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PHARMACOKINETICS OF AMOXICILLIN/CLAVULANIC ACID AND ITS IMPACT ON THE GUT MICROBIOTA OF CALVES

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Amoxicillin/Clavulanic acid (AMC) is an important antibiotic to treat infections in humans and animals, including calves. However, AMC can cause dysbiosis in the gut microbiota, decreasing species diversity and richness and selecting antibiotic resistance genes (ARGs). Among antibiotic resistant bacteria, Extended Spectrum Beta-Lactamases (ESBL) producers, pose a risk for both human and animal health. Furthermore, AMC pharmacokinetics data are ancient. Update of such data with modern technology and from diseased calves could improve the dosage of AMC.

OBJECTIVES

Analysing the impact of AMC on the gut microbiota of calves by 16S targeted metagenomics

Analysing dissemination of ESBL-producing bacteria among calves

Studying the pharmacokinetics of AMC in diseased calves administered intramuscularly

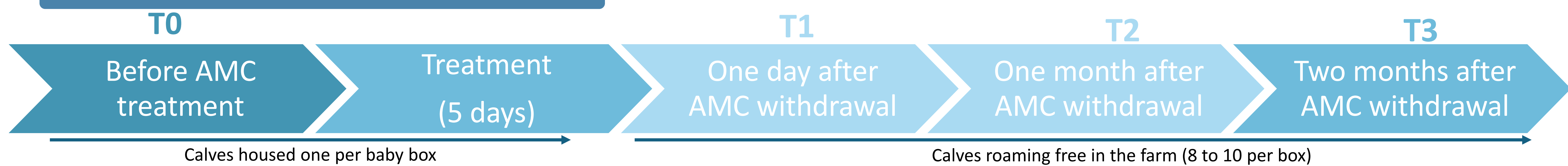
CALVES ENROLLMENT (n = 85) IN FATTENING FARMS

- 15 calves treated for omphalitis by intramuscular injections of AMC (Synulox, 7mg/kg)
- Paired control group : 15 control calves not receiving AMC from the same farm or department and from the same age as the treated calves
- Additional control group : 55 additional calves sampled to reach 10% of the farm population to investigate the ESBL dissemination

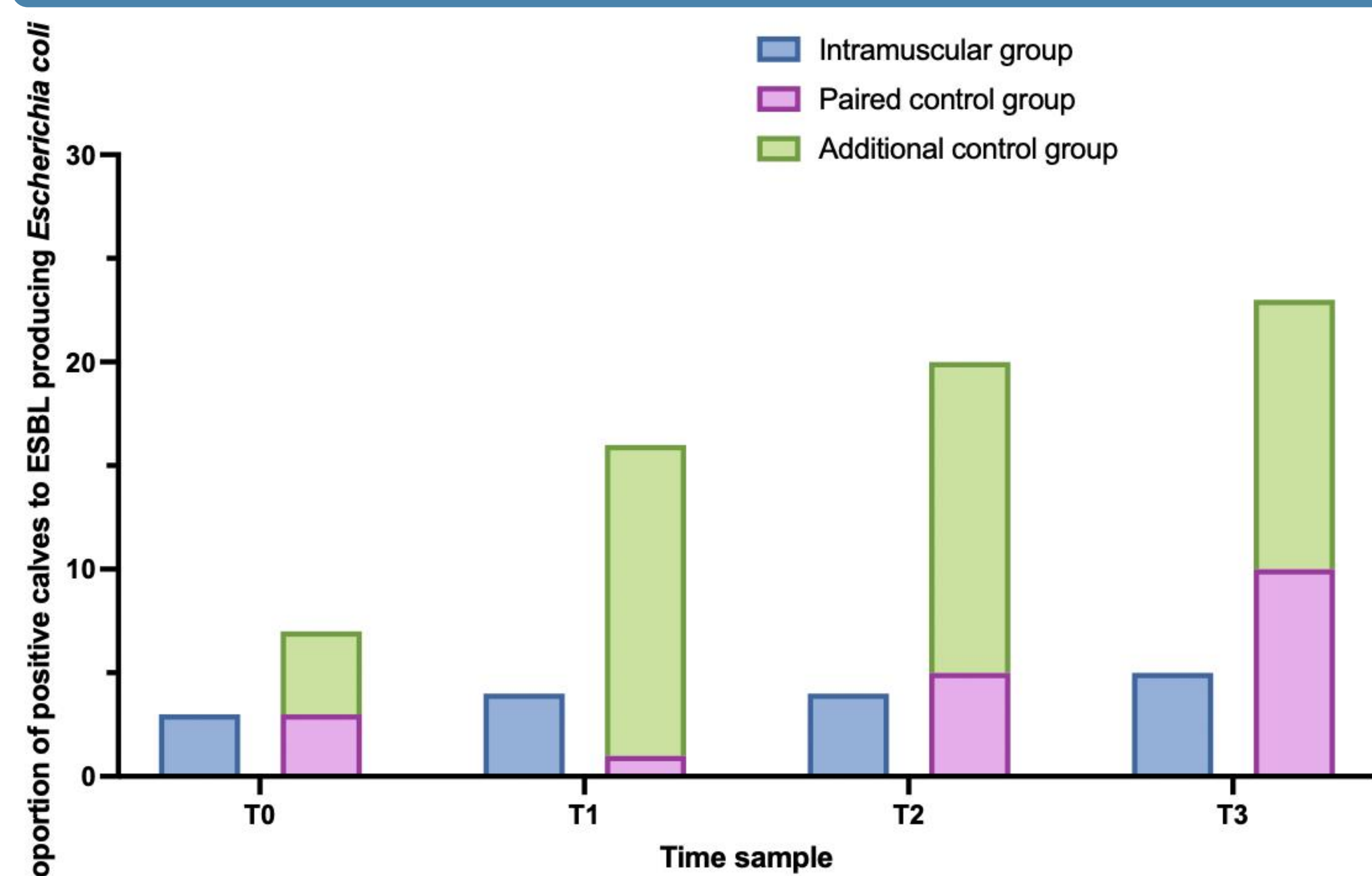
METHODS

- Feces samples**
 - Cultivation on ESBL selective medium (ChromAgar™ ESBL, Chromagar)
 - DNA extraction (DNA mini Stool Kit, Macherey Nagel) and 16S sequencing by 16S Barcoding Kit (Oxford Nanopore Technologies)
- Blood samples**
 - Quantification of amoxicillin in plasma by LC-MS/MS at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4 and 5 hours

SAMPLING TIMEFRAME

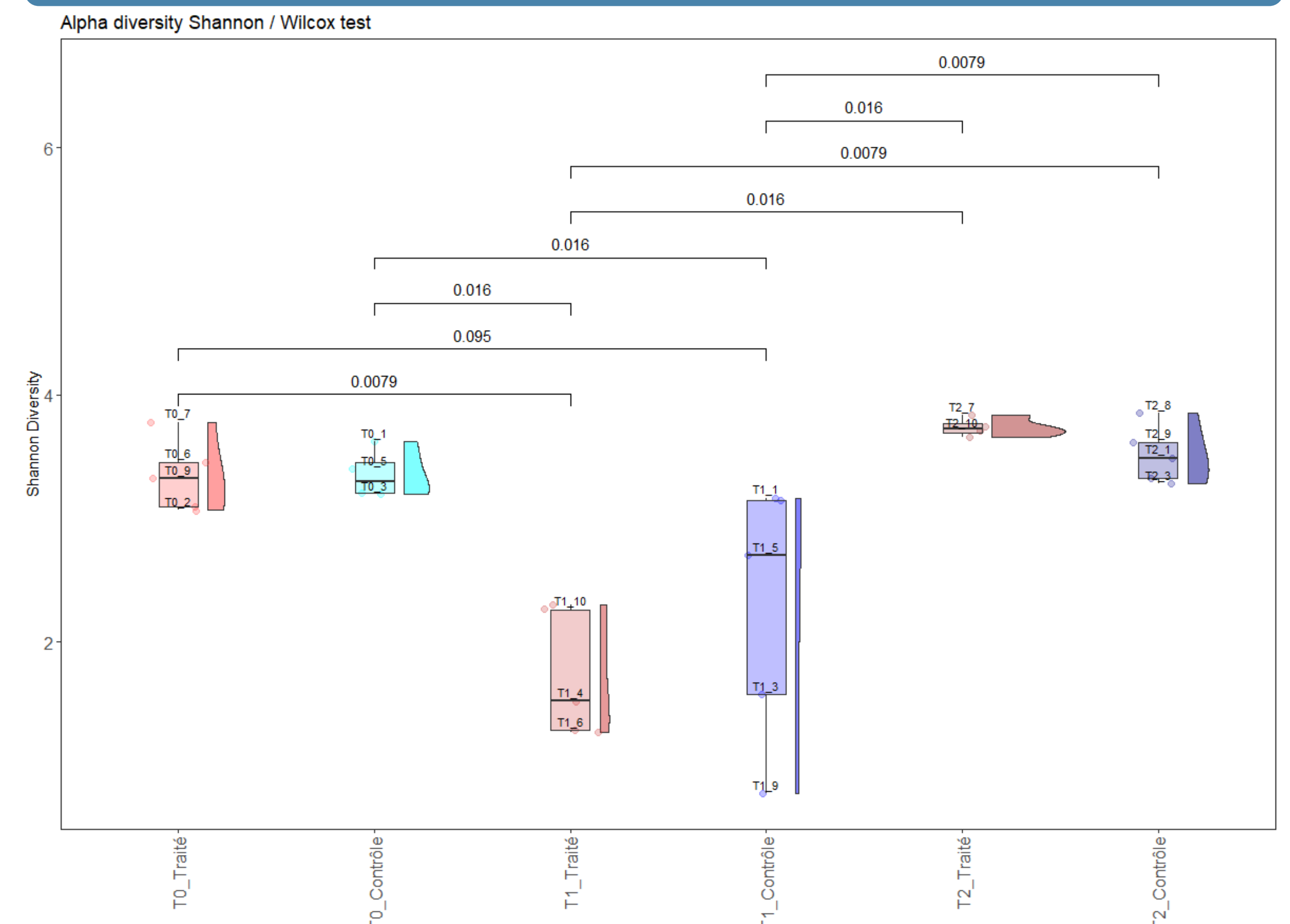


ESBL DISSEMINATION WITHIN THE FARM



- Figure 1 :** Proportion of ESBL presenting an ESBL-producing *E. coli* (n = 15 treated calves – n = 15 paired control calves – n = 55 additional control group)
- Overall, 11.7% calves were positive to ESBL-producing *Escherichia coli* at their arrival in the fattening farm.
 - The proportion of calves positive to ESBL-producing *Escherichia coli* did not change in the group of calves receiving AMC during the study period, whereas an increase of the proportion of calves was observed in the control groups.

ANALYSIS OF ALPHA DIVERSITY



- Figure 2 :** Analysis of alpha diversity by 16S sequencing (n = 5 treated calves – n = 5 control calves, only p-value < 0.05 is shown, Wilcox test)
- Decrease in diversity between T0, before AMC treatment, and T1, one day after AMC withdrawal in the treated groups
 - No significant differences between the two groups at T1, most likely due to the large variability within the control group
 - Resilience of diversity at T2, one month after AMC withdrawal

PHARMACOKINETICS OF AMOXICILLIN IN DISEASED CALVES

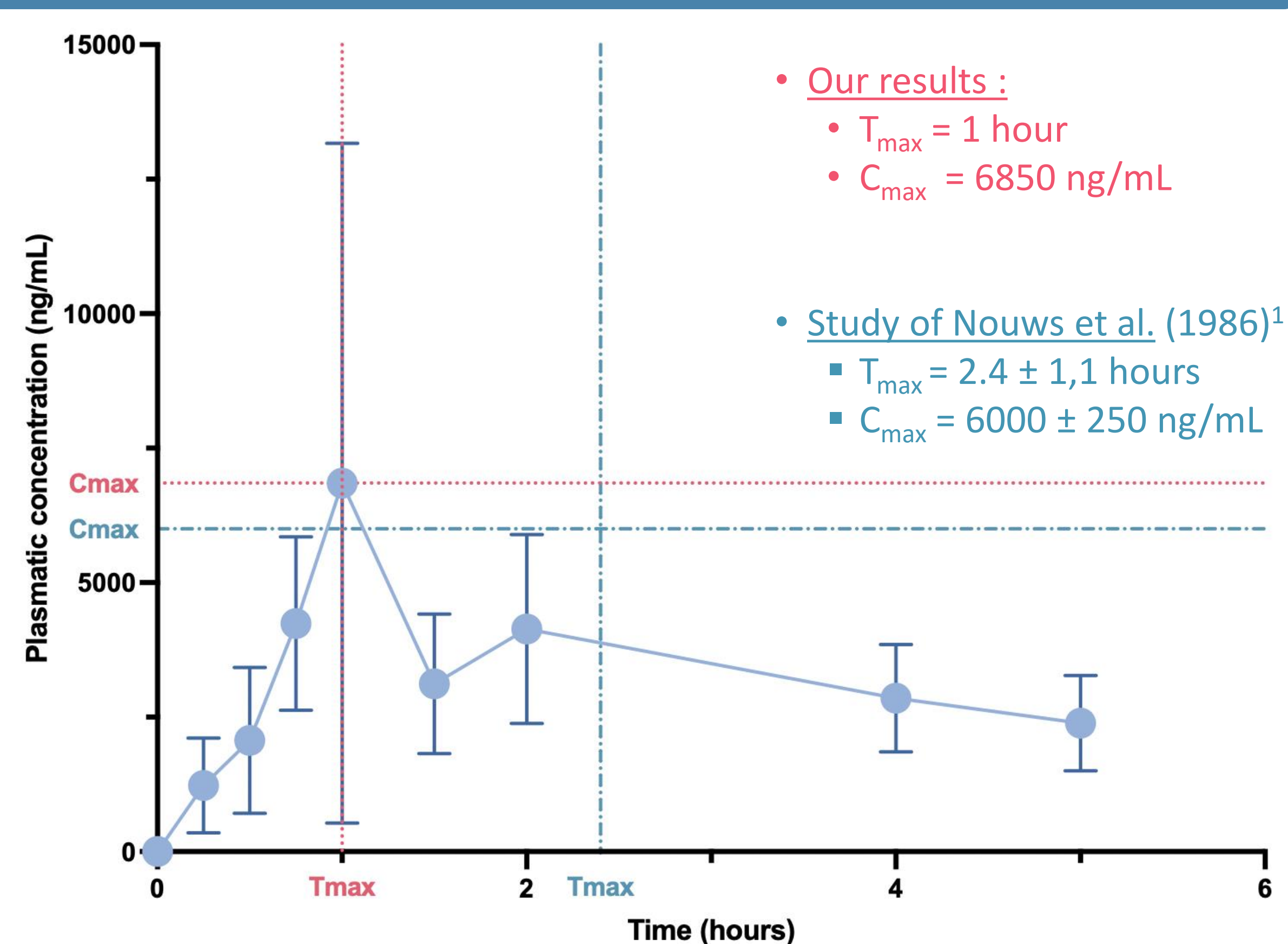


Figure 3 : Pharmacokinetics of amoxicillin in plasma (n = 5 – Mean ± SD)

- Maximum time (T_{max}) to achieve maximum concentration (C_{max}) seems to be earlier than pharmacokinetics performed on healthy calves of the same age with a C_{max} quite similar as observed in the literature¹
- Enrollment of more calves is necessary to confirm differences observed between healthy and diseased calves

¹Nouws JF, Guelen P, Mevius D, Driessens F. Age difference in pharmacokinetics of an amoxicillin trihydrate-15% formulation administered intramuscularly to ruminants. Vet Q. 1986 Oct;8(4):339-42. doi: 10.1080/01652176.1986.9694065.

CONCLUSION

- At their arrival in the fattening farm, calves are carrier of ESBL-producing *E. coli*. Proportion of positive calves for the presence of ESBL-producing *E. coli* raised during the study period.
- Besides AMC treatment, all calves received prophylaxis treatment. Furthermore, during T1 and T2, calves were allowed to move in compartments of the farm, most likely favoring the dissemination of ESBL-producing *E. coli*. Different clustering of calves treatment with AMC in the farm, could have prevented further spread of ESBL-producing *E. coli* in this group.
- 16S analysis displayed a decrease in alpha-diversity amongst the AMC treated group at T1, with a resilience of alpha-diversity at T2 at levels comparable to T0.
- Pharmacokinetics data illustrated a potential shift of a pharmacokinetics parameter (T_{max}) when compared to data reported from healthy calves.

PERSPECTIVES

- 16S sequencing is ongoing for the remaining calves
- qPCR of antibiotic resistance genes is also ongoing
- Enrollment of more calves for the study of pharmacokinetics of AMC

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