Divergent position on the report on Categorisation of antimicrobials in the European Union

Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals
(EMA/CVMP/CHMP/682198/2017)

We, the undersigned, have a divergent position to the report on Categorisation of antimicrobials in the European Union, by the Antimicrobial Advice *ad hoc* Expert Group (AMEG).

The new AMEG categorisation is said to build on the conclusions of the first AMEG report. However, there is a notable departure from the previous AMEG, in that the previous numerical integrated scoring system is no longer utilized that provided a qualitative estimate of the overall probability of antimicrobial resistance (AMR) transfer from animals-to-humans (EMA/AMEG, 2014). Instead, more reliance is placed on specific resistance genes associated with certain antibiotic classes that could have important human health consequences. It is not specific resistance genes but the sum of all AMR mechanisms per class of antibiotic that is the burden to public and animal health. As such, there is a lack of transparency in the new AMEG report of how probabilities of AMR transfer, between animals-to-humans, are taken into account. There is no longer an emphasis on horizontally-transferable genetic elements (e.g. conjugative plasmids containing AMR genes, or mobilisable genes via transposons, integrons, gene cassettes), while the previous numerical scoring system acknowledged horizontally-transferable elements as key importance in the spread of AMR between animals-to-humans. While addressing AMR cross-resistance from specific resistance genes can assist with developing an antimicrobial categorisation system, the lack of focus on AMR co-selection, issues more related to horizontally-transferable genetic elements, leads to a far less meaningful categorisation system to mitigate against AMR risk of public health importance.

The AMEG report outlines its principles of categorisation by describing 4 categories. However, these principles are not followed consistently. Category A is principally for EU authorized human antibiotics only; nevertheless, examples of macrolides (azithromycin, clarithromycin) are in Category C and not authorised in EU veterinary medicine. Category D is also for antibiotics that do not select for resistance to Category A through specific multi-resistance genes; nevertheless, aminopenicillins are in Category D and well known to select for extended-spectrum beta-lactamases (**ESBL**) genes (Monobactams are in Category A) and specific carbepenamase resistance genes (Carbepenams are in Category A) associated with EU food-animal populations (e.g. VIM-1, OXA-23, OXA-61 genes). While the AMEG categorisation is described as NOT a 'risk' assessment, Category D antibiotics are concluded by AMEG as a lower AMR 'risk' compared to Category C. Macrolides and aminoglycosides are concluded by AMEG as a lower 'risk' compared to Category B.

The new AMEG categorization is without fulfilling part of the EC mandate to consider the route of administration. The AMEG chose not to include the route of administration as an additional categorisation criterion, due to the extra level of complexity given all the different formulation/class combinations. Since approximately 90% of annual EU-wide sold veterinary antibiotics are consistently for oral administration, then the AMEG has not explained why different oral formulations (e.g. premixes, oral powders/granules/solutions for drinking water) are too complex to be factored into the categorization tables. GI microbiome studies have shown that oral antibiotics demonstrate hundreds to thousands fold higher selection pressures and persistence of AMR GI microflora compared to other routes of administration (based on randomised controlled studies in rodents). Consequently, AMR GI bacteria are the major types of zoonosis concerns (e.g. ESBL/AmpC/Carbapenemase-producing *E. coli* & *Salmonella spp*., ciprofloxacin-resistant *Campylobacter spp*.).

Contrary to the 'precautionary principle', AMEG will not reconsider WHO critically important antibiotics (CIAs) placed in lower AMEG categories (categories C or D) for common use in animals, unless specific genes in certain bacterial species are found more commonly by the EU surveillance network. However, a WHO sponsored meta-analysis found that targeting primary population

consumption of food-animal antibiotics, especially non-therapeutic indications (e.g. prophylaxis, metaphylaxis), was associated with best AMR reductions (Tang KL, *et al*. *BMJ Global Health* 2019;4: e001710.). Using this approach, another WHO sponsored meta-analysis concluded best AMR reductions were found with macrolides for both *Enterococcus* and *Campylobacter spp*. in food animal faecal samples (Tang *et al*., 2017 *Lancet Planet Health* 1: e316–27). Macrolides are the most sold WHO highest-priority CIA for EU veterinary use (7.4% of total sales of food animal antimicrobials in 31 countries in 2017-91.1% sold for oral use) (9th ESVAC report). AMEG places macrolides in Category C, at odds with the WHO classification as highest-priority CIAs. Macrolides are non-essential, under EU conditions, for *Lawsonia intracelluaris* and *Mycoplasma spp*. with available alternatives (vaccines, non-CIAs: pleuromutilins, tetracyclines). Macrolides are essential for serious zoonotic *Campylobacter spp*. infections in people, due to a high prevalence of ciprofloxacin-resistance. Campylobacteriosis is the most frequently notified EU disease in humans, with >220,000 cases annually. AMEG concludes *Campylobacter spp*. case fatalities are low, but have not considered disability-adjusted life years (DALYs) or costs for hospitalization/prolonged therapy. EFSA/ECDC report (2019) noted proportions of human erythromycin-resistant *C. jejuni* isolates were low (2.0%, but 8-11% in animal *C. jejuni* isolates in some EU countries) but markedly higher in *C. coli* (12.8%) with high to very high (21.4–59.5%) in 4 of 14 countries testing >10 isolates. AMEG only mentions *erm* gene resistant *Campylobacter spp*. as cause for concern, without noting *erm* genes are common in other EU animal bacteria (e.g. gram positives, such as *S. aureus* & LA-MRSA and emerging in Salmonella). In conclusion, macrolides cannot be justified in Category C as this is at odds with public health needs.

AMEG places the WHO CIA class, aminopenicillins (amoxicillin, ampicillin), in Category D (first choice option), which is not in-line with the WHO 6th classification that separates aminopenicillins from non-CIA narrow-spectrum penicillins. EFSA/ECDC (2019) reports both *Campylobacter* and *Salmonella spp.* as the majority of reported EU zoonosis cases. Ampicillin resistance among human Salmonella cases was in the top three highest proportions of *Salmonella spp*. resistant isolates in 2017 (27.5% range:6.4%-81.4% - all non-typhyoid cases; 53.3% range:4.3%-85.7% - *S. Typhimurium* cases), corresponding with similar AMR patterns found from food animal carcasses. Aminopenicillins can also select LA-MRSA and ESBL genes (e.g. CTX-M-1 family, SHV-12, and AmpC (e.g. CMY2)) in *Salmonella spp*. and *E. coli.* EU-based studies using different molecular techniques show the dynamics of ESBL *E. coli* transfer between animal and human populations. High resolution studies (whole genome sequencing) show clonal transfer of ESBL *E. coli* between food animals and farm workers in close contact or highly-related ESBL plasmids (de Been M *et al*., 2014 PLoS Genet 10(12): e1004776.). Medium resolution studies (multi-locus sequence typing) demonstrate ESBL *E. coli* genetic close similarity between meat products and human faecal carriage (Overdevest I *et al*., 2011 *Emerging Infectious Diseases* 17(7):1216-1222), where this faecal carriage can be later decreased after lower food-animal antibiotic consumption (Willemsen I *et al*., 2015 *PLoS One*; 10:e0141765.). Low resolution studies (PCR) show nearly two-thirds of community-acquired ESBL *E. coli* carriers are from human-to-human transmission, with non-human sources accounting for the other third, suggesting ESBL *E. coli* spread alone isn't self-maintained without non-human sources (Mughini-Gras L *et al.*, 2019 *Lancet Planet Health* 2019:3: 357–69). In the Nordic countries, narrow-spectrum penicillins accounted for the majority of penicillins sold (range: 54% to 96% of total penicillins sold), whereas in other EU countries extended spectrum (mainly amoxicillin) was the majority (9th ESVAC report). Nordic countries have sizeable food animal industries, while demonstrating first choice use of narrow-spectrum penicillins and not aminopenicillins, for most Veterinary pathogens. Experimentally in pigs, oral amoxicillin exerted the same selection pressure for gastrointestinal ESBL (CTX-M) *E. coli* as 3rd/4th gen. cephalosporins (Cavaco LM *et al.*, 2008 *Antimicrob Agents Chemother*. 52(10):3612-6.). In conclusion, aminopenicillins cannot be justified in Category D as this directly counteracts the public health benefits of restricting 3rd/4th gen. cephalosporins to Category B.

Keith Baptiste, Niels Christian Kyvsgaard, Paolo Pasquali, Melinda Nemes-Terenyi (CVMP)
Kolbein Gudmundsson, Alar Irs, Daniela Melchiorri, Sinan B. Sarac, Melinda Sobor (CHMP)