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The Antimicrobial Resistance Apocalypse – Not! – Yet? – Path Forward For Antimicrobial Use In Food Animals

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June 4, 2018

Executive summary:

The apocalyptic predictions regarding antimicrobial resistance, and specifically those due to foodborne antimicrobial resistant bacterial infections, are regularly hypothesized. Such predictions, while true for selected resistant bacteria in humans, as it relates to foodborne bacteria, such risks may be in the future, if at all, but not to date.

Antimicrobial resistance development and transfer is a complex and multifactorial process and occurs in the human health, environmental health and animal health (both food and non-food animal) areas. Antimicrobial resistance is a natural biological process of microorganism survival; a microbial defense against substances designed to kill them.

Antimicrobial resistance development and transfer is influenced by selection pressures which are caused by antimicrobial use. The human and food animal reservoirs each have their own influencers and selection pressures. Responsible antimicrobial use practices implemented in the hospital and on the farm do appear each to have impacted the prevalence of resistance in their specific reservoir. However, data to date, does not indicate restrictions to on-farm antimicrobial use have resulted in a public health benefit.

Antimicrobial resistance is a public health concern for which action is needed. Based upon current scientific understanding, with limited human and financial resources, the most prudent path forward is to incorporate a science-based antimicrobial resistance risk analysis into governmental regulatory approval processes. (Figure 1) The focus of the risk analysis efforts should be on those foodborne pathogens of public health concern, specifically fluoroquinolone-resistant *Campylobacter spp.* and fluoroquinolone-resistant non-typhoidal *Salmonella*.

Figure 1

Antimicrobial Use In Food Animals: Prudent Path Forward

"Government laws, regulations, guidelines and private sector policies, practices"

	Therapeutic – Disease treatment, control and prevention	Growth Promotion / production use	Professional / Veterinary Oversight Required	Delivery via Injection or Orally via medicated water or medicated feed	Continuous Use (Note: Use based upon disease needs - pulse use accepted for all)	Concurrent Use (Note: For same disease / bacteria)
Medically Important for Humans ➢ Human Only Use	Not Allowed For Use In Food Animals, Including Not Allowed for Extra-label Use Under Veterinary Oversight ☒ No					
Medically Important for Humans ➢ Shared Class Use ➢ Human and Animal Use	Allowed ☑ Yes	Not Allowed ☒ No	Required ☑ Yes	Allowed ☑ Yes	Not Allowed ☒ No	Not Allowed ☒ No
Not Medically Important for Humans ➢ Shared Class Use ➢ Human and Animal Use	Allowed ☑ Yes	Allowed - Based upon risk assessment ☑ Yes	Not Required ☒ ☑ No / Yes Optional	Allowed ☑ Yes	Allowed – Based upon risk assessment ☑ Yes	Allowed – Under Professional / Veterinary Oversight ☑ Yes
Not Medically Important for Humans ➢ Animal Only Use	Allowed ☑ Yes	Allowed ☑ Yes	Not Required ☒ ☑ No / Yes Optional	Allowed ☑ Yes	Allowed ☑ Yes	Allowed – Under Professional / Veterinary Oversight ☑ Yes

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This risk analysis process includes risk assessments with priority focus on those antimicrobials of most importance for human medicine, and risk management decisions that provide for approval of use yet entails limits to ensure appropriate use. And, risk communication should ensure the proper information garnered from the risk assessment and risk management process is provided to those involved in the decision making and use of the antimicrobial. The overall science-based risk analysis approach is as defined in the 'Antimicrobial Use In Food Animals: Prudent Path Forward' illustration.

Background – history and key questions

Time puts predictions in perspective and claims of an all-encompassing antimicrobial resistance apocalypse are still in the future, if at all.[1,2,3] Antimicrobial resistance is a serious health concern for humans and food animals and resistance continues to evolve. (Figure 2) The time gap in bringing new antimicrobials to market further exasperates this concern. However, predictions the past decades of an impending sweeping apocalypse have not happened, and with good medical care are unlikely to happen near term. Advances in medical care, biosecurity and understanding of antimicrobial resistance have avoided the apocalypse. It needs to be fully recognized that for some particular resistant bacteria in the human sector, antimicrobial resistant bacteria or genes are debilitating or terminal, which is of concern and most unfortunate, and thus emphasizing the need for appropriate prudent use action for the use of all antimicrobials, including antimicrobials used in food animals. Merging the lines around the human health and animal health sectors often confuses and clouds the ability to properly address antimicrobial resistance. Importantly the human health and animal health parts each need to be addressed separately, and collaboratively in the context of a 'One Health' approach.

> *<u>The human health risk</u>: A person becomes sick with a foodborne bacterial infection that cannot be appropriately treated with an antimicrobial as a result of animal-derived antibiotic-resistant bacteria or genes that are from a food animal that has been given an antimicrobial.*

Figure 2

The question is for antimicrobial use in food animals what is appropriate prudent use action – legislative, regulatory and policy – governmental and marketplace? National, regional and intergovernmental bodies have invested major resources to address antimicrobial resistance. Insights from the past three decades of actions globally can provide perspective into what actions may be most impactful and beneficial based upon scientific understanding. A core question regarding actions taken to date, is to what avail and benefit? Apocalyptic predictions can drive change, but with limited resources and time, understanding the scientifically based risks and impacts can help in identifying appropriate policies and actions regarding antimicrobial use in food animals that are sustainable for the long-term benefit of public health. Critically, due to potential health risks, all antimicrobials need to be used prudently now. Yet with limited human and financial resources it is important that resources are used wisely and prioritized where they are most likely to have an impact.

Since the late 1990's major actions around antimicrobial use in food animals have taken place in the legislative, regulatory and marketplace areas. Major human and financial resources have been expended, theoretically to curb antimicrobial resistance for a public health benefit. Countries or regions as the European Union (EU) and the United States (U.S.) have changed legislative controls, modified regulatory processes and even restricted or removed antimicrobials for specific uses.[4,5] Several countries have incorporated antimicrobial resistance risk analysis as part of their food animal regulatory process including Australia, Canada, the EU, Japan and the U.S..

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1 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

2 https://www.express.co.uk/news/science/605633/ANTIBIOTIC-APOCALYPSE-10million-more-people-will-DIE-every-year-if-new-drugs-aren-t-made

3 http://home.bt.com/news/uk-news/post-antibiotic-apocalypse-warning-as-leaders-urged-to-act-on-drug-resistance-11364220267242

4 EU 1999 to 2006 actions for removal of antibiotic growth promotant claims (AGPs). 'Feed additives' under Directive 70/524/EEC 'Growth Promotants' claims - Feed use. 'Veterinary medicines' under Directive 81/851/EEC 'Therapeutics' or disease claims.

5 U.S. in 1996: Animal Drug Availability Act incorporating Veterinary Feed Directive; in 2003: 152 - Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern; in 2012: 209 - The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; and in 2013: 213 - New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209.

WHO (World Health Organization), OIE (Organisation for Animal Health), FAO (Food and Agriculture Organization) and Codex have each, and in efforts collaboratively, advanced scientific understanding and policy approaches.[6]

The core questions as it relates to foodborne antimicrobial resistance, have actions benefited public health? What does the science tell us? What have we learned? Have actions impacted animal or public health? What is the best policy approach? What is the best path forward for antimicrobial use in food animals based upon current known information?

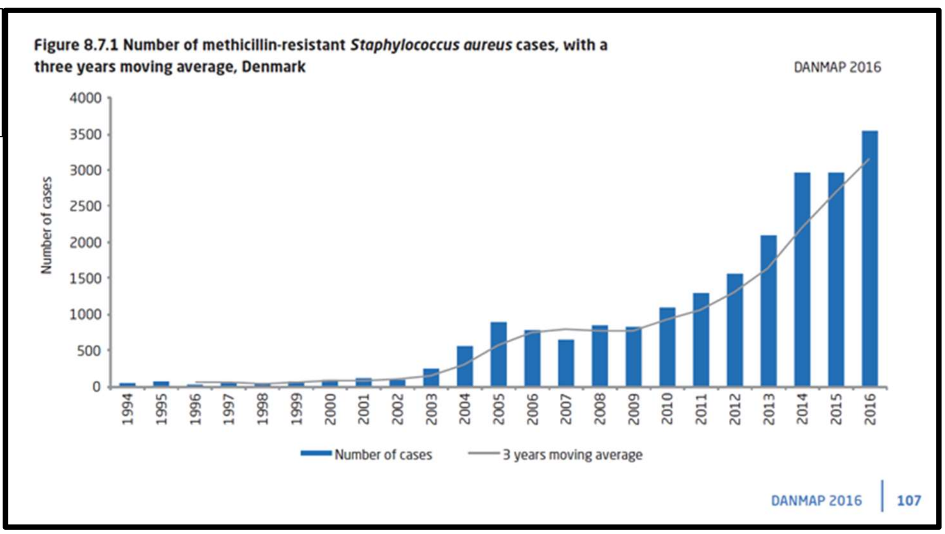
Science - what have we learned

Antimicrobial resistance development and transfer is a complex and multifactorial process and occurs in the human health, environmental health and animal health (both food and non-food animal) areas. Antimicrobial resistance is a natural biological process of microorganism survival; a microbial defense against substances designed to kill them. Antimicrobial resistance can be intrinsic (resistance that is pre-existing in a microorganism and transferable only to offspring) or acquired (resistance that is developed through chromosomal mutations or DNA and plasmid transfer).

Antimicrobial resistance sources are extensive, and the potential paths to exposure many, yet for food animal antimicrobial use, the primary human exposure and transfer paths are through foodborne pathogens and direct human-animal contact. There have been a few documented cases of human-animal transfers and this limited risk, that is primarily to animal caretakers, can be addressed via on-farm biosecurity, housing, animal handling, waste management practices and environmental controls. The foodborne pathway is the one of broader public health concern as all individuals eat food.

Testing for and identifying definitive answers regarding antimicrobial resistance and its transfer is challenging. Testing findings are subject to sampling measures, numbers, methods, resistance thresholds and organism selection, and thus outcomes are indicative of sampling parameters. Initial findings need to be kept in context of sampling, especially if results are to be extrapolated. One can expect that with sampling there will be findings of antimicrobial resistant bacteria and thus these findings need to be put in context with a proper risk assessment. A finding does not need to be an apocalyptic event as has been demonstrated through the years.

Figure 3



Findings of *vancomycin-resistant enterococcus faecium* and e*nterococcus faecalis* (VRE), *methicillin-resistant staphylococcus aureus* (MRSA) and *salmonella typhimurium* DT104 each have come with calamitous predictions and calls for actions to curtail on-farm use. However, the specific restrictive actions regarding food animal use have not resulted in direct public health benefits or

[6] The "Environmental Health Criteria 240, Principles and Methods for the Risk Assessment of Chemicals in Food". The World Organization for Animal Health (OIE) "Terrestrial Animal Health Code Risk Analysis for Antimicrobial Resistance Arising from the Use of Antimicrobial Agents in Animals", Chapter 6.10. The Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, CAC/GL 77- 2011. The World Health Organization "Critically Important Antimicrobials for Human Medicine, 4th Revision 2013". "OIE List of Antimicrobial Agents of Veterinary Importance – May 2015".

Figure 4

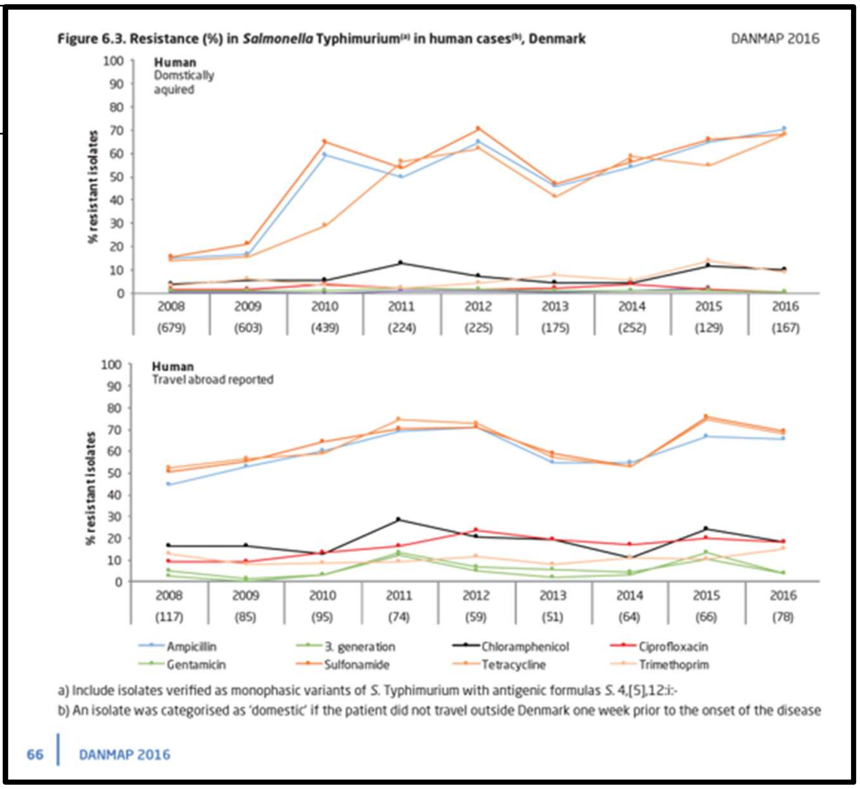
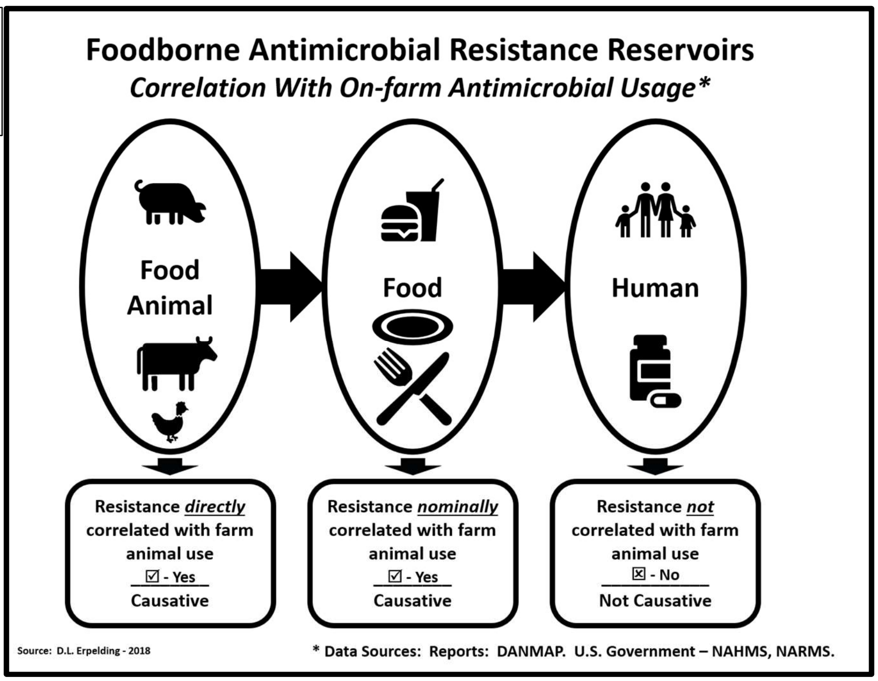


Figure 5

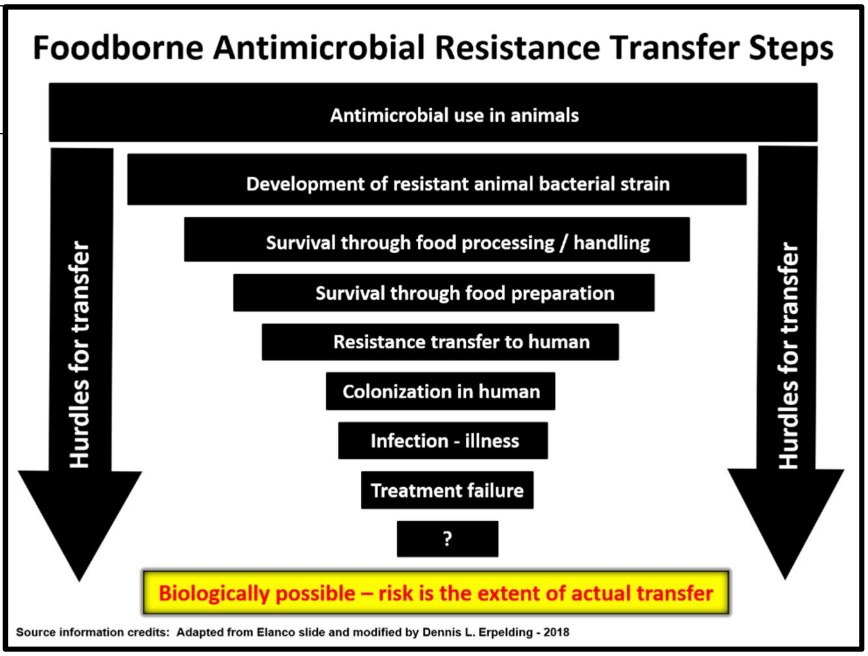


even reductions in resistance findings, likely as such bacteria were community or hospital acquired and thus on-farm actions have had limited or no impact on human findings.[7,8,9] (Figures 3 and 4) Full and proper risk assessments could negate irrational actions, but rather provide insights for appropriate risk management actions based upon the risk assessment. A key context around sampling, is that as sampling increases, one can expect findings will increase, and as the scope of bacterial organisms and determinants broadens, so too does the scope of findings.

Based on insights thus far as one looks at the resistance reservoirs related to foodborne pathogens, antimicrobial resistance in the animal reservoir correlates directly with on-farm usage, antimicrobial resistance in the food reservoir indicates nominal correlation with on-farm usage and antimicrobial resistance in the human reservoir shows no causal impact based upon food animal use.[10] (Figure 5) These insights would indicate that antimicrobial use results in more selection pressure, especially in the food animal, as would be expected. Yet as one follows this through the food channel, various interventions diminish the transfer and findings of antimicrobial resistant pathogens in the food reservoir. And as one looks at the human reservoir additional interventions and hurdles

[7] https://www.danmap.org/Downloads/Reports.aspx (note DANMAP reports, findings, tables and charts through the years of 1996 to 2016)
[8] https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms
[9] https://www.cdc.gov/narms/index.html
[10] https://www.danmap.org/Downloads/Reports.aspx (note DANMAP reports, findings, tables and charts through the years of 1996 to 2016)

Figure 6



negate the ability to trace antimicrobial resistance pathogen transfer from antimicrobial use on the farm to treatment failure in humans. (Figure 6) Importantly, in today's food systems there are numerous interventions at the farm level with animal care and biosecurity, by the food industry with the use of pathogen reduction technologies, carcass rinses and heat treatments, and in the home with better food handling and cooking practices. Scientific understanding through on-farm antimicrobial use monitoring and antimicrobial resistant pathogen surveillance will help all involved continue to implement risk management and intervention practices that collectively minimize potential public health impacts.

Through the years, there have been hypothesis of associations or temporal relationships regarding the use of antibiotics on the farm and treatment failures in humans, but such have not been scientifically proven; granted such is challenging considering the multiple steps and hurdles involved for foodborne antimicrobial resistance transfer, and that such often needs to be done retroactively.

<u>Impact – to what avail or public health benefit</u>

Antimicrobial resistance development and transfer is a natural biological process that can be influenced by selection pressures which can be caused by antimicrobial use. The human and food animal reservoirs each have their own influencers and selection pressures. Responsible antimicrobial use practices implemented in the hospital and on the farm do appear each to have impacted the prevalence of resistance in their specific reservoir. However, data to date, does not indicate restrictions to on-farm antimicrobial use have resulted in a public health benefit.

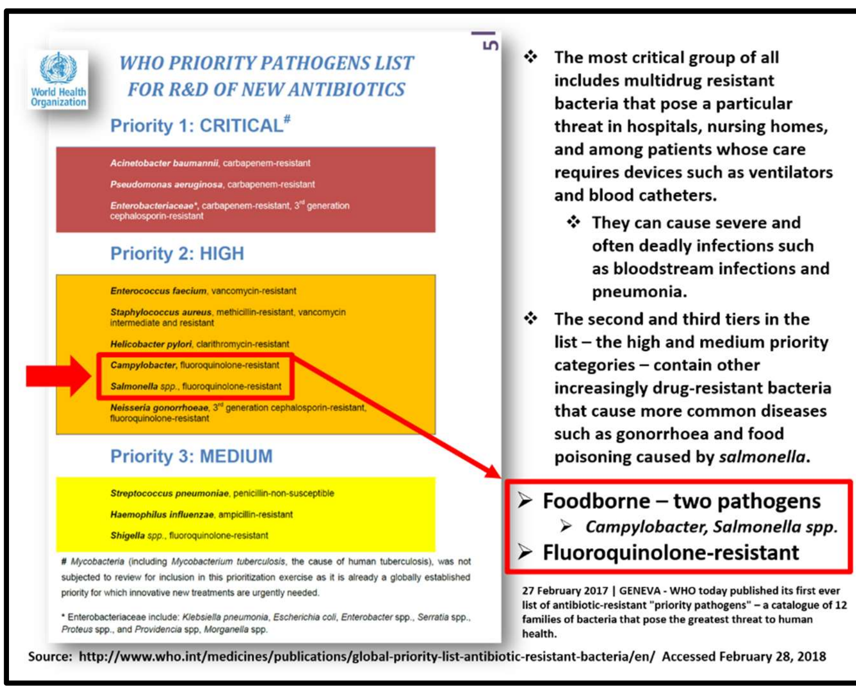
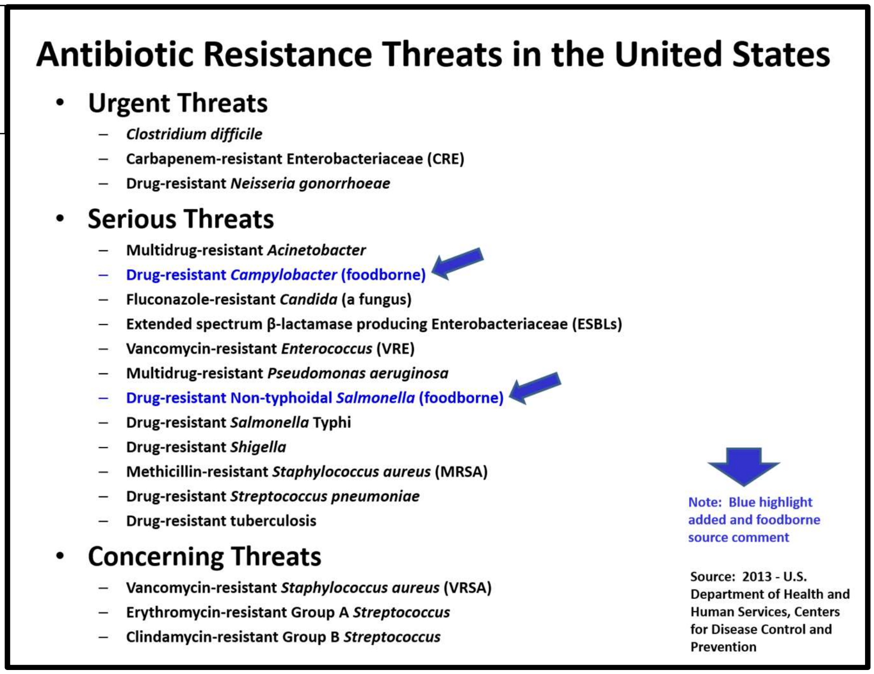


Figure 7

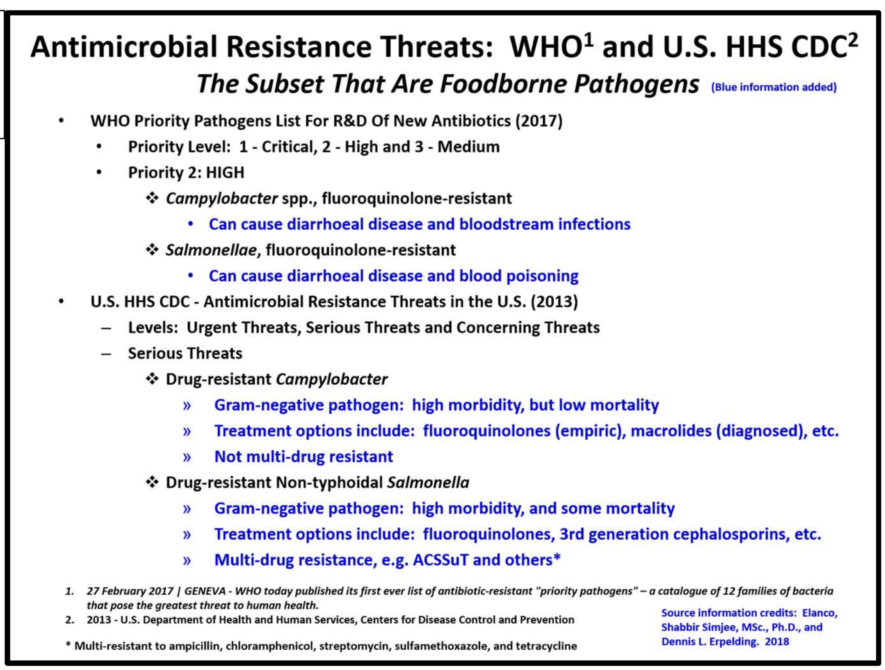
Figure 8



When one considers the current public health concerns, WHO recently published their priority list of pathogens for research and development of new antibiotics. Within the WHO list of 12, there are two pathogens of concern in the second tier, 'Priority 2: High', that are foodborne, *Campylobacter* and *Salmonella*. And specifically, for these two pathogens, fluoroquinolone-resistance is the primary area of need. (Figure 7) Further, the U.S. Centers for Disease Control and Prevention published their list of antibiotic resistance threats in 2013. Within the U.S. CDC list of 18, there are two pathogens of concern in the second tier, 'Serious Threats', that are foodborne, *Campylobacter* and *Salmonella*, the same two as for WHO.[11,12] (Figure 8)

The WHO and U.S. CDC lists provide insight into why actions at the farm level will have limited to no impact in humans. Of all the public health concerns and priority needs regarding resistant bacteria, the 12 listed by WHO and the 18 listed by U.S. CDC, only two are foodborne pathogens. (Figure 9) The human reservoir resistant threats are primarily due to community or hospital acquired bacteria and thus major impact will be derived from actions within the human health sector.

Figure 9



United Kingdom learnings reflect this understanding also as they outline in their strategic plan, noting: "Increasing scientific evidence suggests that the clinical issues with antimicrobial resistance that we face in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals."[13] U.S. and Denmark data support this evolving scientific understanding. Selection pressures and resistance prevalence are in part transient dependent upon the specific bacteria, the antimicrobial used and the resistance mechanisms.

[11] http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
[12] https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
[13] UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. Page 8, Section 2.1

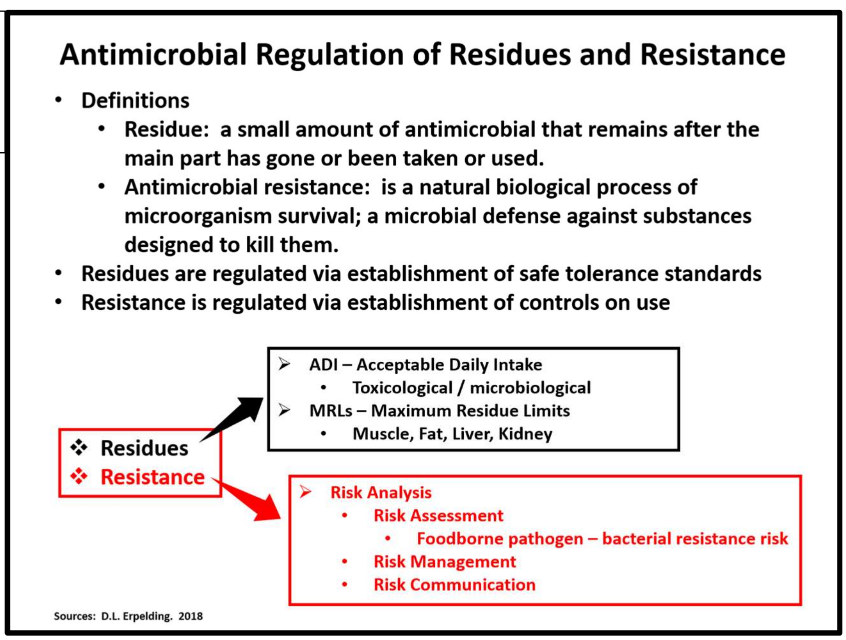
The food animal sector needs to ensure they take actions to minimize resistance for the foodborne pathogens of *Campylobacter* and *Salmonella*. Further, for animal care purposes, the sector should seek to reduce resistance selection pressures as it relates to all bacteria due to animal care needs. And, additionally, the food animal sector needs to use all antimicrobials responsibly to minimize overall selection pressure from a wholistic impact on the global resistance reservoir and consistent with the 'One Health' collaborative efforts amongst the human, animal and environment sectors. When one considers the antimicrobial resistance threats, fluoroquinolone-resistant *Campylobacter spp*. and fluoroquinolone-resistant non-typhoidal *Salmonella* are the key ones of concern and thus the need for focus as resistance threats relate to food animals.

When one considers antimicrobial resistance selection pressure, logic would indicate that maintaining the maximum number of antimicrobials available is important to minimize the selection pressure around a given antimicrobial. Further, this provides for likely having the right antimicrobial to treat, control or prevent an infectious disease. Recognizing food animals do get sick, reducing the overall number of approved products and approved uses, results in either higher levels of animal disease and death, more intense selection pressure on those approved, or the need to use antimicrobials for unapproved uses. Maximizing the number of approved antimicrobials and use indications for food animals will provide so that when a specific bacterial infection is present one can select the right antimicrobial, for the right species, at the right time, for the right route, for the right dose and for the right duration.

<u>Path forward – science-based risk analysis</u>

Antimicrobial resistance is a public health concern for which action is needed. Based upon current scientific understanding, the best path forward for food animal antimicrobial use is to incorporate a science-based antimicrobial resistance risk analysis into governmental regulatory approval processes. The focus of a risk analysis should be on those foodborne pathogens of public health concern, specifically fluoroquinolone-resistant *Campylobacter spp.* and fluoroquinolone-resistant non-typhoidal *Salmonella*.

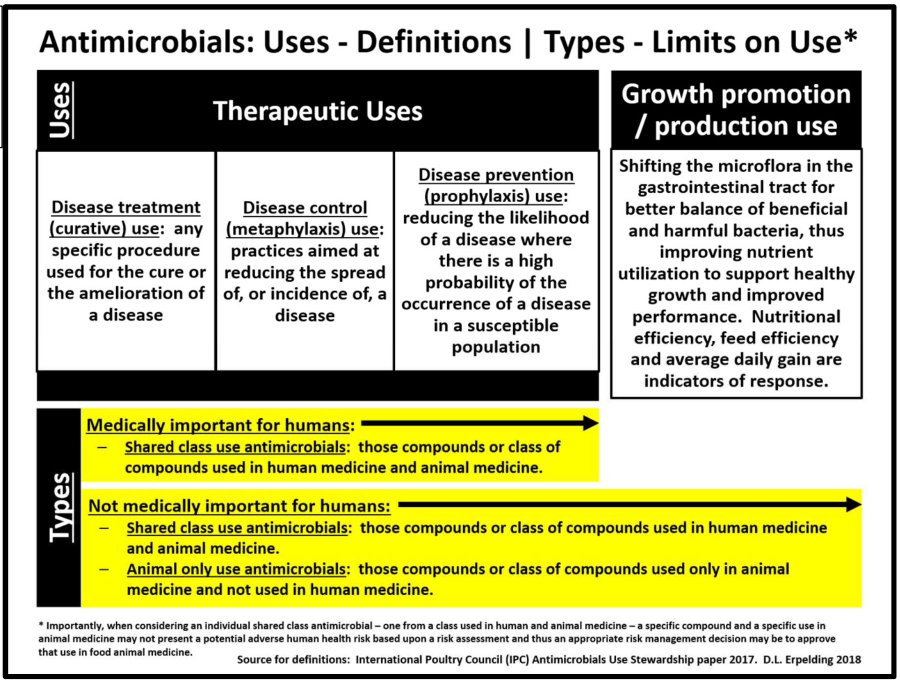
Figure 10



In assessing antimicrobial resistance as part of a regulatory process, it is important to recognize that resistance and residues are both addressed as part of the process. For residues, safety tolerance standards are established, and for resistance, controls on use are determined. (Figure 10)

The core components of the path forward include, first definitions around 'uses' and 'types'. The "International Poultry Council (IPC) Antimicrobial Use Stewardship Paper" provides sound definitions on 'uses'. For 'types', they can generally be categorized as 'medically important for humans' which encompasses most all shared class use antimicrobials, or 'not medically important for humans' which encompasses a few shared class use antimicrobials and animal only use antimicrobials. (Figure 11)

Figure 11



Second, regulatory authorities should incorporate an antimicrobial resistance risk analysis into their approval process, initially applying this to all new approvals, and over time assessing all those currently approved products. Prioritization for the risk analysis should be for those antimicrobials considered the most medically important for humans and then later for those considered not medically important for humans. This prioritization can be guided by the WHO list of critically important antimicrobials. (Figure 12) Also, the WHO 'Global Priority List of Antibiotic-resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics' can be referenced.[14,15] Further, countries may have their own list of most important antimicrobials for human medicine.

Figure 12

WHO Critically Important Antimicrobials for Human Medicine - By Antimicrobial Class*

CRITICALLY IMPORTANT ANTIMICROBIALS	HIGHLY IMPORTANT ANTIMICROBIALS	IMPORTANT ANTIMICROBIALS	ANTIMICROBIAL CLASSES CURRENTLY NOT USED IN HUMANS
<---------- *Medically Important for Humans* ---------->			*Not Medically Important for Humans*
Highest Priority Critically Important Antimicrobials	Amidinopenicillins	Aminocyclitols	Aminocoumarins
Cephalosporins (3rd, 4th and 5th generation)	Amphenicols	Cyclic polypeptides	Orthosomycins
Glycopeptides	Cephalosporins (1st and 2nd generation) and cephamycins	Nitrofurantoins	Phosphoglycolipids
Macrolides and ketolides	Lincosamides	Nitroimidazoles	Polyethers/Ionophores
Polymyxins	Penicillins (anti-staphylococcal)	Pleuromutilins	Quinoxalines
Quinolones	Pseudomonic acids		
High Priority Critically Important Antimicrobials	Riminofenazines		
Aminoglycosides	Steroid antibacterials		
Ansamycins	Streptogramins		
Carbapenems and other penems	Sulfonamides, dihydrofolate reductase inhibitors and combinations		
Glycylcyclines	Sulfones		
Lipopeptides	Tetracyclines		
Monobactams			
Oxazolidinones			
Penicillins (natural, aminopenicillins, and antipseudomonal)			
Phosphonic acid derivatives			
No Drugs used solely to treat tuberculosis or other mycobacterial diseases			

Risk analysis prioritization

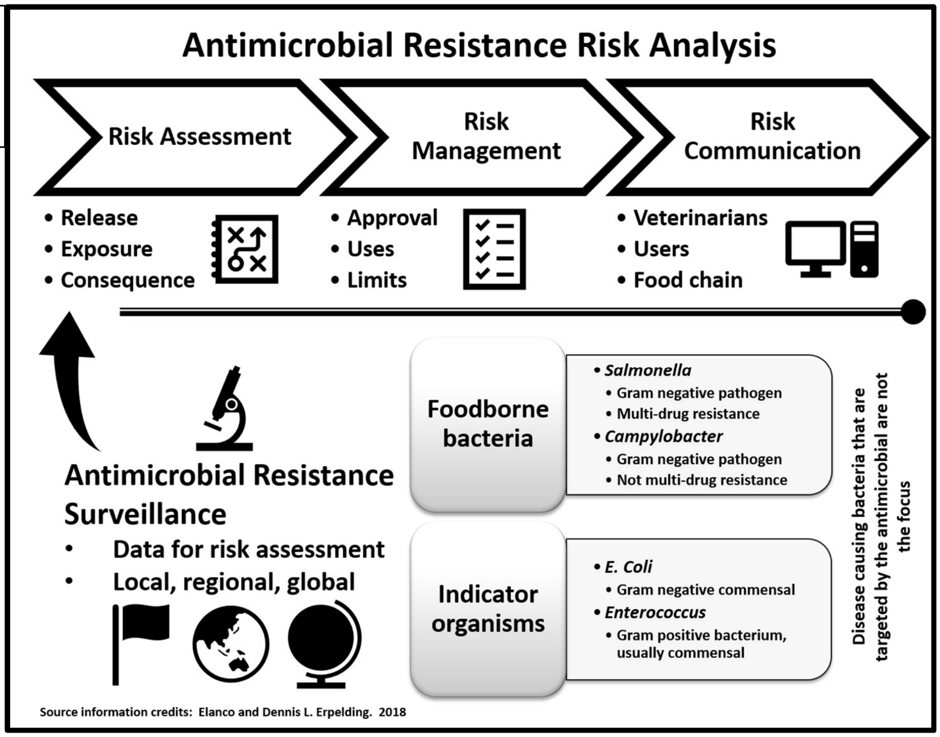
- Highest priority critically important antimicrobials
- High priority critically important antimicrobials
- Highly important antimicrobials
- Important antimicrobials
- Antimicrobial classes currently not used in humans

* *Adapted from "Critically Important Antimicrobials for Human Medicine. 5th Revision 2016. Ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use."* See full report for details and footnotes regarding criteria, categorization, prioritization and class and compound information.

Antimicrobial resistance risk analysis has a defined process with the first step of risk analysis being risk assessment which considers release, exposure and consequence. (Figure 13) Excellent references include the OIE "Terrestrial Animal Health Code Risk Analysis for Antimicrobial Resistance Arising from the Use of Antimicrobial Agents in Animals", Chapter 6.10, and

[14] http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/
[15] http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/

Figure 13



the U.S. Food and Drug Administration Center for Veterinary Medicine Guidance 152.[16,17] Further, scientific experts have conducted and published full risk assessments as was done by Hurd et al. for macrolides.[18] This process allows one to incorporate antimicrobial resistance surveillance data into the risk assessment. This data allows one to put proper context and perspective on bacterial resistance findings. Ultimately, the risk assessment should provide insights for risk managers to determine the appropriate approved uses of and controls for a given antimicrobial.

Risk management is the second step of risk analysis in which the determination of appropriate risk management measures is key. This step considers whether the antimicrobial should be approved, the indications for uses and then the limits and controls around use. Risk management can consider the antimicrobial's importance for human medicine needs as well as its importance for animal care needs, such as defined by OIE.[19] Governmental authorities need to recognize that animal disease needs vary by country and species and animal caretakers have an ethical responsibility to provide proper care for animals under their stewardship. The risk management measures can go from non-approval, to approval with limits on use, to approval with customary use directions. Initial high-level views as one looks toward risk management can be that those 'medically important' are only approved for therapeutic uses, treatment, control and prevention, and those 'not medically important' can be used for therapeutic or production uses. The IPC paper provides an in-depth list of risk management options for considerations. (Figure 14) Non-approval is usually not the best option as animal disease needs do necessitate proper animal care, rather, risk management can be viewed as placing appropriate controls and limits on use. These include the role of veterinarians and professionals, label restrictions on needs for a prescription, and if group or individual use may be appropriate. Further consideration of in-feed use, as relates to in-country controls is important, as often feed mills are best designed to ensure proper inclusion rates.

Risk management decisions around claims for use and route of administration need to be considered, but for these efficacy and animal care practices should be considered. Ultimately, once these risk management decisions are determined they should be placed on product labels or package inserts.

Risk communication is the third step of risk analysis. Based upon the risk assessment and risk management decisions, the risk communication is critical to ensure the proper information garnered from the risk assessment

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16 http://www.oie.int/our-scientific-expertise/veterinary-products/antimicrobials/

17 https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf

18 https://www.researchgate.net/publication/8555522_Public_Health_Consequences_of_Macrolide_Use_in_Food_Animals_A_Deterministic_Risk_Assessment

19 http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf

Figure 14

Risk Management Options

Most Restrictive	⟵	⟶	Least Restrictive
Non approval			Approval
Veterinary use only	Veterinary oversight	Professional oversight	On-farm use
Prescription			No prescription
Available only for veterinary use			Available over the counter for farmer use
Single animal use			Group of animals use
Commercial feed mill mixing only	(Extent of Current Good Manufacturing Practices)		On farm feed mixing
Disease treatment	Disease control		Disease prevention
Via injection*	Orally via water* (medicated water)		Orally via feed* (medicated feed)
Restrictions for use defined on the label			

*Bioavailability may determine the appropriate route of administration to be effective

Source: International Poultry Council (IPC) Antimicrobials Use Stewardship paper - 2017

and risk management process is provided to those involved in the decision making and use of the antimicrobial. This communication needs to include veterinarians, professional advisors, users and food chain stakeholders as all seek to do their part to develop sound antimicrobial use policies and practices. Farmers need to understand and work with their veterinarians and professional resources to ensure they implement proper antimicrobial use at the farm level. With the risk communication, ultimately there should be governmental enforcement mechanisms in place as well to ensure compliance by all. The objective of risk communication should be that all antimicrobials are used properly, used as appropriate yet minimized, and thus diminishing the potential for contributing to antimicrobial resistance development.

Summarizing, the most prudent path forward for antimicrobial use in food animals is to incorporate a science-based antimicrobial resistance risk analysis process into governmental regulatory approval processes. This includes risk assessments with priority focus on those antimicrobials of most importance for human medicine, and risk management decisions, that provide for approval of use, yet entails limits, to ensure appropriate use. And, risk communication should ensure the proper information garnered from the risk assessment and risk management process is provided to those involved in the decision making and use of the antimicrobial. The overall science-based risk analysis approach is as defined in the 'Antimicrobial Use In Food Animals: Prudent Path Forward' illustration. (Figure 1)

Noting that countries have limited resources, the initial steps for the path forward can include: 1) establish and incorporate an antimicrobial resistance risk analysis into the regulatory approval process, at first relying upon other countries' assessments to start the national process, 2) establish a basic antimicrobial resistance bacteria surveillance program for building a database to support full national risk analyses and 3) initiate communication efforts to educate those involved in the antimicrobial selection and use decisions. This multi-step process can provide for building core capability and competency that works toward a comprehensive system. Importantly also, this can provide a basis for evidence-based decisions thus establishing long-term processes that will best yield public health benefits while maintaining antimicrobials for use in food animals; and avoid precautionary actions that have no impact nor provide any benefit. Resource rich countries have been engaged in modifying laws, regulations and policies for over two decades to address antimicrobial resistance, so resource limited countries need to take a long-term view and look at this as a process over time.

Predictions of an antimicrobial resistance apocalypse may continue, however, with implementation of a prudent path forward that seeks to ensure appropriate antimicrobial use, an all-encompassing apocalypse is unlikely in our lifetime. Strategic prioritization and allocation of resources seeking a collaborative 'One Health' approach, with stewardship by all, should provide for antimicrobials that meet public health needs, and animal care needs, globally.

Figure 1

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"Government laws, regulations, guidelines and private sector policies, practices"

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Medically Important for Humans ➢ Shared Class Use ➢ Human and Animal Use	Allowed ☑ Yes	Not Allowed ☒ No	Required ☑ Yes	Allowed ☑ Yes	Not Allowed ☒ No	Not Allowed ☒ No
Not Medically Important for Humans ➢ Shared Class Use ➢ Human and Animal Use	Allowed ☑ Yes	Allowed - Based upon risk assessment ☑ Yes	Not Required ☒ ☑ No / Yes Optional	Allowed ☑ Yes	Allowed – Based upon risk assessment ☑ Yes	Allowed – Under Professional / Veterinary Oversight ☑ Yes
Not Medically Important for Humans ➢ Animal Only Use	Allowed ☑ Yes	Allowed ☑ Yes	Not Required ☒ ☑ No / Yes Optional	Allowed ☑ Yes	Allowed ☑ Yes	Allowed – Under Professional / Veterinary Oversight ☑ Yes

Source: D.L. Erpelding: Adapted from Elanco slide that was modified and solely represents author perspective. 2018 ☑ - Yes ☒ - No

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* Dennis L. Erpelding retired from Elanco, a division of Eli Lilly and Company, December 31, 2017 after over 28 years traveling globally engaging with governments and all food chain stakeholders advancing policy that supported innovation in the animal health sector. He has broad experience formulating policies to address antimicrobial resistance in the legislative, regulatory, food chain and scientific areas; including helping shape laws in the Americas, Asia and the European Union. He has chaired national and international industry projects on antimicrobial resistance.

Mr. Erpelding has been an expert participant or invited speaker at numerous global, regional and national antimicrobial forums and workshops hosted separately or in collaboration by FAO, OIE, WHO and national governments. He has spoken on topics ranging from guiding public health policy, governmental food animal use policy, risk management options, trends of use, private sector involvement and stakeholder engagement in locations including Norway, the European Union, Canada, Vietnam, Thailand, China and the United States of America.

Mr. Erpelding has served in numerous volunteer leadership roles including as Chairman of the Food and Agriculture Export Alliance, on the Executive Committee of the U.S. Dairy Export Council and as Chairman of the U.S. Meat Export Federation. Now he is a consultant and speaker leveraging his global experiences and networks for the betterment of food animal production and food consumers. He can be contacted via email at dennisindy@me.com.