FACTSHEET
Macrolides in the context of critically important antimicrobials

The WHO report "Critically Important Antimicrobials for Human Medicine, 4th Edition" is a guideline that is used to develop risk management strategies to minimize the impact of antibiotic use in animals on human health. The degree to which the use of any one class of antibiotics impacts human health is estimated by asking two questions: 1) Is the antimicrobial class the sole, or one of limited available therapies, to treat serious bacterial infections in people?, and 2) does the treatment of animals with the antibiotic class result in the emergence of antibiotic-resistant foodborne bacteria, or their mobile genetic elements, that are transferable to humans? If the answer to these two questions is "Yes", then the antibiotic is deemed critically important (WHO, 2016).

This ranking strategy works very well for antibiotic classes that are known to be critical for treating potentially fatal nosocomial infections that are caused by multidrug-resistant (MDR) bacteria. For example, the glycopeptide antibiotic vancomycin is used to treat serious MDR enterococcal infections and MDR MRSA in hospital patients and the use of the glycopeptide antibiotic avoparcin in animals selects for enterococci and MRSA with vancomycin resistance (WHO, 2016). However, for some antibiotics more information must be considered to truly determine the impacts to human health. A case in point is the macrolide class of antibiotics. Macrolides have been categorized as Critically Important. However, the available scientific data supports a classification of Highly Important or Important. The reasons for this are as follows:

- Macrolides are classified as critically important mainly because they are first-choice treatement for Campylobacteriosis. Whilst antibiotic treatment in not recommended in most cases of campylobacteriosis, it is a frequent disease. However, in comparison to MRSA infections, campylobacteriosis is not a serious disease. The disease is self-limiting and the majority of ill people will recover without ever seeing a doctor. The fatality rate of campylobacteriosis in the EU is extremely low at 0.03% (EFSA, 2016). The mortality rates for nosocomial MRSA infections are 36 – 59%, depending on the treatment regimen (Brown and Paladino, 2010).

- The majority of all cases of campylobacteriosis caused by *C. jejuni* in the EU (98,5%) remained treatable with azithromycin (EFSA, 2016). Other treatment options are also available including doxycycline, ampicillin, trimethoprim-sulfamethoxazole, ciprofloxacin and gentamicin (Sanford, 2010; Deckert, 2013).

- An inability to treat campylobacteriosis with azithromycin may not impact the health of a patient. Although antibiotic treatment is available, it does not appear to significantly impact the clinical outcome of campylobacteriosis. Therapy was found to shorten the duration of diarrhea by just 1.3 days (Ternhag, 2007) In patients with invasive disease, antibiotic treatment did not shorten hospital stays or decrease mortality (Feodoroff, 2011).

- The use of macrolide antibiotics in animals does not jeopardize the effective treatment of MDR *Salmonella* infections in people with azithromycin. This macrolide antibiotic, which is only used in humans, has activity against *Salmonella* and other Gram-negative bacteria but older macrolide antibiotics do not (Olson, 2002; Wagner, 2008; Retsma, 1987). Thus, the use older macrolide antibiotics such as tylosin and tilmicosin will not select for azithromycin-resistant strains of *Salmonella* (or their mobile genetic elements) that can be transferred to humans.

- Shigellosis and Legionnaires' disease were used to categorize macrolide antibiotics as CIA. There is no relationship between the use of macrolide antibiotics in animals and the effective treatment of these diseases. Humans are the sole reservoir of *Shigella* and the bacterium is transmitted by the fecal oral route (Prince, 2010). *Legionella* is transmitted to humans via the inhalation of contaminated water droplets (Fields, 2002). Azithromycin-resistant strains of *Shigella* have been isolated that contain the resistance determine *ermB* (MMWR, 2014). The gene was likely acquired from human gut flora; the gene was first detected in humans some 30 years ago (LeBlanc, 1986) and is still be found in the saliva and feces of

healthy people in the EU today (Card, 2014). Macrolide-resistant strains of *L. pneumophila* have not been isolated (Bruin, 2012).

- Macrolide resistance imposes a fitness cost on *C. jejuni* (Luangtongkum, 2012) and the undesirable mutations are readily purged from the genome (Wilson, 2008). However, transferable macrolide resistance has been recently described and warrants specific surveillance (Wang, 2014)

- The majority of all cases of campylobacteriosis in the EU are caused by *Campylobacter jejuni* and chicken meat is a primary vehicle of transmission (EFSA, 2016). Only a small fraction of the *C. jejuni* in broilers (5,9%) and chicken meat (1,6%) were resistant to macrolides antibiotics (EFSA, 2016). The prevalence of macrolide-resistant *C. jejuni* isolated from humans with campylobacteriosis is very low (1.5%) (EFSA, 2016).

- Some 8% of all speciated *Campylobacter* strains isolated from humans are *C. coli* (EFSA, 2016). Although macrolide-resistant strains of *C. coli* are isolated from both humans and pigs, (EFSA, 2016) pork is an unlikely source for campylobacteriosis. Pork contains very low levels of *C. coli*. Genetic-based attribution data suggests that only 1% of the *C. coli* strains that cause campylobacteriosis in humans originate in pigs (Sheppard, 2010). *Campylobacter coli* isolated from broiler meat has a 17% macrolide resistance rate in the EU, but remains a uncommon occurrence in human disease (EFSA, 2016)

- The recently published WHO Global Priority list of Antibiotic Resistant Bacteria does not include macrolide-resistant species except *Helicobacter pylorii* which cannot be considered as linked to animal use today.

The World Animal Health Organization (OIE) has categorized macrolide antibiotics as Veterinary Critically Important Antibiotics (VCIA) because they are one of a few antibiotics that can be used to treat mycoplasma infections in pigs and broiler and hemorrhagic digestive disease in swine and liver abscesses in cattle (OIE). These key tools must remain available to veterinarians. Mycoplasma infections remain extremely prevalent in poultry productions systems of developing countries and there is a real need to treat such infections early in order to prevent chronic respiratory disease that involves an additional infection with Escherichia coli that is much more difficult to treat and necessitates other classes of antibiotics.

This data suggests that macrolide antibiotics can be used in animals without significantly impacting human health so long as they continue to be used judiciously. It is also important to be noted that most of the indications of macrolides include bacteria that grow fairly fastidiously and therefore sensitivity testing is sometimes difficult. We recommend the following risk management measures for the use of macrolides in animals:

- Some registrations that allow the use of low concentrations of macrolide in feed should be removed, and growth promotion with macrolides should be phased-out
- All macrolides should be under veterinary oversight in accordance with the product indications.
- Off label uses of products containing macrolide antibiotics should be limited to the strict application of local legislation on the cascade.
- The use of macrolide antibiotics for prevention should be restricted to the indications on the product label.
- The susceptibility of *Campylobacter* from animals to macrolide antibiotics should continue to be monitored

REFERENCES

Beauté, J., E. Robesyn and B. de Jong, on behalf of the European Legionnaires' Disease Surveillance Network. 2013. Legionnaires' disease in Europe: all quiet on the eastern front? Eur. Respir. J. 42:1454-1458.

Brown, J., and J. A. Paladino. 2010. Impact of rapid methicillin-resistant Stapylococcus aureus polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. Pharmacoeconomics. **28**:567-575.

Bruin, J. P., E. P. F Ijzerman, J. W. den Boer, J. W. Mouton, and B. M. W. Diederen. 2012. Wild-type MIC distribution and epidemiological cut-off values in clinical *Legionella pneumophila* serogroup 1 isolates. Diagn. Microbiol. Infect. Dis. **72**:103-108.

Card, R. M., P. J. Warburton, N. MacLaren, P. Mullany, E. Allan, and M. F. Anjum. 2014. Application of microarray and functional-based screening methods for the detection of antimicrobial resistance genes in the microbiomes of healthy humans. PLOS ONE **9**:e86428.

Centers for Disease Control. 2014. Notes from the field: *Shigella* with decreased susceptibility to azithromycin among men who have sex with men – United States, 2002-2013. MMWR **63**:132-133.

DANMAP 2000 - Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark.

http://www.danmap.org/Downloads/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2000.ashx Accessed March 17, 2014.
DANMAP 2012 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. http://www.danmap.org/Downloads/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202012/Danmap_2012.ashx Accessed March 17, 2014.
Deckert, A. E., R. J. Reid-Smith, S. E. Tamblyn, L. Morrell, P. Seliske, F. B. Jamieson, R. Irwin, C. E. Dewey, P. Boerlin, and S. A. McEwen. 2013. Antimicrobial resistance and antimicrobial use associated with laboratory-confirmed cases of *Campylobacter* infection in two health units on Ontario. Can. J. Dis. Med. Microbiol. **24**:e216-e21.
Fields, B. S., R. F. Benson, and R. E. Besser. *Legionella* and Legionnaires' disease: 25 years of Investigation. Clin. Microbiol. Rev.15:506-526.
EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2016. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2015. EFSA Journal 2016;14(12):4634, 231 pp. doi:10.2903/j.efsa.2016.4634
EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2016. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014. EFSA Journal 2016;14(2):4380, 207 pp. doi:10.2903/j.efsa.2016.4380
EMA (European Medicines Agency). Public consultation regarding the request to the European Medicines Agency from the European Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. EMA/776691/2013 Veterinary Medicines Division. 16 December 2013
Feodoroff, B., A. Lauhio, P. Ellström, and H. Rautelin. 2011. A nationwide study of *Campylobacter jejuni* and *Campylobacter coli* bacteremia in Finland over a 10-year period, 1998-2007, with special reference to clinical characteristics and antimicrobial susceptibility. Clin. Infect. Dis. **53**:e99-e106.
Jong Ad, Bywater R, Butty P, Deroover E, Godinho K, Klein U, Marion H, Schliessl B, Simjee S, Smets K, Thomas V, Vallé M and Wheadon A. 2009. A Pan-European survey (EASSA) of antimicrobial susceptibility towards human-use antimicrobial drugs among zoonotic and commensal enteric bacteria isolated from food producing animals. Journal of Antimicrobial Chemotherapy, 63: 733-744
Jong Ad, Thomas V, Simjee S, Godinho K, Schiessl B, Klein U, Butty P, Vallé M, Marion H, Shryock TR. 2012. Pan-European monitoring of susceptibility to human-use antimicrobial agents in enteric bacteria isolated from healthy food producing animals. Journal of Antimicrobial Chemotherapy, 67:638-651**LeBlanc, D. J., J. M. Inamine, and L. N. Lee.** 1986. Broad geographical distribution of homologous erythromycin, kanamycin, and streptomycin resistance determinants among group D streptococci of human and animal origin. Antimicrob. Agents Chemother. **29**:549-555.
Luangtongkum, T., Z. Shen, V. W. Seng, O. Sahin, B. Jeon, P. Liu, and Q. Zhang. 2012. Impaired fitness and transmission of macrolide-resistant *Campylobacter jejuni* in its natural host. Antimicrob. Agents Chemother. **56**:1300-1308.
NARMS. 2014. NARMS Integrated report: 2014. https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059103.htm
Olson, M. E., H. Ceri, D. W. Morck, A. G. Buret, and R. R. Read. 2002. Biofilm bacteria: formation and comparative susceptibility to antibiotics. Can. J. Vet. Res. **66**:86-92.
Retsema, J., A. Girard, W. Schekly, M. Manousos, M. Anderson, G. Bright, R. Borovoy, L. Brennan, and R. Mason. 1987. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered ring macrolide with improved potency against Gram-negative organisms. Antimicrob. Agents Chemother. **31**:1939-1947.
Gilbert DN , Moellering RC , Eliopoulos GM , Chambers HF , Saag MS editor. 2010. The Sanford Guide to Antimicrobial Therapy**,** 40th ed.. Sperryville, VA: Antimicrobial Therapy, Inc.
Sheppard, S. K., J. F. Dallas, D. J. Wilson, N. J. C. Strachan, N. D. McCarthy, K. A. Jolley, F. M. Colles, O. Rotariu, I. D. Ogden, K. J. Forbes, and M. J. C. Maiden. 2010. Evolution of an agriculture-associated disease causing *Campylobacter coli* clade: evidence from national surveillance data in Scotland. PLoS One. **5**:e15708.
Ternahg, A., T. Asikainene, J. Giesecke, and Karl Ekdahl. 2007. A meta-analysis on the effects of antibiotic treatment on duration of symptoms caused by infection with *Campylobacter* species. Clin. Infect. Dis. **44**:696-700.
Wang Y, Zhang M, Deng F, Shen Z, Wu C, Zhang J, Zhang Q and Shena J, 2015. Emergence of Multidrug-Resistant Campylobacter Species Isolates with a Horizontally Acquired rRNA Methylase. Antimicrobial Agents and Chemotherapy, 58, 5405–5412.
Wagner, R. D., S. J. Johnson, and C. E. Cerniglia. 2008. In vitro model of colonization resistance by the enteric microbiota: effects of antimicrobial agents used in food-producing animals. **52**:1230-1237.
WHO, 2016. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). . Critically important antimicrobials for human medicine, 4th edition.
WHO, 2017. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 downloaded 1st of March 2017
Wilson, D. J., E. Gabriel, A. J. H. Leatherbarrow, J. Cheesbrough, S. Gee, E. Bolton, A. Fox, C. A. Hart, P. J. Diggle, and P. Fearnhead. 2008. Rapid evolution and the importance of recombination to the gastroenteric pathogen *Campylobacter jejuni*. Mol. Biol. Evol. **26**:385-397.

This factsheet was produced by experts working together in HealthforAnimals, the global animal medicines association. www.healthforanimals.org