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# “EXCIPIENT FEEDSTUFFS”: A MUST FOR ANTIMICROBIAL STEWARDSHIP

**Jérôme R. E. del Castillo**, D.M.V., I.P.S.A.V, M.Sc., Ph.D.

Alireza Jafarzadeh, Jabin Sultana, Araceli Garcia Ac & Xavier Banquy

Université de Montréal, Colleges of Veterinary Medicine and Pharmacy

# OUTLINE

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## Introduction

Antimicrobial overuse in Canadian livestock: focus on pork production

Antimicrobial stewardship: shift focus to refining the necessary uses

Feed-drug interactions: a neglected topic in antimicrobial stewardship

In vitro drug dissolution: a tool for predicting oral drug absorption

## Pilot study on drug dissolution from medicated feedstuffs

Hypotheses and objectives

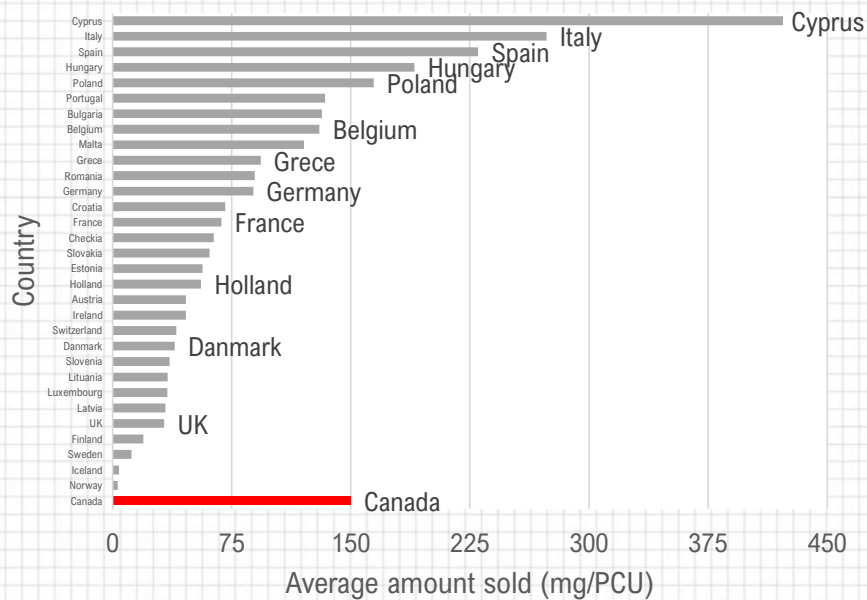
Methods

Main results

## Implications for further research

# ANTIMICROBIAL OVERUSE IN CANADIAN LIVESTOCK

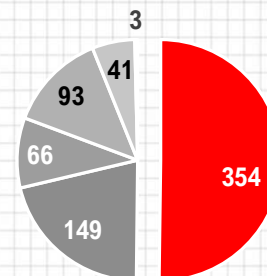
## Veterinary antimicrobials: Canada (2018) vs. Europe (2017)



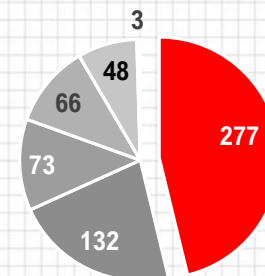
## Species distribution of veterinary antimicrobials sold in Canada

- Largest use in **pork production**
  - Use decreased between 2018 and 2019: antimicrobial stewardship?

2018: 705 mg/PCU



2019: 600 mg/PCU



- Pigs
- Poultry
- Cattle
- Aquaculture
- Companion
- Others

# ANTIMICROBIAL STEWARDSHIP (AMS) IN PIGS

AMS: multifaceted approaches aiming to sustain the efficacy of antibiotics and minimize the emergence of antimicrobial resistance

**5R principle:** Responsibility, Reduction, Replacement, Refinement, and Review

Current focus is on the first three R's

**Responsibility:** veterinary prescription, improving compliance, new regulations

**Reduction:** biosecurity, hygiene, diagnosis, cut growth promotion uses

**Replacement:** alternatives to antimicrobials

**Refinement:** water medication

**Review:** AMU benchmarking

Can we further refine the necessary uses of antibiotics in pigs?

# ORAL DRUG ABSORPTION IN PIGS IS LOW

## Bioavailability

Fraction of the dose that reaches the systemic bloodstream

## Oral drug bioavailability: humans vs. pigs

<b>Drug</b>	<b>Humans</b>	<b>Pigs</b>
Oxytetracycline	60%	5%
Doxycycline	93%	22%
Amoxicillin	96%	25%

## A physiological or a biopharmaceutical problem?

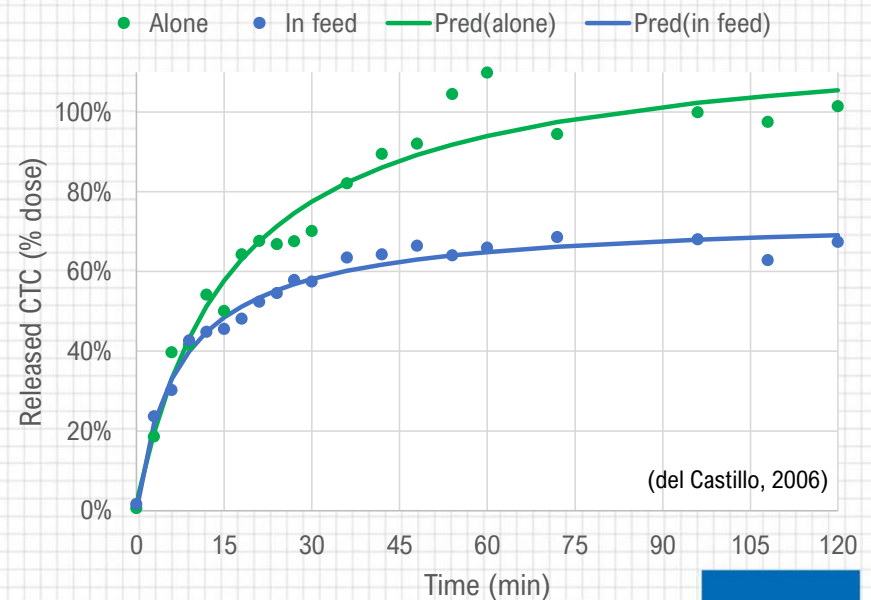
Pigs are a model for human digestive physiology: similar structure and function

Same active drug substances, but their dosing formulations differ

# FEED-DRUG INTERACTIONS ARE NEGLECTED IN AMS

- Always investigated for human oral drugs, not for drugs used in livestock
  - Fixed-dose label, whatever the type of feed
- Some studies in pigs, but 30 years ago
  - Bioavailability in fasted vs. fed pigs
  - Effects of feed moisture or acidifiers
- Interaction mechanisms are unknown
  - Pharmacokinetic?
  - Pharmacodynamic?
  - Nutritional status?

In vitro dissolution of chlortetracycline  
Dietary premix alone vs. medicated feed



# PILOT IN VITRO DRUG DISSOLUTION STUDY

## Hypotheses

Because of their water-holding capacity (WHC), the feedstuffs limit the availability of the digestive fluids in which the oral drugs must dissolve

The WHC may favor the adsorption of the dissolved drug to the feedstuff particles

Therefore, feedstuffs with lower WHC should improve the release of the oral drugs

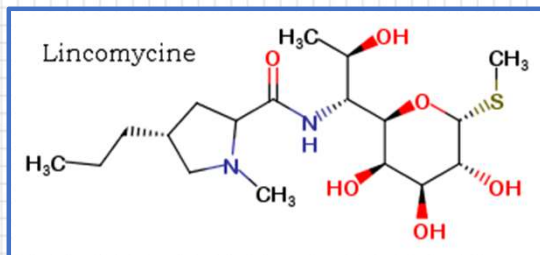
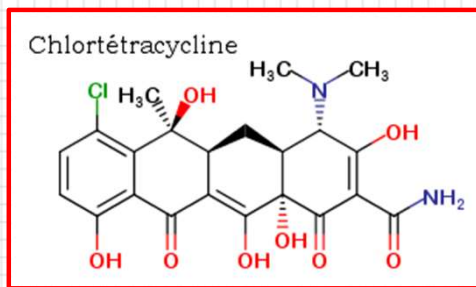
## Objectives

Measure the WHC of major porcine feedstuffs and find their nutritional determinants

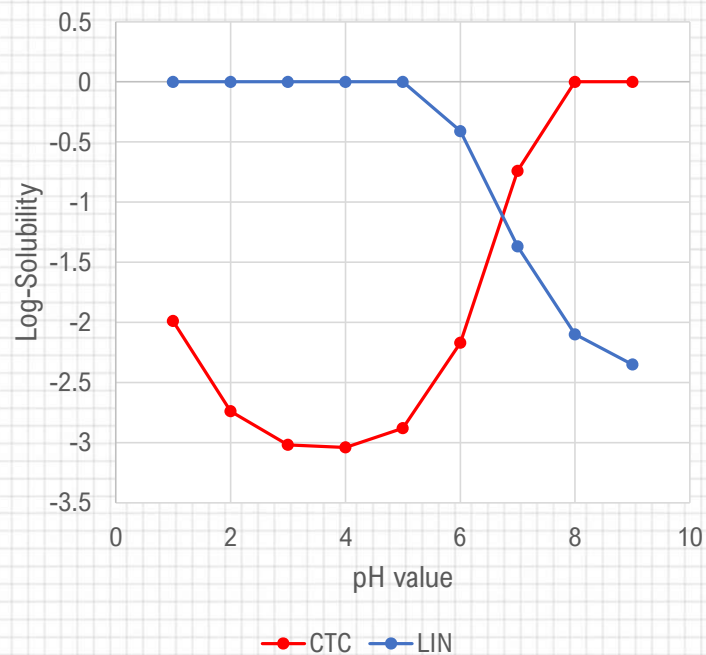
Measure the effect of feedstuff WHC on the in vitro drug release

Two unrelated dietary premixes: chlortetracycline and lincomycin

# TESTED DRUG PREMIXES



Water solubility in function of pH



Drug	Premix particle hardness (N)
CTC	19,35
LIN	7,50



# METHODS

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## WHC of major porcine feedstuffs

Method of Robertson (1981): soaking → paper filtration → freeze drying  
Corn, Rye, Wheat, DDGS, Soybean meal

## Nutritional determinants of WHC

Crude protein, energy, fiber, amino acids, ash, minerals, etc.

## In vitro drug dissolution kinetics

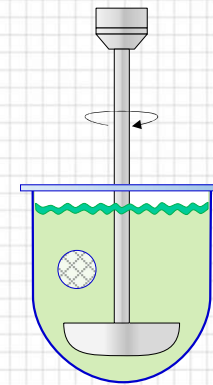
USP type-2 apparatus

Premixes tested alone or mixed into each feedstuff

Simulated porcine physiological conditions

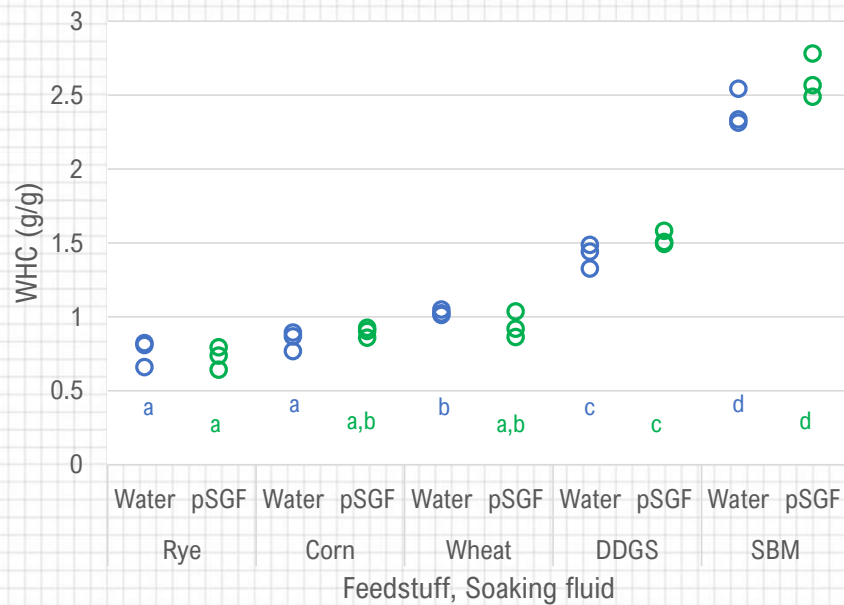
Temperature: 40°C

Gastrointestinal pH: 1.6 (stomach) → 5.8 (duodenum) → 6.2 (proximal jejunum)



# RESULTS (1): WHC OF TESTED FEEDSTUFFS

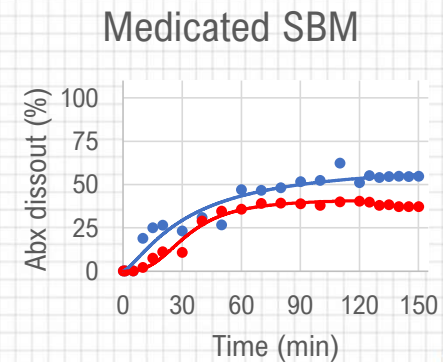
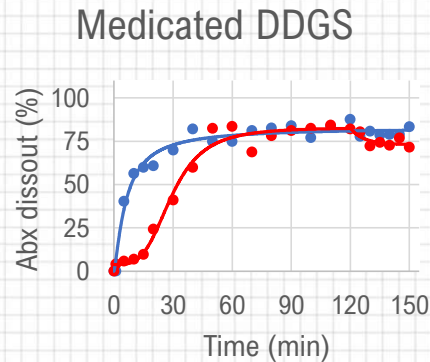
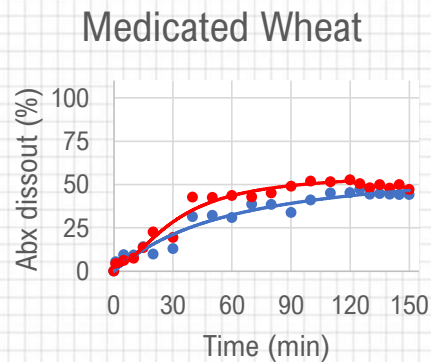
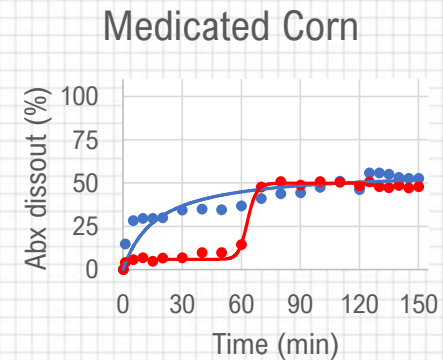
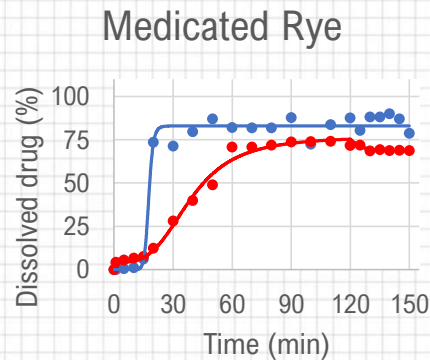
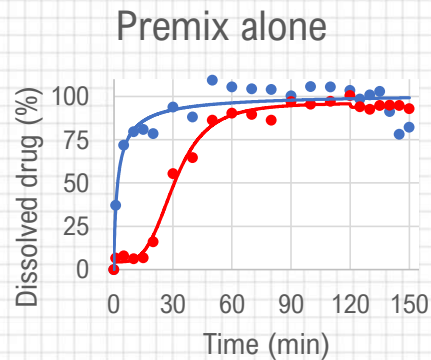
The WHC differs among feedstuffs, with minimal effect of the soaking fluid used



The differences in WHC are associated with the feedstuff's nutrient contents

Nutrient	Est.	SE	F	Pr > F
Lys	-3,40	0,88	14,94	0,0006
Trp	3,75	0,83	20,29	<0,0001
Asp	2,00	0,55	13,10	0,001
K	-0,83	0,36	5,19	0,03
E.Dig.	0,054	0,024	5,19	0,03

# RESULTS (2a): DISSOLUTION EXPERIMENTS



LIN  
CTC

Rye and DDGS had the least interference in the release of CTC and LIN



## RESULTS (2b): DETERMINANTS OF DRUG DISSOLUTION

Effect	Level	Solutions of fixed effects		Type III test	
		Estimate	SE	F	P-value
Intercept		93,3	13,2		
Drug	CTC	-26,0	17,0	2,33	0,13
	LIN	0	-		
Time		0,12	0,15	7,17	0,008
Time x Drug	CTC	0,34	0,22	2,45	0,11
	LIN	0	-		
WHC		-119,4	17,0	49,16	< 0,0001
pH		-0,55	0,57	0,93	0,34
Ash		37,7	6,0	39,03	< 0,0001

# DISCUSSION

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## In vitro drug dissolution: a tool for predicting oral drug absorption

USP type-2 apparatus: used in the pharmaceutical industry for almost 50 years

Quality control, bioequivalence testing, formulation changes, etc.

## WHC: a new feed-drug interaction mechanism

The availability of the solvent becomes the limiting step to drug release

## The ash content of feedstuffs favored the release of the dietary drug

“Salting-in” effect?

## Increasing solvent pH slightly decreased the release of both drugs

Expected for both LIN (decreased ionization) and CTC (drug-metal complexation)

# NEXT STEPS

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## Additivity of the WHC hindering effect when using mixtures of feedstuffs

Is it affected by the proportions of feedstuffs?

Weaner, grower, finisher, breeder feeds

Is it affected by the choice of feedstuffs?

Replacing the usual feedstuffs with « excipient feedstuffs »

## Affinity of the feedstuffs towards the dissolved drug molecules

Does water medication circumvent this problem?

Dosing regimens for weanling pigs

## In vitro – in vivo correlations

Do we need to further refine our in vitro system?

# THANK YOU! ANY QUESTIONS?



- Funding
- Test materials
- Freeze dryer



ONTARIO PORK



GRUPE DE RECHERCHE SUR  
LES MALADIES INFECTIEUSES  
EN PRODUCTION ANIMALE



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