VetCAST meeting in Schiphol, Amsterdam, 16-03-18, 10am-4pm.


1. Welcome and tour-de-table.
   a. NB: Several attendees had joined as VetCAST members in the past 5-6 months. Dik Mevius gave a warm welcome to all new VetCAST members!

2. Status of the JPIAMR project (Dik Mevius)
   a. The VetCAST JPIAMR network project is nearing completion. Dik explained how we have accomplished the four main objectives of the project:
      ii. Roadmap to access and handle PK data: the SOP has been finalized, but is yet to be published on the EUCAST homepage.
      iii. Training course on PK/PD and breakpoint determination: a successful course was held in Toulouse in September 2017, and a small follow-up course had been held in Uppsala in December 2017 + another follow-up course is scheduled for the EAVPT Congress in Wroclaw, Poland, June 2018.
      iv. Development of one clinical breakpoint: we have all data required to set a breakpoint for florfenicol in Pasteurellaceae.
   b. Follow up to ensure sustainability of VetCAST
      i. EMA: the Steering Committee (SC) is in contact with EMA. Although EMA cannot fund VetCAST, our EMA contact person has promised to draft how the working relationship will function.
      ii. DG Sanco. Using a standard letter, CVOs from 4 countries have contacted DG SANCO requesting support for VetCAST.
      iii. A recently commenced Horizon 2020-funded project on phenotypic resistance ("IMPART") incorporates activities relevant to VetCAST, including setting of ECOFFs. Kees Veldman is the coordinator.
      iv. Other VetCAST-related networks/projects have recently been applied for by members of the SC.
      v. In 2019, a new JPIAMR call on AMR surveillance will be launched. This is likely to be relevant for VetCAST.

3. VetCAST position paper (Pierre-Louis Toutain)
   a. This paper addresses the VetCAST approach to establishing clinical breakpoints; it highlights some of the veterinary-specific challenges. After a long and difficult review process, the paper was finally published in Frontiers in Microbiology in December 2017: https://www.frontiersin.org/articles/10.3389/fmicb.2017.02344/full
   b. The paper has been extensively both viewed and downloaded from the journal homepage since publication (>1200 views, >300 downloads)
   c. The paper is Open Access and will soon be uploaded to the EUCAST homepage.

4. Collection of MIC data (Kees Veldman)
a. Kees presented the collected MIC data, which primarily comprises tetracycline, as this drug was the first one in focus.

b. In the last year the principal focus changed to florfenicol; a good quantity of florfenicol MIC data has been gathered from VetCAST members and from CEESA publications. Based on these data, the following ECOFFs will soon be proposed to EUCAST (NB: data yet to be validated):
   i. Actinobacillus pleuropneumoniae (proposed ECOFF=8 g/L),
   ii. Mannheimia haemolytica (proposed ECOFF=2 g/L),
   iii. Bordetella bronchiseptica (proposed ECOFF=0.5 g/L)

c. The criteria and methods used to establish ECOFFs were presented. It was agreed that we should attempt, together with John Turnidge and Gunnar Kahlmeter, to define tentative ECOFFs (=TECOFFs) for some of the smaller data-sets we have collected.

d. All VetCAST members are encouraged to contact Kees (kees.veldman@wur.nl) if they have additional florfenicol or tetracycline MIC data they wish to contribute.

e. The QC criteria for setting ECOFFs were explained – and these are also freely available on the EUCAST homepage. Some important points;
   i. Minimum of 5 distributions from different labs
   ii. Minimum of 15 observations/distribution
   iii. Minimum of 100 observations in total
   iv. The host source is inconsequential, and not relevant if isolates are for clinical pathogen or commensal organisms

f. Kees uses two methods for setting ECOFFs:
   i. Eyeball method
   ii. ECOFFinder (available on CLSI website, and a newer version was kindly provided by John Turnidge)

g. Prospective MIC data collection will be facilitated by the new project IMPART led by Kees. In this project, 50,000 Euros are allocated for Sensititre MIC plates, which will be distributed to various partners of the project. Currently, the partners are designing 3 different plates (8 concentrations per drug / 12 drugs per plate)

h. Truncation is a major problem encountered when using commercially available MIC panels. Ideally, MIC panels should be designed to avoid truncation of MIC distributions.

5. Collection of PK data (Ludovic Pelligand)
   a. Two years ago, Ludovic made a list of those tetracyclines and cephalosporins licensed in EU member states. This gave a unique insight into what is commercially available + the different dosages used.
      Suggestion: perhaps we should make a similar list for florfenicol as well.
   b. A roadmap/SOP was prepared (see section 2 above)
   c. Florfenicol PK data. A PK/PD breakpoint has been proposed by VetCAST using Monte Carlo simulation, based on PK data from approximately 50 calves representing 3 separate studies.
   d. Tetracycline PK data. At this time, we only have data for 10 calves from a study by Peter Lees. We have tried unsuccessfully to obtain additional PK data from the literature, the FARAD database, and pharmaceutical companies. More PK data are needed to establish PK/PD breakpoints.
e. Fluoroquinolone PK data. Ludovic has asked a few pharmaceutical (pioneer and generic) companies for individual PK data in dogs. Responses have been received but no data so far.

f. Obtaining more PK data? Various ideas on how to increase access to PK data were discussed. Ronette Gehring proposed moving away from population modelling to physiological modeling. If this is done, data from the FARAD database may be useful.

6. PK study – perioperative use of cefazolin (Petra Cagnardi)
   a. Petra outlined the results of a PK study on the perioperative use of cefazolin in dogs. Analysis of cefazolin from samples obtained from 78 dogs at 8 time points allowed the computation of a PK/PD cut-off of 2 G/L.

7. Florfenicol CBP (Pierre-Louis Toutain)
   a. Using a model developed by Lena Friberg, it was decided to use AUC/MIC as the best PK/PD index to correlate with outcome
   b. Probability of target attainment (PTA) analysis: the PK/PD cut-off was determined to be 1 µg/ml
   c. Based on this cut-off and the florfenicol ECOFFs (see point 4 above), we need now to set a CBP. Ideally, clinical efficacy data should be used to support the decision of a CBP. Furthermore, the decision process to reach a CBP should be formalized in a publicly available rationale document / SOP, as is the case for EUCAST.
   d. Clinical efficacy data
      Such data are not readily available. It was proposed that clinicians representing VetCAST could discuss this issue with European colleagues to help to establish a suitable clinical cut-off.
   e. Note: Kees is expecting additional MIC data to support the selection of ECOFF.

8. Which breakpoints should be prioritized next? (Ludovic Pelligand and Pierre-Louis Toutain)
   a. Azalides for treatment of food animals. There are available PK data required to determine CBPs, but there is an unsolved issue concerning the fact that MICs in serum are much lower than in broths. For example, for tulathromycin there can be up to 50-fold difference for M. haemolytica and P. multocida.
      i. Ideally, we should establish and use a "scaling factor" for each azalide/pathogen combination to adjust for this difference. Potentially, a few isolates could be then tested in serum, and many more isolates could be tested in broth as usual
      ii. One challenge is how to standardize serum for these tests, an issue recently addressed in the literature by Dahlhoff.
   b. Amoxicillin for injection and oral use in pigs: most PK data needed to propose CBPs are available
   c. General speculation on how to prioritize CBPs in the future:
      i. We can review missing CBPs in CLSI
      ii. We can ask what clinicians need and propose
      iii. We can note which PK data we now have and then use that.

9. EUCAST news (Christian Giske)
a. Christian introduced the standing and ad hoc EUCAST subcommittees, and he presented the worldwide implementation of EUCAST standards and national antimicrobial committees

b. Ongoing EUCAST consultations
   i. Definition of intermediate susceptibility category
   ii. Discussions on breakpoints that may require revision/updating

c. Examples of new breakpoints were given (e.g. Aeromonas). There are also visual reading examples to ensure correct interpretation of results

d. There is a dosage table to highlight which dosage breakpoints relate to.

e. There are several new EUCAST publications, e.g. on colistin AST and on the flaws of MIC-based dose-adjustments

10. Declaration of conflicts (COI) of interest (Peter Damborg)
    a. Peter explained the VetCAST COI policy and mentioned that only about 50% of VetCAST members have filled out and returned the ESCMID DOI form. All VetCAST members are now requested to return completed forms in the near future (a reminder and the form will be re-circulated soon).

11. General discussion
    a. Some members of the SC have expressed a wish to step-down from making major contributions in the coming years. Younger people should be encouraged to take over, but continuity requires that this should be a gradual process.
    b. Heavy work pressures on SC members can be relieved if working groups are established among VetCAST members. Such groups are yet to be defined, but SC members may appoint people to such groups in the future.
    c. Christian Giske explained that most of the time CHMP and EUCAST agree on newly proposed CBPs. If they disagree on CBPs, EMA and EUCAST can in theory publish their own breakpoints, although this approach may over time compromise the relation between the organisations, and has therefore thus far been avoided.

/Peter Damborg