimicrobials via multiple mechanisms, of which active efflux system is one of the most common resistance machineries and the efflux systems in the resistance-nodulation-cell division (RND) family are most frequently found in A. baumannii. To date, 4 RND efflux systems have been identified in A. baumannii, including AdeABC, AdeFGH, AdeIJK and AdeDE. However, knowledge of their distribution and contribution to antimicrobial resistance in the A. baumannii clinical isolates is still limited. The A. baumannii clinical isolates (n=100) were obtained from the stock of bacterial strain collection of the Department of Microbiology, Faculty of Medicine, Mahidol University, Bangkok, Thailand. They were isolated from samples, including sputum, pleural fluid, blood and urine, from patients admitted to Siriraj hospital in Thailand during 2001-2008. The MICs to 15 clinically important antibiotics were tested using two-fold agar dilution. Expression of 4 RND efflux pump genes, including adeB, adeG, adeJ and adeE, were determined by using RT-PCR. Specificity of the assay was confirmed by sequencing of PCR amplicons. All the isolates were multi-drug resistant (100%) and the predominant resistance patterns were AMK-ATM-CAR-CAR-CAZ-CHL-CIP-ERY-GEN-KAN-NEO-PIN-PIP-SPE-STR-TET-TMP (65%). All the isolates were resistant to erythromycin, spectinomycin and trimethoprim. The highest resistance was observed for chloramphenicol (99%), streptomycin (95%) and aztreonam (95%). The expression of adeB, adeG, adeJ and adeE was detected in 83, 61, 97 and 0% of the isolates, respectively. All the isolates expressed 5 patterns of the RND efflux pump; expression was identified, including AdeB-AdeG-AdeJ (52%), AdeB-AdeJ (31%), AdeG-AdeJ (9%) and AdeJ only (5%), and 3 isolates (3%) did not express any RND-efflux systems tested. In conclusion, the results of this study suggested the widespread of MDR A. baumannii in the hospital. The expression of the AdeABC, AdeFGH and AdeIJK efflux systems is common and could play an important role in antimicrobial resistance among MDR A. baumannii. Further studies are suggested to investigate the exact contribution of these efflux pumps to antimicrobial resistance in the A. baumannii clinical isolates.
The largest pork producer in the Netherlands has installed an antibiotic residue screening programme as part of the company’s own private quality assurance systems. On average, about 10,000 samples a year are being collected at 3 different abattoirs in the Netherlands. One pig per herd is being sampled and samples consist of one kidney and a piece of lean meat per pig. Kidney and meat samples are subsequently transported to the laboratory of RIKILT. At the laboratory, samples are subjected to a bacterial growth inhibition test, the Nouws Antibiotic Test (NAT). Microbial inhibition methods rely on the inhibitory action of antibiotics against bacteria: the presence of antimicrobial residues is manifested as absence of growth of the test organism. These effect-based bioassays can be operated at very low cost and high throughput as they do not require sophisticated equipment or specialised technicians, which makes them very attractive for large scale monitoring. The NAT has specifically been developed to comply with the maximum residue limits (MRLs) of EU Commission Regulation 37/2010. The NAT is an integrated two step screening system for slaughter animals, involving the initial analysis of renal pelvis fluid, and subsequently the analysis of muscle and/or kidney samples of suspect animals. It is a multi-plate antibiotic group specific test. The test plate showing the largest inhibition reveals the group specific identity of the residue. Samples showing inhibition in the second screening step are judged along a control sample spiked at the MRL, ensuring a minimum number of samples are forwarded for LC-MS$^2$ confirmation, keeping monitoring costs as low as possible. The group specific identification and semi-quantitative approach significantly reduce confirmatory efforts and costs. All methods have been validated according to EU Commission Decision 2002/657/EC. This tiered approach provides maximum compliance and efficiency at the lowest costs. Preliminary results of the screening program will be presented.
ACTIVITIES TOWARDS RESPONSIBLE USE OF VETERINARY ANTIMICROBIALS IN THE CZECH REPUBLIC

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Systemic measures and approach towards responsible use of veterinary antimicrobials in the Czech Republic at national level is briefly described and divided to ongoing activities, planned activities and timing. Long-term already in place: (i) National Antibiotic Programme, human + veterinary (since 1995); (ii) definition of the VMPs under ‘prudent use’: cephalosporins 3rd and 4th generation, (fluoro)quinolones, certain aminoglycosides, ansamycins (since 1998); and (iii) national legal provisions, i.e., Decree No 344/2008, §2, Conditions for prescribing and handling with the antimicrobials under ‘prudent use’ regimen, including penalties (since 2008) and medicated feedingstuffs (veterinary prescription, licensed feed mills only, self and official controls, rules/limits for cross-contamination, ban to use medicated premixes off-label). Working Group on Antimicrobials under the Ministry of Agriculture (since 2013): stakeholders Ministry of Agriculture + regulatory bodies, laboratories, veterinary practitioners, breeder/farmer associations, academia/research, Ministry of Health and veterinary pharmaceutical industry representatives. Monitoring: (i) national system of consumption of veterinary antimicrobials (since 2003; ESVAC since 2009; ESVAC pilot project collection per species (pigs) participation since 2014); (ii) zoonotic and indicator agents (Decision 2013/652/EU); and (iii) residues (including residues of ATM). Short-/medium-term already in place: (i) Action Plan of the National Antibiotic Programme 2011-2013, human + veterinary; (ii) targeted inspections at veterinarians with the highest rate of prescription + analysis of consumption patterns (priority targeted on fluoroquinolones and cephalosporins 3rd and 4th generation highest use) + checking of laboratory protocols based on which the ATM were prescribed; and (iii) prescription habits of veterinary practitioners (national level (2010/2011) and HMA prescription habits questionnaire (UK + CZ + FVE as project leaders)). Other activities: (i) EPRUMA – translation into Czech, promoting + availability to vets; (ii) Antibiotic Day (Central European Veterinary Congress, Brno, 2012 and 2014); and (iii) Antibiotic Awareness Day (Ministry of Agriculture, November 2013). Planned measures: (i) national pilot project for monitoring of target animal pathogens (2015-2016); (ii) elaboration of recommendations/guidelines (correct sampling for testing of the relevant veterinary pathogens; first/second line treatment – main diseases/ main indications/major food-producing animal species/antimicrobials/alternatives for treatment without antimicrobials; and review of national list of antimicrobials classified as ‘prudent use’); (iii) review SPCs for VMPs (national MA); (iv) system of network of veterinary diagnostic laboratories (standardisation, methodology, quality assurance, interpretation criteria); (v) methodology for official controls (e.g., first/second line treatments, sensitivity testing, preventative measures at farm/vet level); (vi) national farm quality evaluation system (based on the concept of preventive medicine); and (vii) research.
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BIOSECURITY AND HYGIENE AS AN OPPORTUNITY IN REDUCTION OF ANTIBIOTIC USE

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One of the key topics in responsible antibiotic use and its reduction is to prevent the introduction and survival of animal and human pathogenic microorganism in the food supply chain. One of the most important sources and reservoirs of pathogenic and other microorganisms is the drinking water system. To provide animals with water in the needed quantity and quality, water from different sources is used in open systems. These systems are not designed with a focus on hygiene and are often not handled in a suitable hygienic manner. Animals are often treated with drugs via water and the water is also used as a vehicle for nutrients, vitamins and minerals. Microorganisms are able to grow and sustain biofilms in this environment. We show that drinking water and the water supply chain in animal houses contains very often high amounts of different microorganisms, also after treatment with disinfectants. We could demonstrate that antibiotic residuals remain over a long period and are still present after common practice procedures of cleaning and disinfection. Those residuals can lead to development of multi-resistant microorganisms in animal production and can also negatively influence other products and measures applied via water like probiotics and live vaccines. Improved techniques to ensure hygienic production conditions need to be implemented with the objective to reduce the use of antibiotics as a way to ensure animal and human health today and in the future. These improved techniques start with the safeguarding of water sources with good dosing systems and with hygienically designed water supply systems. They also must include effective cleaning and disinfection systems and methods as well as appropriate monitoring systems. Furthermore, on farm level trainings to understand the importance of hygiene must target veterinarians and farmers as partners in the field of effective production of safe human food. All the data available in the production chain of integrations or in the supply chain should be linked and analysed economically as well as under microbiological and safety aspects. Today, healthy food production means and requires preventive measures from intensive livestock farming, from feed industry and other supplier industry, from pharmaceutical industry and veterinarians. To overcome the current situation with reduced opportunities of treatment and increasing health problems in animals and humans our efforts must be concentrated on prevention as well as on general and specific prophylaxis of diseases.
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**WIDESPREAD DISTRIBUTION OF ANTIMICROBIAL RESISTANCE OF SALMONELLA ISOLATED FROM RETAIL PORK AND HUMANS IN NORTHEASTERN THAILAND**

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Salmonella enterica is a major foodborne pathogen that has affected public health and economy worldwide, including Thailand. The situation is getting more complicated because of emergence and spread of multi-drug resistant Salmonella isolates. The Northeastern Thailand (Isan) is the biggest area of the country, with the largest population of pigs. However, information on prevalence and genetic backgrounds of antimicrobial resistance is still limited. Therefore, we characterised antimicrobial resistance of Salmonella isolated from humans and retail pork in Northeastern Thailand. A total of 141 Salmonella isolates from humans (n=77) and retail pork (n=64) was collected in Northeastern Thailand during 2010-2011. All isolates were determined for antimicrobial susceptibility by the two-fold agar dilution method (CLSI, 2008). Class 1 integrons and Salmonella Genomic Island 1 (SGI1) were characterised by PCR and DNA sequencing. Ciprofloxacin and nalidixic acid-resistant strains were examined for mutation of quinolone resistance determining region (QRDR) of gyrA, parC. All were screened for plasmid-mediated quinolones resistance (PMQR), including qnr genes (qnrA, qnrB and qnrS), aac(6')-Ib-cr and qepA. All the Salmonella isolates were resistant to at least one antibiotic and 93% were resistant to at least three different classes of antibiotics (multi-drug resistance; MDR). Most isolates were highly resistant to sulfamethoxazole (97.8%), streptomycin (92.9%) and tetracycline (83.6%). 10 and 18% from the human and retail pork isolates, respectively, were positive to intI. Of all intI1- positive Salmonella, 24 isolates contained resistance gene cassettes, including aadA4, bla-PSE and dfrA12-aadA2. SGI1-like was found in a S. anatum. Single point mutations in gyrA were found in six quinolone-resistant isolates (i.e., three nalidixic-resistant isolates and three ciprofloxacin-resistant isolates) leading to Ser-83-Phe, Ser-83-Tyr, Asp-87-Asn substitution in GyrA. A point mutation G-147-C leading to Trp-49-Cys in ParC was observed in a nalidixic-resistant isolate. The qnrS gene was detected in a human isolate and two pork isolates. The qnrB gene was found in two pork isolates. None were found to carry qnrA, qepA and aac(6')-Ib-cr. In conclusion, the MDR-Salmonella are widespread among retail pork and humans in Northeastern Thailand. Antibiotic resistance mechanisms located on either chromosome or plasmids play an important role in distribution of antimicrobial-resistant Salmonella in the region. The results warrant the requirement of guidelines for responsible use of antibiotics in livestock, AMR surveillance programmes and AMR strategic control policies.
OPINIONS OF DUTCH VETERINARIANS ON ANTIMICROBIAL USE IN FARM ANIMALS

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Veterinarians play a pivotal role in reducing antimicrobial use in food animals. Prescribing decisions of physicians are influenced by clinical reasoning as well as personal characteristics (knowledge and attitudes) and patient preferences. Little is known about determinants that influence prescribing behaviour of veterinarians. A questionnaire was sent out in the Netherlands to quantify opinions of veterinarians regarding antimicrobial use in farm animals and farmers’ influences in improving prudent use of antimicrobials. Questions consisted of 5-point Likert items. Factor analysis and reliability testing was performed, followed by Two Way Cluster analysis. 450 questionnaires were returned. Of the respondents’ working time, 3% was spent on poultry, 13% swine, 46% cattle and 5% veal calves. Assessment of the data enabled us to categorise respondents in three main subgroups. Dependents (n=135) were on average 13.7 years in practice (55% practice owner) and supported the reduction of veterinary antimicrobial use (μ4.05) and the introduction of a veterinary quality system (μ3.93). Non-compliance of farmers with management standards (μ4.00) and veterinary advices (μ4.10) were regarded important causes of antimicrobial overuse. They experienced the least confidence to act as an independent and critical advisor for farmers and to refuse (strong) demands of farmers (μ2.84). Progressives (n=145) were on average 16.4 years in practice (60% practice owner) and also had positive attitudes towards antimicrobial reduction (μ4.23) and the introduction of a veterinary quality system (μ4.17). They experienced the most confidence to act as an independent and critical advisor for farmers (μ3.95). Non-compliance of farmers with management standards (μ3.90) was also seen as an important cause of antimicrobial overuse, although non-compliance of farmers to veterinary advice was experienced less often (3.48). Conventionalists (n=104, on average 17.2 years in practice, 75% practice owner) did not feel an urgent need to reduce veterinary antimicrobial use (3.08) and to introduce a veterinary quality system (μ3.06). They did not regard non-compliance of farmers with management standards (μ2.98) and veterinary advices (μ3.26) as important causes of antimicrobial overuse in farm animals. In conclusion, dependent and progressive veterinarians have positive attitudes towards reduction of antimicrobial use and veterinary quality systems. The generally younger dependent veterinarians might require additional support (training, guidelines) to act more independently of farmers’ demands. Conservative veterinarians are more sceptical about the necessity to reduce veterinary antimicrobial use and the introduction of veterinary quality systems. The challenge is to convince them of the possible risks related to overuse of veterinary antimicrobials.
INCREASE IN RESISTANCE OF SALMONELLA FROM FOOD TO FLUOROQUINOLONES AND CEPHALOSPORINS – AN OVERVIEW OVER 10 YEARS

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Food of animal origin is an important source for Salmonella infections in humans. We analysed the presence of Salmonella spp. in meat with respect to the involved serovars and their resistance towards ciprofloxacin and 3rd generation cephalosporins from 2003 to 2012. We included data on 8,176 isolates from meat that were characterized and tested for antimicrobial resistance in the National Reference Laboratories at the Federal Institute for Risk Assessment in Berlin, Germany. Results show substantial differences in antimicrobial resistance between serovars and isolates from different origins. Frequent serovars are mostly associated with one type of meat (e.g., S. Paratyphi B dT+ 80% from broiler meat, S. Saintpaul 66 % from turkey meat). This points to factors beyond selective pressure of antimicrobial treatments influencing the prevalence of specific serovars in certain groups of animals. Resistance to ciprofloxacin has increased in the period under study (2003/04: 10.3 %, 2011/12: 23.6 %). Likewise, the proportion of isolates that are resistant to 3rd generation cephalosporins increased, although the level of resistance was lower compared to ciprofloxacin (2003/04: 0.2 %, 2011/12: 3.0 %). The increase in resistance towards the two substance groups was most obvious in isolates from poultry meat, 18.5 to 54.0 % and 0 to 9.2 %, respectively. Although the number of reported human cases of salmonellosis in Germany has been decreasing substantially in recent years (2003: 63,093 cases, 2012: 20,824 cases), results underline a substantial exposure of consumers to Salmonella that are resistant to critically important antimicrobials.
Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) have been found in various farm animal species throughout the world. It was the objective of this study to estimate the prevalence of MRSA in different cattle food production chains (milk, beef, veal) in Germany and to analyse the MRSA diversity along each food chain. Samples were collected between 2009 and 2012 from dairy herds (bulk tank milk), veal herds (dust from the stables), and veal calves and beef cattle at slaughter (nasal swabs). Sampling was proportionally distributed over the country according to the cattle population (on farm sampling) or slaughterhouse capacity (abattoir samples). MRSA were isolated from all sample types and populations investigated. The highest proportion of positive samples was found in nasal swabs from veal calves at slaughter in 2012 (45.0 %), the lowest rate in bulk tank milk from dairy herds in 2009 (4.1 %). On veal farms, 19.2 % of the dust samples yielded MRSA. Beef cattle, tested at the abattoir had a substantially lower prevalence rate as compared to veal calves (8.7 vs. 45.0 %). Most of the 490 isolates submitted to the National Reference Laboratory were from *spa*-types t011 and t034. Both have been assigned to the clonal complex (CC)398. The *spa*-types differ with respect to the SCC*mec* cassettes they harbour. *Spa*-type diversity was greater in veal calves than in beef animals or dairy cattle. Only three isolates (0.6 %) were from *spa*-types not associated with the CC398, namely t002, t009 and t1919, respectively. These might be human associated, although t002 has also been identified in poultry production. All three were identified from veal calf herds (1) or veal calves at slaughter (2). Results show that the prevalence of MRSA in veal calves is substantially higher than in other cattle populations and that veal calves show a high heterogeneity of MRSA.
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THE USE OF THE ‘HIGHEST PRIORITY CRITICALLY IMPORTANT ANTIMICROBIALS’ IN AUSTRIAN PIG FARMS

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The monitoring of antimicrobial consumption in animal husbandry is crucial for the interpretation of resistance development. Besides the knowledge about the overall antimicrobial use, the monitoring of the usage of substances declared by the World Health Organization as ‘highest priority critically important antimicrobials’ (HPClAs) is of particular importance. Macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptid antibacterials are considered essential for the treatment of specific human infections, for which no or only few therapeutic alternatives exist. Consequently, their use in animal diseases should be restricted to exceptional cases in order to preserve their effectiveness in human medicine in the future. To date, information about the use of HPClAs in livestock is collected and regularly published in the frame of the ESVAC project, however without giving any information about the animal species and the diagnoses these antimicrobials are prescribed for. This detailed information can only be gathered at an on-farm level. In this study, electronic on-farm data, which were recorded directly by farmers from 2008 until 2011, were evaluated. In total, 75 conventional pig farms (49 farrow-to-finish, 21 fattening and 5 breeding farms), producing on average 12,005,125 kg biomass per year, were involved. The antimicrobial consumption was expressed per year using the indicator ‘Product-related Daily Dose’ (PrDD). The PrDD was defined for each veterinary pharmaceutical product for the main indication in one species as the maximum dose recommended by the manufacturer and adjusted by a factor of 0.8, correcting for the fact that the maximum dose indicated is not used with every treatment. Results were referred to the pigs’ biomass and evaluated per age class. The focus was especially laid on HPClAs and the therapy indication. The consumption of the HPClAs in the study population was on average 0.6 PrDDₚ/kg/year. This represents about 22% of the total antimicrobial consumption. Fattening farms consumed the highest amount of HPClAs. The biggest portion of HPClAs was applied to weaner pigs, piglets and fattening pigs <60 kg (30, 27 and 23% of total HPCA consumption). In piglets, 40% of the total consumption was related to HPClAs. Within the HPClAs, macrolides played the most important role and were mainly prescribed for digestive tract diseases, but also considerably for metaphylactic and prophylactic measures. This study shows that the collection of drug consumption data at on-farm level enables authorities to provide detailed and profound information about the use of HPClAs in animal husbandry.
GERMAP, THE GERMAN REPORT ON ANTIMICROBIAL USE AND RESISTANCE – WHY ALL THESE DATA?

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The project GERMAP started in 2005 in order to strengthen the interdisciplinary cooperation between human and veterinary medicine on the issue of antimicrobial resistance. GERMAP is a very helpful collaborative work to gain more knowledge and understanding for this interdisciplinary approach. It shall help to promote the prudent and intelligent use of antimicrobial agents in human and veterinary medicine. The Federal Office of Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL), the Paul-Ehrlich-Society for Chemotherapy e.V. (Paul-Ehrlich-Gesellschaft für Chemotherapie, PEG) and the Division of Infectious Diseases, University Hospital Freiburg (Infektionszentrum am Universitätsklinikum Freiburg, iF) are the editors of GERMAP. Three reports have been published until now, GERMAP 2008, GERMAP 2010, and GERMAP 2012. Most resistance data in human medicine derived from studies of the PEG, from the Surveillance of Antimicrobial Use and Antimicrobial Resistance in Intensive Care Units (SARI) and from the European Antimicrobial Resistance Surveillance Network (EARS-Net). Furthermore, data of the national reference centres for surveillance of important bacterial pathogens and of Antimicrobial Resistance Surveillance (ARS), initiated by the Robert Koch-Institute, were considered. ARS provides data on the distribution of antimicrobial resistance in ambulatory and hospital care. Data on the use of antimicrobials in human medicine are provided by the Scientific Institute of the AOK (Wissenschaftliches Institut der Allgemeinen Ortskrankenkassen, WIdO) for ambulatory treatments and by some other projects (e.g. SARI, ADKA-if) for inpatient treatments. Resistance data of veterinary pathogens, derived from diseased animals, are essentially based on the results of the national resistance monitoring GERM-Vet, which has been carried out by the BVL since 2001, and on some regional studies. Data are presented according to animal species, type of production, age of animals, and therapeutic indications. Sales data of veterinary antimicrobials, which are collected based on legislation, were published in GERMAP 2012 for the first time. GERMAP reports represent a full account of national data on the use of antimicrobials and on the spread and development of antimicrobial resistance in human as well as veterinary medicine. Each report contains a huge amount of information about the most important trends and besides deals with varying current topics on the development and spread of antimicrobial resistance. Many colleagues from different healthcare sectors have made contributions to this collaborative network in order to get the best possible view on the situation in Germany.
THE GERMAN NATIONAL RESISTANCE MONITORING (GERM-VET) – RESISTANCE DATA OVER A PERIOD OF 13 YEARS ON THE EXAMPLE OF *E. COLI*

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The use of antimicrobial agents in human and veterinary medicine inevitably results in a selection pressure for drug resistance in exposed bacteria. However, the use of antimicrobial agents is essential in therapy for humans and animals. An intelligent and rational application is needed to minimise the development and the spread of antimicrobial resistant bacteria and their resistance genes as far as possible. The survey on the current resistance situation serves as an important tool to detect the changes of the resistance level especially regarding to antimicrobials which are categorised as ‘critically important antimicrobials’. An annual representative German-wide monitoring study of bacterial isolates derived from diseased animals is given by a random sampling plan. This plan is adapted annually to the results from the previous study. The susceptibility of bacteria to 24 antimicrobial agents is determined using the broth microdilution method in accordance to CLSI document VET01-A4. The determined minimal inhibitory concentration (MIC) values were correlated, if available, with CLSI veterinary clinical breakpoints for classification (CLSI VET01-S2). Otherwise MIC\textsubscript{90} values were used for evaluation. Annually, about 1,000 *E. coli*-isolates were included in each study. Highest resistance rates were detected with isolates derived from enteritis from calves (ampicillin 70-80%, tetracycline 70-75%) and trimethoprim/sulfamethoxazole (50-52%) and swine (ampicillin 60-70%, tetracycline 72-80%) and trimethoprim/sulfamethoxazole (50-62%). The rate for ESBL positive isolates from calves is still increasing from 7% in 2006 to 20% in 2012. Furthermore, the MIC\textsubscript{90} values for cephalosporins of the 3rd and 4th generation are high for bacterial strains isolated from calves. Low resistance rates were determined from mastitis isolates. Therefore, the maximum rate was detected for ampicillin with 17%. The resistance rates for poultry are lower as those for isolates from calves and pigs: ampicillin (40-60%), tetracycline (40-70%) and trimethoprim/sulfamethoxazole (20-40%). Rates against enrofloxacin were low (max. 10%) for turkeys as for broilers as well. In conclusion, a representative antimicrobial resistance monitoring serves as a valid tool in risk management. With these representative and quantitative data we are able to monitor and to estimate the development of antimicrobial resistance in veterinary pathogens also with special consideration of cephalosporins, fluoroquinolones, and macrolides.
ORAL VACCINATION AGAINST LAWSONIA INTRACELLULARIS SHOWS SIMILAR GROWTH PERFORMANCE AS ANTIBIOTIC MEDICATION

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Lawsonia intracellularis (L.i.) may cause ileitis. Infected growing pigs have a decreased average daily weight gain (ADG). Between 70-100% of Northern European pig herds are infected with L.i., causing a large economic impact. Negative effects can be controlled by vaccination or by antibiotic medication. The aim of this study was to determine the effect of L.i. vaccination with Enterisol® Ileitis versus antibiotic medication with Tylan® on growth performance of pigs. The study was done on a Dutch farm (270 sows - 2,000 finishing pigs) with a history of ileitis. The study comprised 9 subsequent weeks, 3 weekly batches per group: (i) group 1, Tylan® (391 pigs); (ii) group 2, Tylan® + Enterisol® (404 pigs); and (iii) group 3, Enterisol® (362 pigs). Vaccination was performed at 21 days of age by oral drench. Pigs received antibiotics orally at 10-13 weeks and 16-17 weeks of age (70 g/1,000 l drinking water). During the study period, only curative antibiotic treatments were allowed. Growth performance was defined as ADG during total life from birth to slaughter. Birth weight was neglected compared to live weight at slaughter. Live weight was calculated individually according to the formula: (1.3*sw) – (0.0025*sw²) + (0.2075*sw), where sw was slaughter weight (kg). Differences between the three study groups were tested by a nonparametric Kruskal-Wallis test in SPSS 18. ADG differed significantly between study groups (p<0.000) with group 2 higher than group 1 or 3. (Table 1). On this particular farm, treatment with Tylan® (group 1) gave the same growth results as treatment with Enterisol® (group 3). In conclusion, to reduce antibiotics, but still control ileitis, Enterisol® Ileitis vaccination showed a good alternative on this farm.

Table 1.

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<th>Group</th>
<th>Mean ADG (g/day)</th>
<th>95% confidence interval</th>
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References