MITACS_MSRI_AFMnet-CRM Workshop on Therapeutic Efficacy in Population Veterinary Medicine
19-22 October 2005, BIRS

Report
  • **General**
This workshop has been organized by the MITACS BIO5 team around the general theme of therapeutic efficacy in population veterinary medicine at Banff International Research Station. It has brought researchers working in applied mathematics, veterinary sciences, behavioural sciences as well as in microbiology and nutrition. Additional to academic researchers, speakers and participants from other public sectors attended the workshop: Agriculture and Agri-Food Canada and the Public Health Agency of Canada. Representatives of Pfizer Animal Health and Elanco Animal Health were present. The representatives of Scheringer-Plough Animal Health and Avantis, who are among the sponsors of the workshop, were not able to attend but asked for a follow up on the workshop outcomes. The conferences covered different aspects relating to animal collective therapy, in particular in swine and poultry, in terms of determinants and outcomes, spanning the areas of: animal behaviour, quantification of feeding behaviour and its relationship with pharmacokinetics, pharmacodynamics and antibiotic resistance, risk assessment in terms of antibiotic use and genetic determinants for antibiotic resistance and its different transfer modes, resistance to infection diseases, zoonotical borne viruses, identification of contamination sources, characterization of microbial hazards and manure, impact on the environment. A complete portrait of animal behaviour in the context of therapeutic efficacy has been drawn. A whole overview of the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS/PICRA) has been given to explain the national program of antimicrobial use in food animals and surveillance system for antimicrobial resistance arising from food animal production. An update of PK/PD analysis in antibiotics was very useful to highlight the role of the prudent use of antibiotics in preserving their effectiveness and to clarify the objectives of the seed project. A general idea of mathematical approaches used to handle biological complexity has been given with emphasis on the need for collaborative efforts between mathematical sciences and experimental research. The keynote speakers have given their own ideas of possible collaborations with the MITACS' team, in terms of their research interests/expertise and in complement to the current MITACS project. Very interesting discussions took place, always balanced between the different areas of research. Presence of industrial researchers from Pfizer Animal health in particular, allowed gaining a clear idea of the pharmaceutical industry expectations and practices.

  • **Financial support of the workshop**
      - MITACS
      - AFMnet
      - MSRI
      - CRM
      - Pfizer Animal Health
      - Scheringer-Plough Animal Health
      - Avantis

- **Organizing Committee**
  - Chair, Fahima Nekka, Université de Montréal
  - Jérôme del Castillo, Université de Montréal
  - Renée Bergeron, Université Laval
  - Jacques Bélair, Université de Montréal
  - Jun Li, Université de Montréal
  - Don Schaffner, Rutgers University
  - Heidi Shraft, Lakehead University/AFMnet
  - Claude Miville, FPPQ
  - Jeff Lucas, MITACS

- **Minutes from the discussion about collaborations and perspectives, October 22ⁿᵈ**

Were present at this last day meeting researchers from MITACS team (F. Nekka, J. del Castillo, R. Bergeron, J. Bélair); from FPPQ (C. Miville); from AFMnet (A. Paulson, M. McLaughlin, H. Schraft, L. Truelstrup, H. Eberl, J. France); from Pfizer Animal Health (Bruce Groves). The objective was to identify potential collaborations to be added to the current MITACS project or to make it a joint MITACS-AFMnet project, to identify additional funding sources and to address the involvement of pharmaceutical companies.

1. Discussion on research avenues

The following questions have been suggested as being important to be addressed:
- Is the veterinary use of antibiotics (AB) appropriate?
- How could we improve AB use to make it safer and more efficient: *this is the main aim of the seed project which is centred around the* **judicious use** *of antibiotics.*
- How does the risk of using the labelled dose compare with the risk of using an unapproved one?
- It would be interesting to model withdrawal time according to dosage.
- Another avenue is to compare the efficacy of alternatives to AB versus AB efficacy.
- The risk of using the approved dose must be weighed against the risk of using an off-label dose.
- One concern about risk assessment is that it may lead to a ban on AB use.

Three main areas of research have been identified for the full project
- Impact of feeding behaviour on dosage efficacy
- Alternatives to AB and their assessment
- Risk analysis, including assessment, policy making and risk communication. Qualitative risk rating systems show major limitations (for example, passing from high-dimensional information to low-dimensional evaluation causes loss of information). Use of more/new mathematical methods, including Rapid Risk Rating Technique, for quantitative human health impact of continued animal use of antibiotics.
- With MITACS funding, we have to make sure that new mathematics are being developed. In the seed project, from the mathematical point of view, we have used

dynamical systems (represented by the multi-compartmental approach defined by systems of ODE) with stochastic input. We analyzed the statistical properties in terms of stability and conservation of the dynamical system. This approach is new in pharmacokinetics. Use of this approach has to be widespread in biological problems and include other sources of stochasticity and analyse their impacts since the generally-used assumption of determinism are questionable when considering the randomness involved in biological reality. We have also introduced competition mechanisms in collective behaviour which accounts for dynamical interactions between individuals (the interaction between individuals is incorporated in the evolution of the group). The approach we have used to model competition situations has to be put within the framework of hierarchical nonlinear models used for repeated measurement data.

2- <u>Stakeholders and potential funding sources</u>

- Veterinary Drugs Directorate (VDD) Divisions
- Health Canada
- Public Health Agency of Canada (PHAC)
- Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- Canadian Food Inspection Agency (CFIA)
- Agriculture and Agri-Food Canada (AAC)
- Pork producers' associations (Alberta Pork, Sask Pork, Manitoba Pork, Ontario Pork, etc.).
- Fonds québécois de la recherche sur la nature et les technologies (FQRNT)
- Conseil des recherches en pêche et en agroalimentaire du Québec (CORPAQ)
- Pharmaceutical industry
- Nutrition companies and integrators
- CIHR – NSERC
- NSERC – strategic
- AFMnet
- CVMA (Canadian Veterinary Medical Association)
- CAHI (Canadian Animal Health Institute)

3- <u>Discussion regarding the involvement of pharmaceutical companies in the project</u>

- The pharmaceutical industry is product oriented. Mathematics are used in drug development, but not much in resistance studies.
- Pharmaceutical companies work with approved products, and research using off-label dosage may place them in an awkward position. They report to Health Canada and must demonstrate that they comply with their guidelines.
- Pharmaceutical companies may not be interested in funding a project that may benefit their competitors, for instance, research that may eventually lead to approval of the off-label dosage of a non-proprietary drug. However, they may want to fund projects that would evaluate the risk of using the approved dose of a medication.

- Perhaps suppliers of CTC (the antibiotic used by MITACS team in the seed project) would be willing to get involved in our project, given that it may lead to the approval of a higher dosage for their product.
- Much research has been done on newer antibiotics. In fact, new antibiotics are in general derivatives of known families of drugs. Old antibiotics appear to be used the most and yet have not been documented as much.

List of participants to the workshop
- Fahima Nekka : Université de Montréal
- Jérôme del Castillo : Université de Montréal
- Renée Bergeron : Université Laval
- Candido Pomar, Agriculture & Agri Food Canada
- Jacques Bélair : Université de Montréal
- Marray McLaughlin : AFMnet
- Heidi Schraft : Lakehead University
- Lisbeth Truelstrup: AFMnet / Dalhousie University
- Hermann Eberl : AFMnet / University of Guelph
- Ann Letellier : Université de Montréal
- Claude Miville : Fédéreation des Producteurs de Porcs du Québec
- Tony Hayes : University of Guelph
- Harold G. Gonyou: Prairie Swine Centre
- Alan Paulson: AFMnet / Dalhousie University
- Richard Reid-Smith: Public Health Agency of Canada
- James France AFMnet / University of Guelph
- Judith Lafrance: Université Laval
- Caroline-Emmanuelle Petit-Jetté: Université de Montréal
- Dave Bernier : Université de Montréal
- Steven Sanches: Université de Montréal
- Bruce Groves: Pfizer Animal Health Canada
- Alan Theede: Pfizer Animal Health Canada
- Madonna Benjamin: Elanco Animal Health
- Laurence T. Yang: St. Francis Xavier University
- Jeff Lucas: MITACS

Invitations have been sent to US researchers. Unfortunately, due to delays in reply of the first invited researchers, tentative to reach other persons were not successful for different reasons (other meetings on similar subjects at the same period in Europe in particular).