Webinar SIPAS
6 Maggio 2021

Optimizing and reducing the use of antimicrobials: what did we learn from the past?

A PRACTICAL APPROACH

Bart ENGELEN
Global Technical Support
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Insert PictS/logos

Optimizing and reducing the use of antimicrobials: agenda

Dopharma

A. Past, present and future of veterinary antimicrobial therapy

B. Practical measures to decrease and optimize antimicrobial use

1. Farm management
2. Feed and additives
3. Alternatives to AM's
4. Diagnostics
5. Vaccination
6. Optimize Antibiotic treatment
7. Supportive therapies

Responsible Use

decrease the need for AM's

Rational Use

Use AM's better

Ultimate goal:
reduction of resistant bacteria
in animals & humans
role of transmission

A. Past, present and future of veterinary antimicrobial therapy

Discovery, knowledge

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1920 Discovery of first sulfonamide

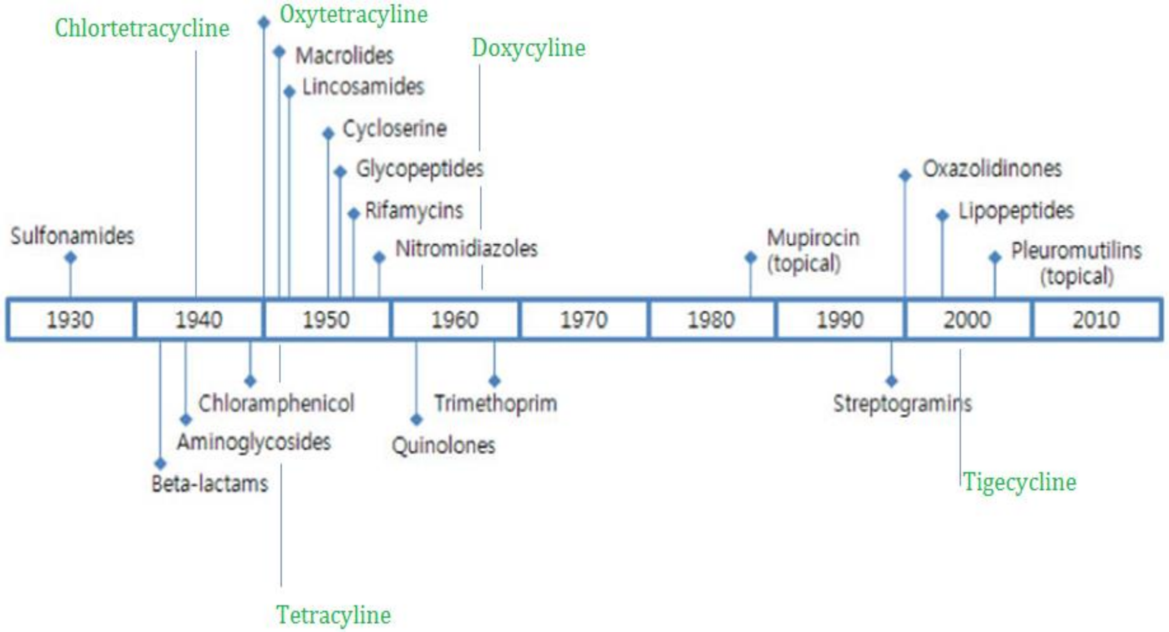
1928 Discovery of penicillin

1940 Purification of penicillin

1940 Screening soil bacteria

1950 Golden era of antibiotics

1960 Scientific awareness of Antimicrobial Growth Promotors (AGP) and Antimicrobial Resistance (AMR)



We have to use what we have (and make it better)

AGP and change of perception

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- 1974 Ban of penicillins and tetracyclins as AGP
- 1999 EU decided to gradually ban all AGPs
- 2005 Finding MRSA transmission between pigs and humans

Methicillin-resistant *Staphylococcus aureus* in Pig Farming

Andreas Voss, Frans Loeffen, [...], and Mireille Wulf

Additional article information

Abstract

We conducted a study among a group of 26 regional pig farmers to determine the methicillin-resistant *Staphylococcus aureus* prevalence rate and found it was >760 times greater than the rate of patients admitted to Dutch hospitals. While *spa*-type t108 is apparently a more widespread clone among pig farmers and their environment, we did find other *spa*-types.

Keywords: MRSA, pigs, farming, *spa*-typing, dispatch

Relation of MRSA in pigs with MRSA in hospitals?

Voss A et al. Methicillin-resistant Staphylococcus aureus in pig farming. Emerg Infect Dis. 2005;11(12):1965-1966

A. Past, present and future of veterinary antimicrobial therapy

Pressure on AM use reduction

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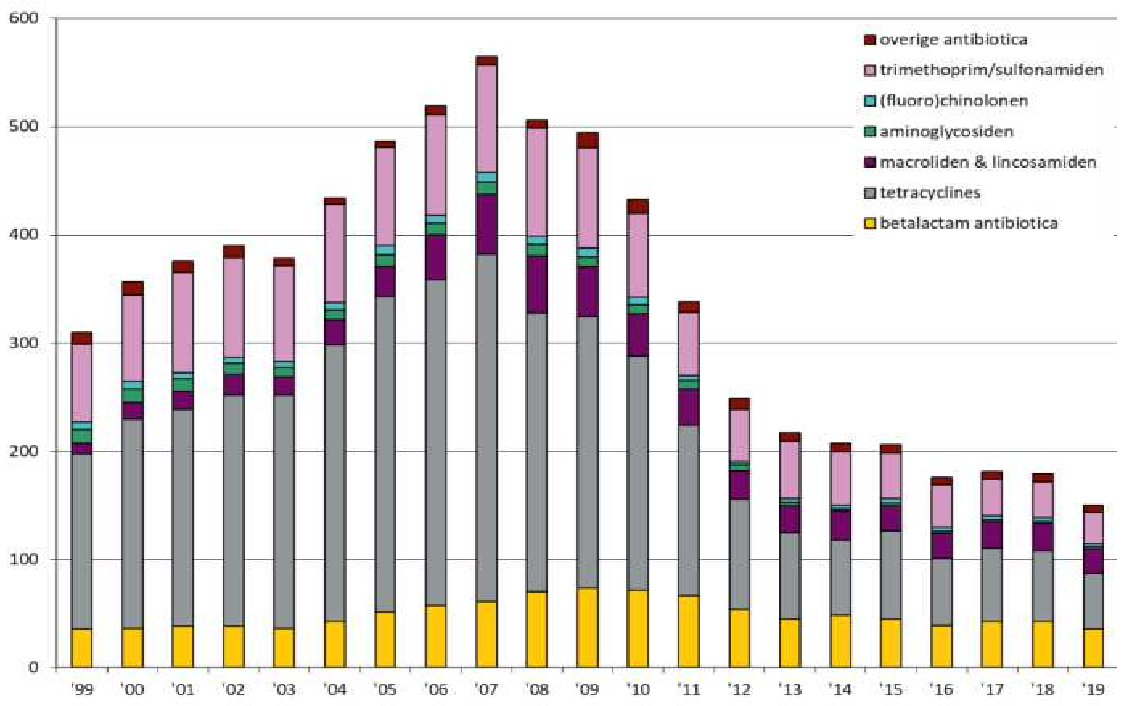
- 2007 NL: government's pressure on antibiotic use in food producing animals
- 2008 NL: on farm monitoring Antimicrobial Use (AM's use)
- 2011 NL: farm protocols
  - Increased vaccination rates
  - Individual treatments to replace herd treatments
  - Delayed weaning of piglets
  - Supportive treatments with nsaids or bromhexine
  - Stricter use of hygiene protocols

A. Past, present and future of veterinary antimicrobial therapy

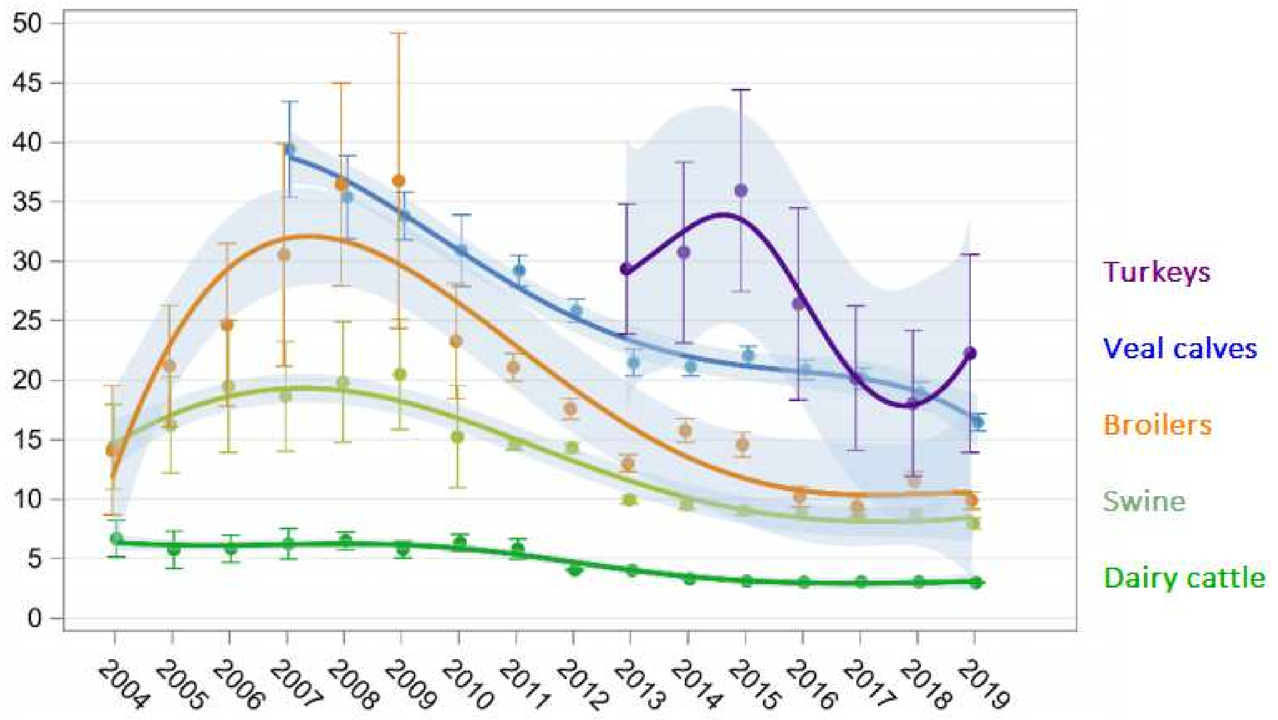
Reduction of use

2013 NL: reduction goals achieved: 20% in 2011; >50% in 2013

Sales of antibiotics in NL (kg active substance x 1000)



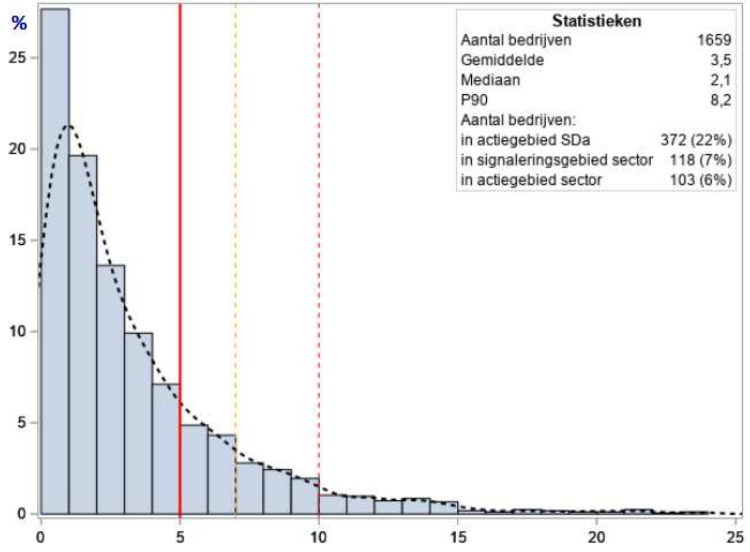
Defined Daily Doses



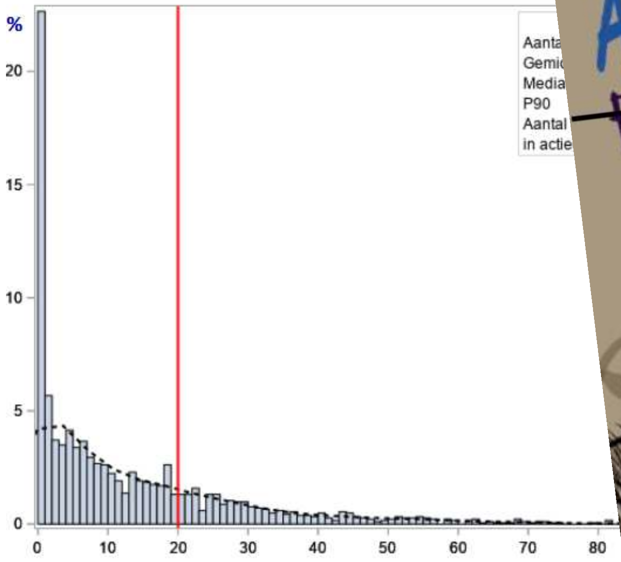
New focus

- 2014 NL: benchmarking veterinarians (antibiotic prescriptions)
- 2015 Shift: from focus on reduction → to focus on farms with high antimicrobial use

DDDA for sows and piglets in 2019



DDDA weaned piglets in 2019



A. Past, present and future of veterinary antimicrobial therapy

The One Health concept

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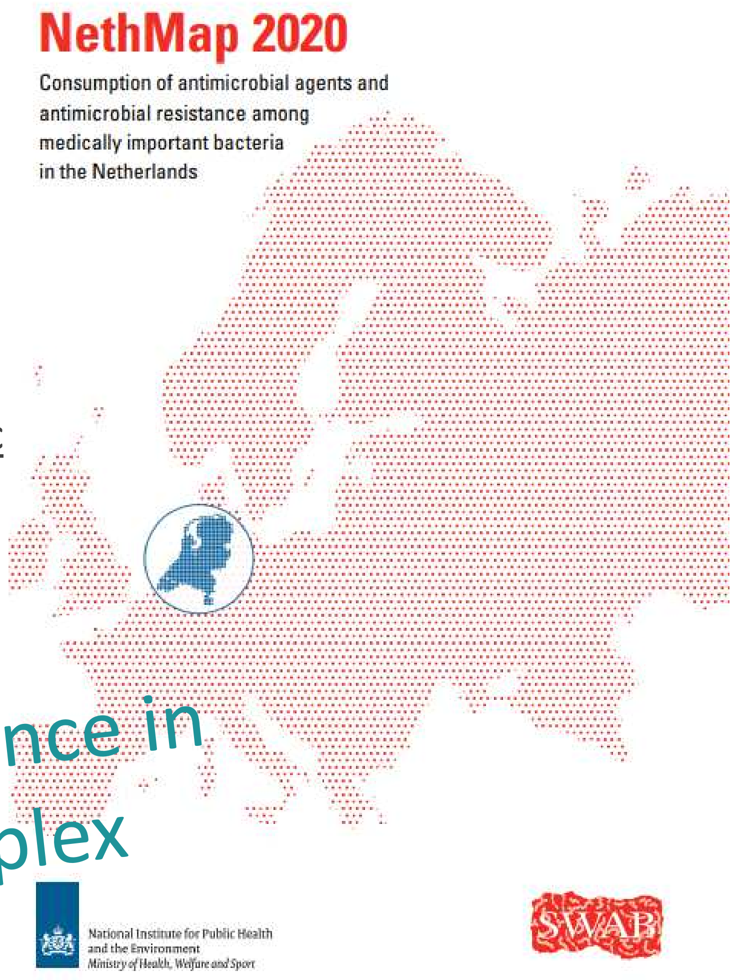
- 2011 EU: monitoring sales antimicrobials (ESVAC)
- 2017 EC: One Health Action Plan
- 2020 EC: Farm to fork strategy
- 2020 NethMap/MARAN: monitoring AMR in humans and animals

The first results of a comparative study suggest an overall low genetic relatedness between LA-MRSA isolates from livestock (pigs and poultry) and humans.

Moreover, the emergence of a more virulent (PVL-positive) LA-MRSA subclade is probably transmitted independent of livestock exposure.



Epidemiology of resistance in bacteria is very complex

A. Past, present and future of veterinary antimicrobial therapy

Redution of E.coli resistance

–2020 NethMap/MARAN: monitoring AMR in humans and animals

Figure Eco01 Trends in proportion of resistance (%) of *E. coli* isolated from faecal samples of broilers, slaughter pigs, veal calves and dairy cattle in the Netherlands from 1998 - 2019.

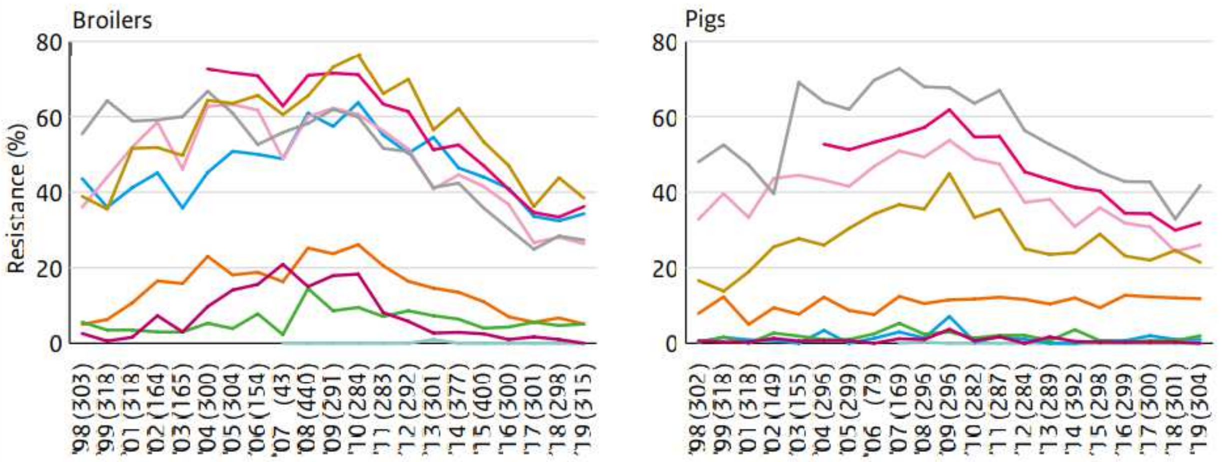
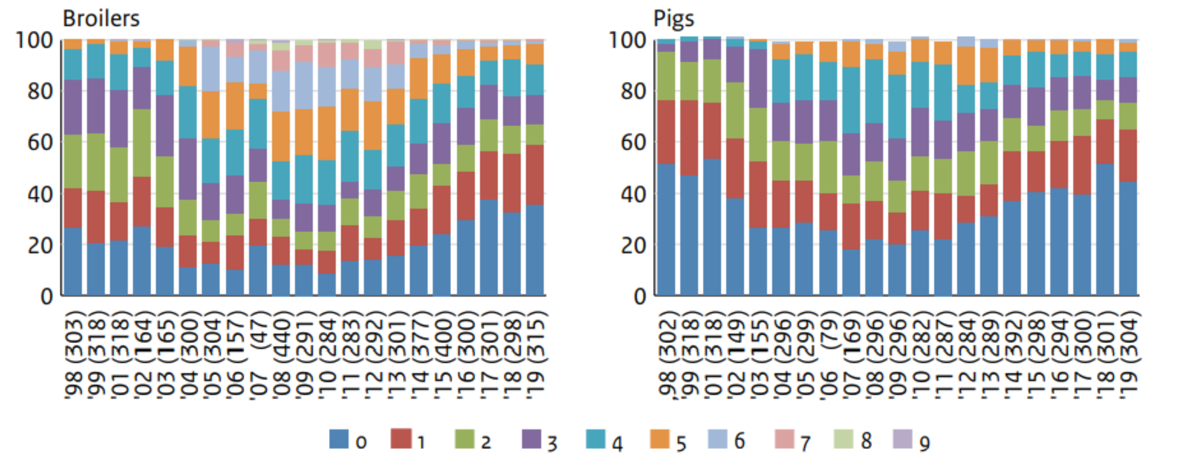


Figure Eco02 Resistance percentages (R%) of *E. coli* isolated from faecal samples of broilers, pigs, dairy cows, white veal calves and rosé veal calves in the Netherlands in 2019.



What the future holds…

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2022 **EU Regulation 2019/6 (VMP) and EU Regulation 2019/4 (MF)**

- **Monitoring and restrictions**
  - Criteria and list of AM to be reserved for human use
- **Practical use**
  - Cascade more flexible + EU data base (availability)
  - SPC harmonisation (and dose optimisation)
- **Antibiotics in feed**
  - Medicated feed for max. two weeks & contain only one Active Ingredient
  - New Maximum levels of cross-contaminations for AM in (non-target) feed

https://eur-lex.europa.eu/eli/reg/2019/6/oj

Practical measures

Insert Picture CG

B. Practical measures to decrease (responsible) and optimize (rational) antimicrobial use

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1. Farm management
2. Feed and additives
3. Alternatives
4. Diagnostics
5. Vaccination
6. Antibiotic treatment
7. Supportive therapies

Alternatives to the use of antimicrobial agents in pig production: A multi-country expert-ranking of perceived effectiveness, feasibility and return on investment

Merel Postma[a,*], Katharina D.C. Stärk[b], Marie Sjölund[c,d], Annette Backhans[c,d], Elisabeth Grosse Beilage[e], Svenja Lösken[e], Catherine Belloc[f], Lucie Collineau[b], Denise Iten[g,1], Vivianne Visschers[g], Elisabeth O. Nielsen[h], Jeroen Dewulf[a], on behalf of the MINAPIG consortium[2]

Antimicrobial use and antimicrobial resistance: standpoint and prescribing behaviour of Italian cattle and pig veterinarians

G. Pozza , A. Pinto , S. Crovato , G. Mascarello , L. Bano , M. Dacasto , A. Battisti , B. Bartoli , L. Ravarotto & S. Marangon

To cite this article: G. Pozza , A. Pinto , S. Crovato , G. Mascarello , L. Bano , M. Dacasto , A. Battisti , B. Bartoli , L. Ravarotto & S. Marangon (2020) Antimicrobial use and antimicrobial resistance: standpoint and prescribing behaviour of Italian cattle and pig veterinarians, Italian Journal of Animal Science, 19:1, 905-916, DOI: 10.1080/1828051X.2020.1807419

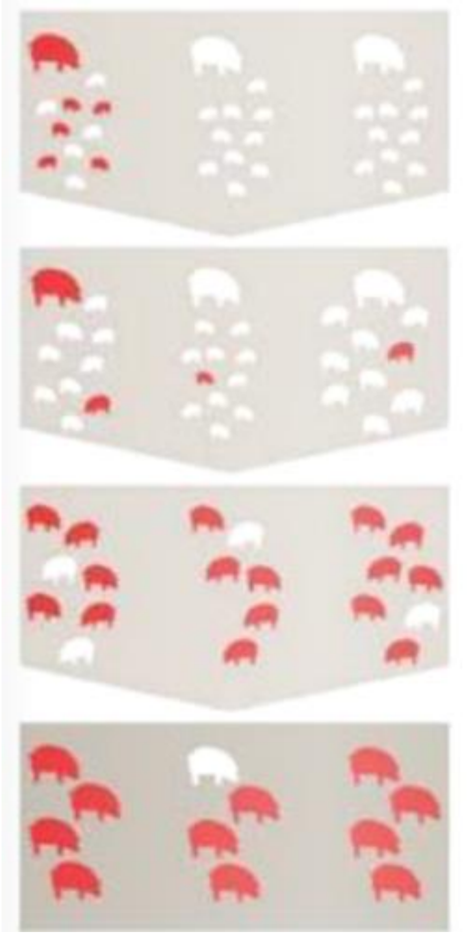
Postma et al. Alternatives to the use of antimicrobial agents in pig production: A multi-country expert-ranking of percieived effectiveness, feasibility and return on investment. PREVET (2015), http://dx.doi.org/10.1016/j.prevetmed.2015.01.010

Pozza G et al. Antimicrobial use and antimicrobial resistance: standpoint and prescribing behaviour of Italian cattle and pig veterinarians. Italian Journal of Animal Science. 2020;19(1):905-916, DOI: 10.1080/1828051X.2020.1807419

B. Practical measures to reduce AM's use

1. *Improve farm management - biosecurity and hygiene*

Uniform by body weight



Focus on not mixing, keeping litters together

Make a protocol for suckling piglets

- Optimize colostrum and milk supply
- Think how to move piglets when necessary

Make a protocol for weaning

- Farm specific possibilities
- Maximize number of different litters per pen

Diergeneeskundig Memorandum. Varkensgezondheid: zorg voor dierenartsen. September 2010-02

B. Practical measures to reduce AM's use

2. *Feed and additives*

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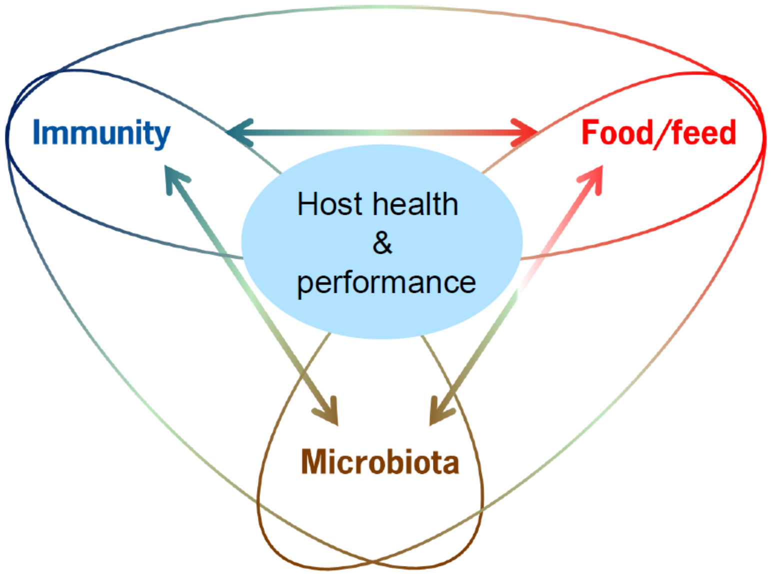
- Feed → cost price in pig production
- Quality of raw materials




WAGENINGEN
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Translational pig model for microbiota management and its effects on intestinal health

Mark Bouwens, Stéphanie Vastenhouw, Frank Harders, Jan Cornelissen, Marga van Setten, Helmi Fijten, Dirkjan Schokker, Annemarie Rebel, Alex Bossers, Norbert Stockhofe, Astrid de Greeff

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Which kind of "direct" alternatives to antibiotics?

Examples of non-antibiotic treatment of bacterial diseases?

PAPER

Treatment of clinical *Brachyspira hyodysenteriae* with zinc chelate in pigs: a blinded, randomised controlled trial

Gerwen Lammers,[1] Robbert van Berkel,[1] Daisy Roijackers,[1] Carly Vulders,[1] Henriëtte Brouwer-Middelesch,[2] Jobke van Hout[2]

Abstract
Background *Brachyspira hyodysenteriae* infection in pigs ('swine dysentery') leads to decreased feed conversion, growth losses and mortality. Current countermeasures have the downside of antibiotic resistance (antibiotics) and ecotoxicity (zinc oxide). The aim of this study was to evaluate the effect of a novel zinc chelate (Intra Dysovinol (ID)) on clinical signs of swine dysentery and shedding of *B hyodysenteriae* under field conditions.
Methods In a randomised, double-blinded, controlled trial under Good Clinical Practice on two commercial farms, 58 *B hyodysenteriae* positive pigs from 16 pens received drinking water containing ID, or placebo, during six consecutive days. Faecal quality (consistency, colour, additions) was scored and faeces were analysed for presence of *B hyodysenteriae* by PCR. ID treatment positively affected faecal quality (consistency) and daily growth rates.
Results At the last treatment day, *B hyodysenteriae* was not detectable in the faeces of any of the ID-treated animals, while all placebo animals remained *B hyodysenteriae* positive by PCR. All ID-treated animals recovered, while 5 placebo-treated animals died and 12 placebo pigs required additional treatment before the end of the study (up to 14 days after treatment start).
Conclusion This non-antibiotic treatment stopped the clinical signs and shedding of *B hyodysenteriae* in naturally infected pigs.

Lammers G et al. Treatment of clinical Brachyspira hyodysenteriae with zinc chelate in pigs: a blinded, randomised controlled trial. Veterinay Record 2019. https://doi.org/10.1136/vr.105523

B. Practical measures to reduce AM's use
4. Diagnostics

High quality & accessible diagnostics essential for:

- Vaccination (autogenous vaccines!)
- Optimization AB-treatment
- Supportive therapies
- On farm testing

B. Practical measures to reduce AM's use

4. Diagnostics

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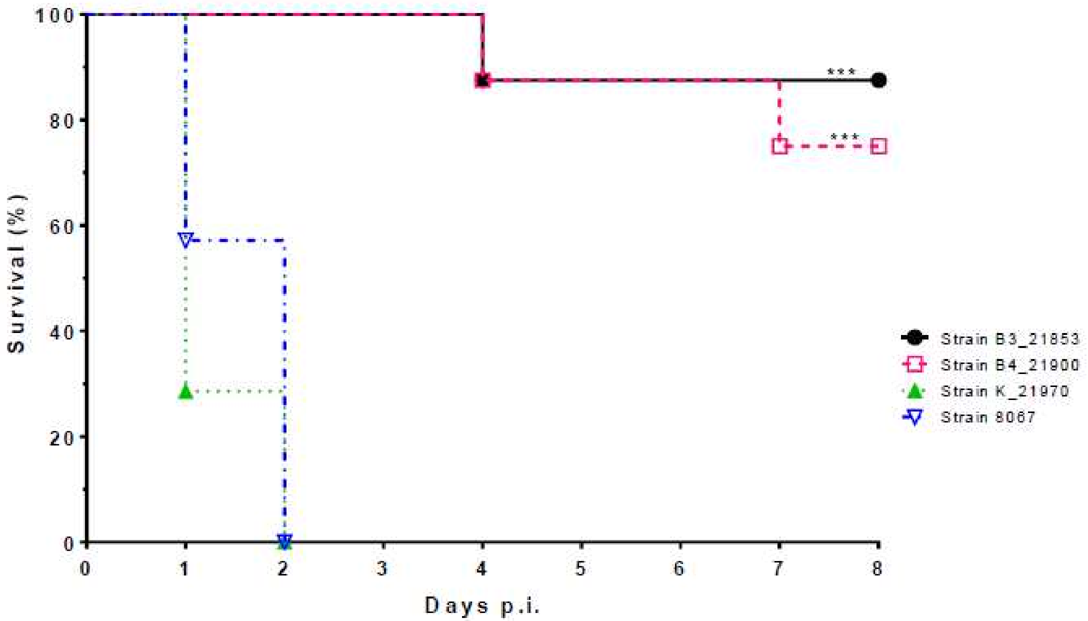
Need for new diagnostics tests

- Comparison ***S. suis* serotype 9** from lesions and tonsils of healthy animals
  - ➢ Difference in virulence



Public-Private cooperation
Streptococcus suis serotype 9

1HEALTH 4FOOD

amc Academisch Medisch Centrum Universiteit van Amsterdam
GD
Topigs Norsvin
MSD
DE VARKENS PRAKTIJK Een stap vooruit
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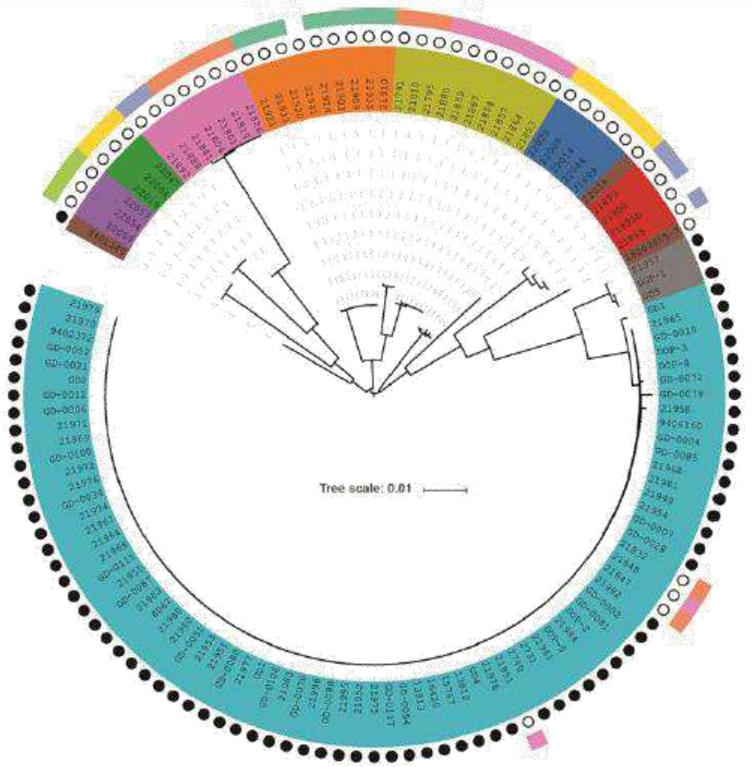
Bioveterinary Research WAGENINGEN UNIVERSITY & RESEARCH

Example of New diagnostics tests for Strep suis

- Comparison *S. suis* from lesions and tonsils of healthy animals
  - ➢Difference in sequence analysis
  - ➢Difference in capsule gene
- Development PCR-test to discriminate between virulent and non-virulent strains → validation
  - ➢Epidemiology: screening farms
  - ➢Stamping out?



Vaccination to decrease the need for antibiotics

- E.g. prevention pleuropneumonia

New regulation EU 2019/6 includes autogenous vaccines (excl. in current EU guideline)

- When no licensed vaccines are available (e.g prevention of *Streptococcus suis* infections)
- Good Manufacturing Practice rules will apply → additional legislation will be layed down
- Uniform rules for production and use of autogenous vaccines in all EU Member states

B. Practical measures to reduce AM's use

6. *Rationalization of AB-treatment*

EMA recognizes the need for optimization of AM treament:

- New Regulation...: objective to harmonize antimicrobial SPCs across Europe
- AM dosage review based on updated field information based on computer modelling

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 January 2021
EMA/CVMP/849775/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on dose review and adjustment of established veterinary antibiotics in the context of SPC harmonisation

Adopted by CVMP for release for consultation	19 July 2018
Start of public consultation	27 July 2018
End of consultation (deadline for comments)	31 January 2019
Adopted by CVMP	10 December 2020

B. Practical measures to reduce AM's use
6. *Rationalization of AB-treatment*

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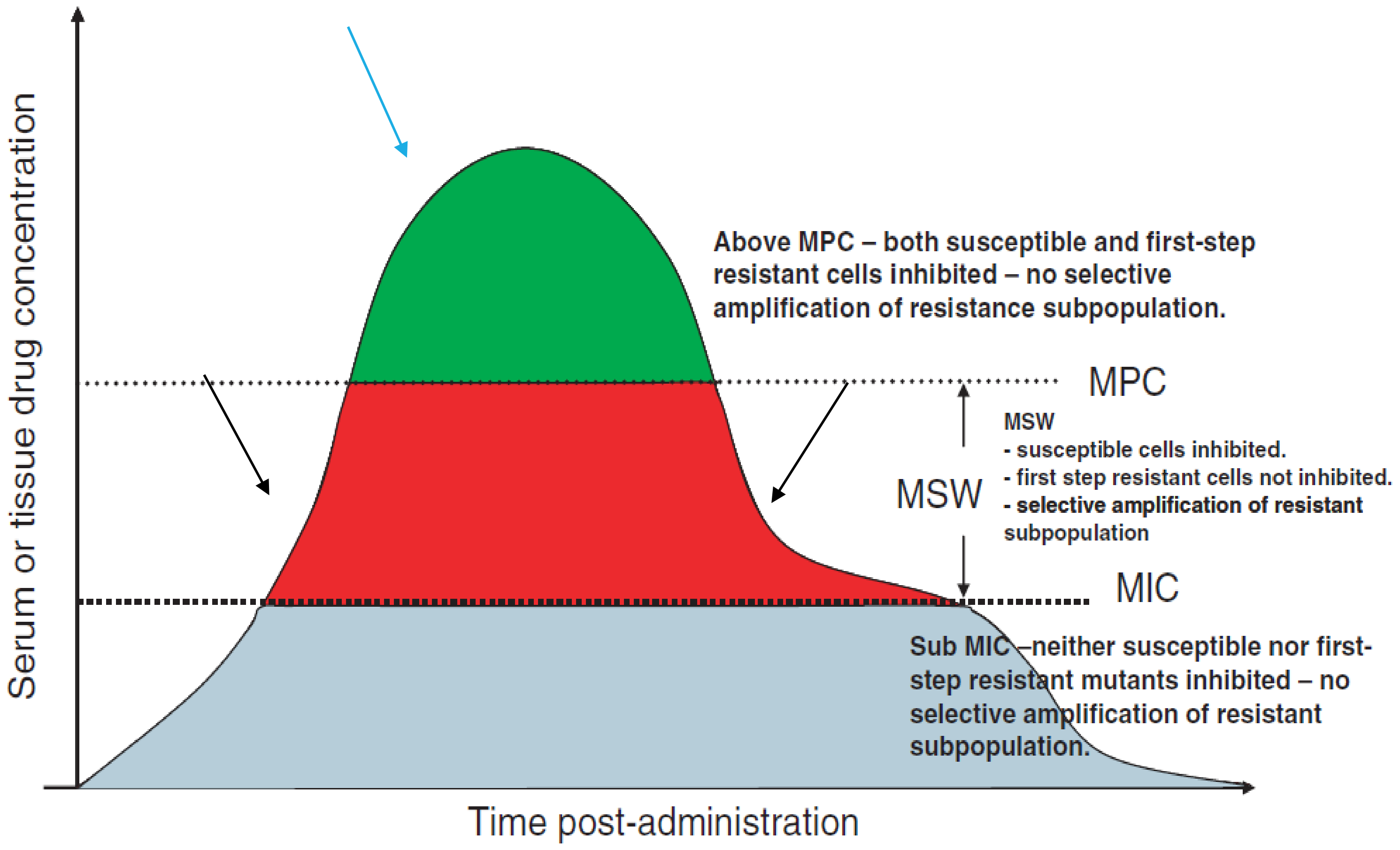
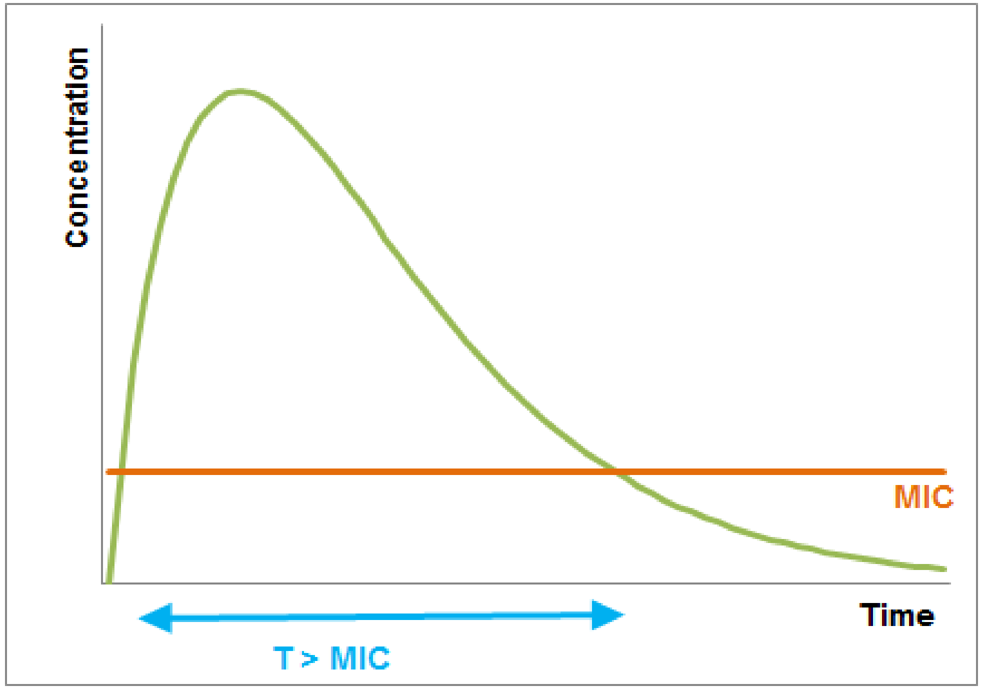
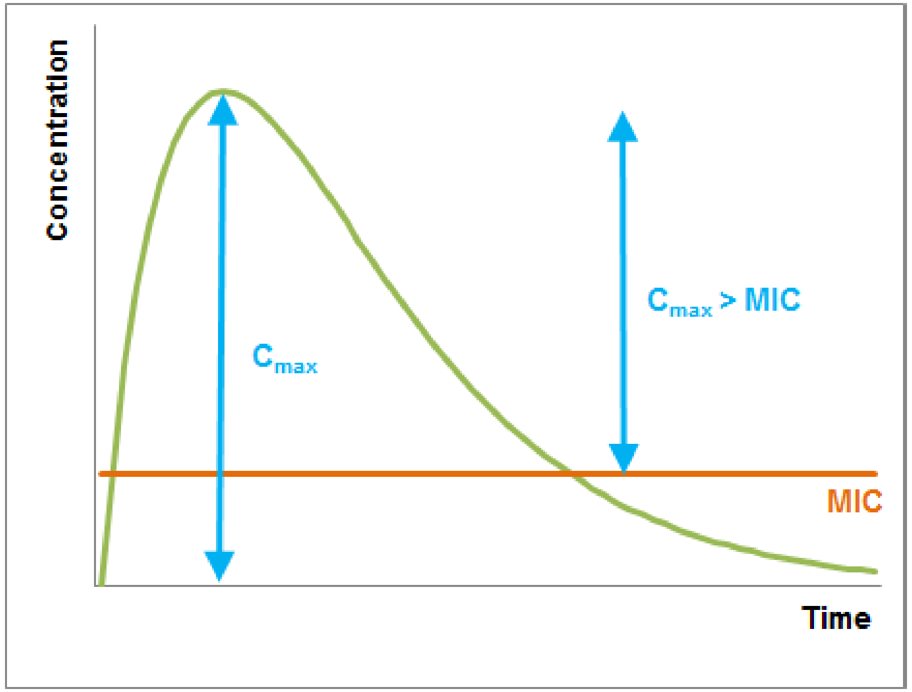
Review of AM dosages: efficacy + managing resistance



Blondeau JM et al. The role of PK/PD parameters to avoid selection and increase of resistance: Mutant prevention Concentration. Journal of Chemotherapy 2004;3(3):1-19

Shift from in-feed antibiotic towards treatment via drinking water





B. Practical measures to reduce AM's use
6. Rationalization of AM's' treatment

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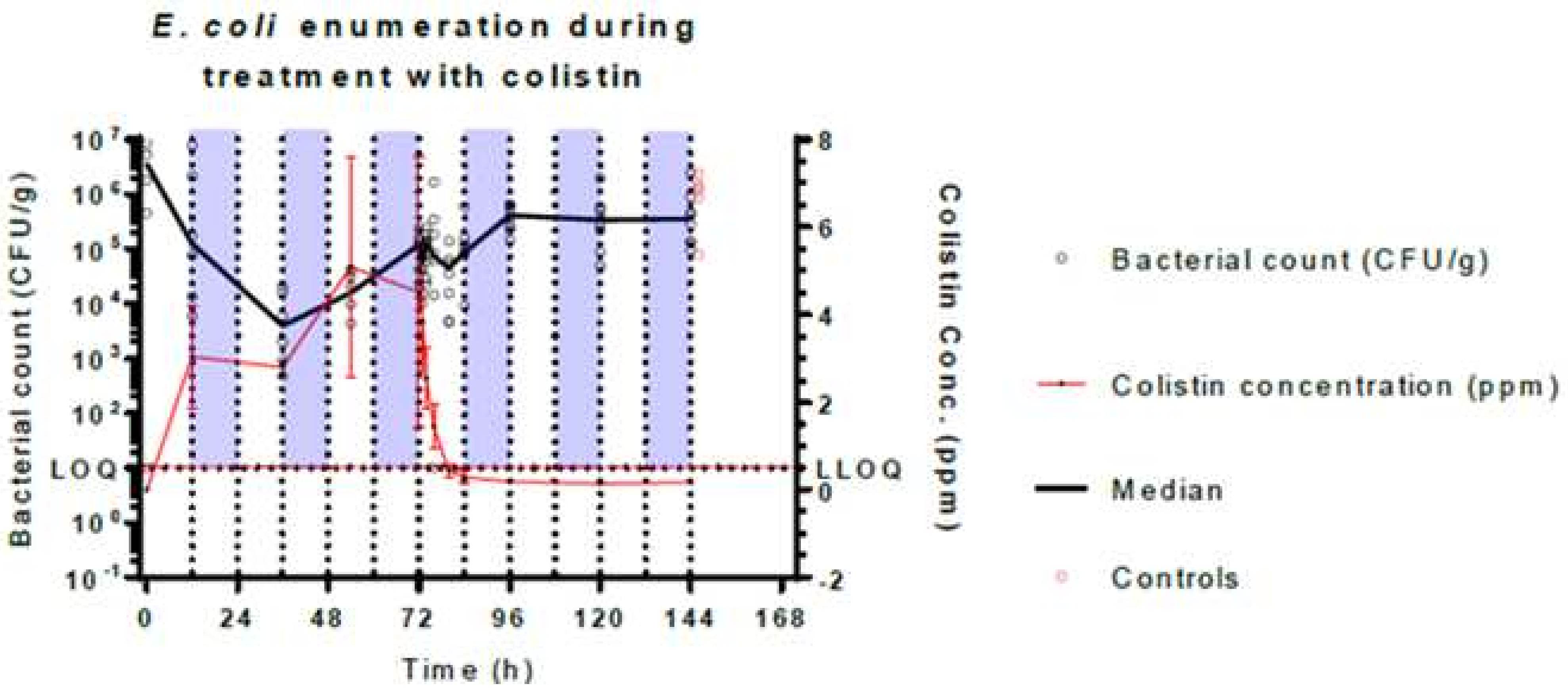
Several pharmacokinetic study projects to optimize antibiotic treatment

Some examples…

- Doxycycline
- Amoxicillin
- Colistin

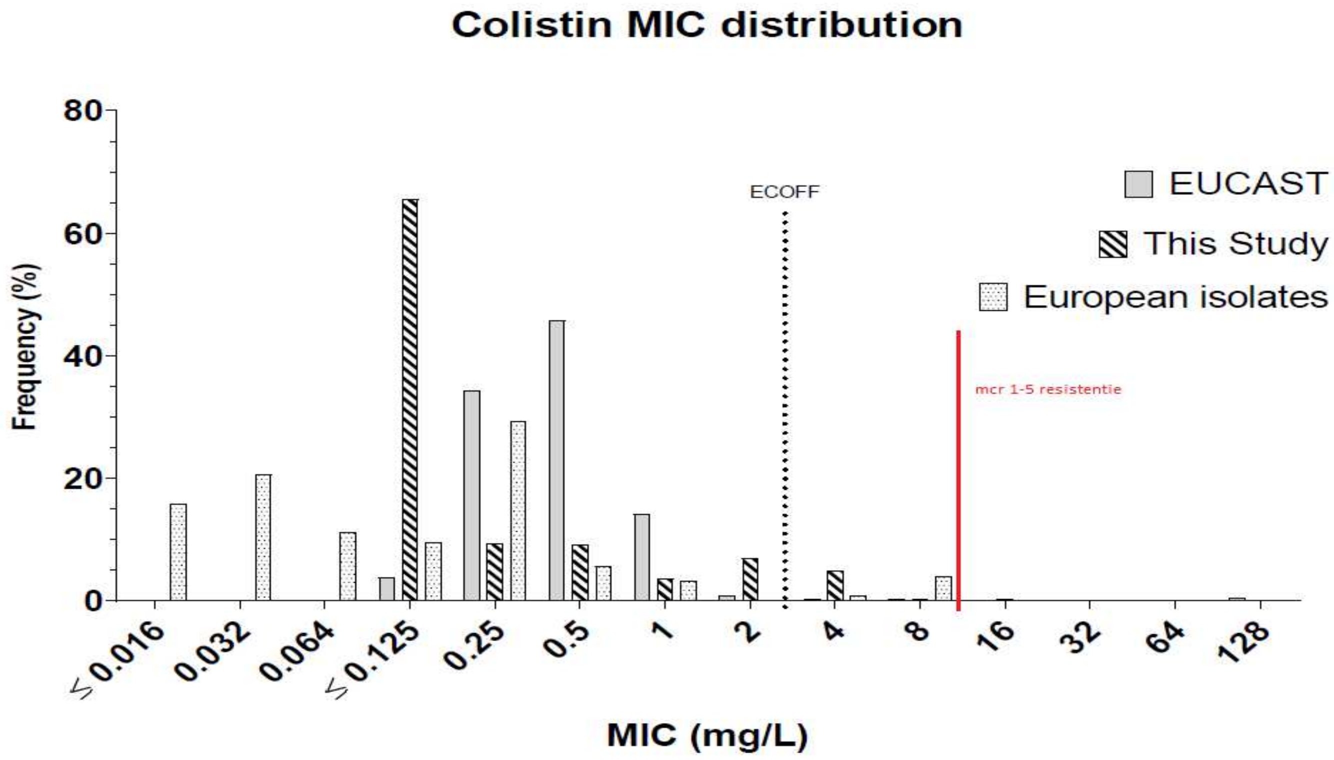
6. *Rationalization of AB-treatment*

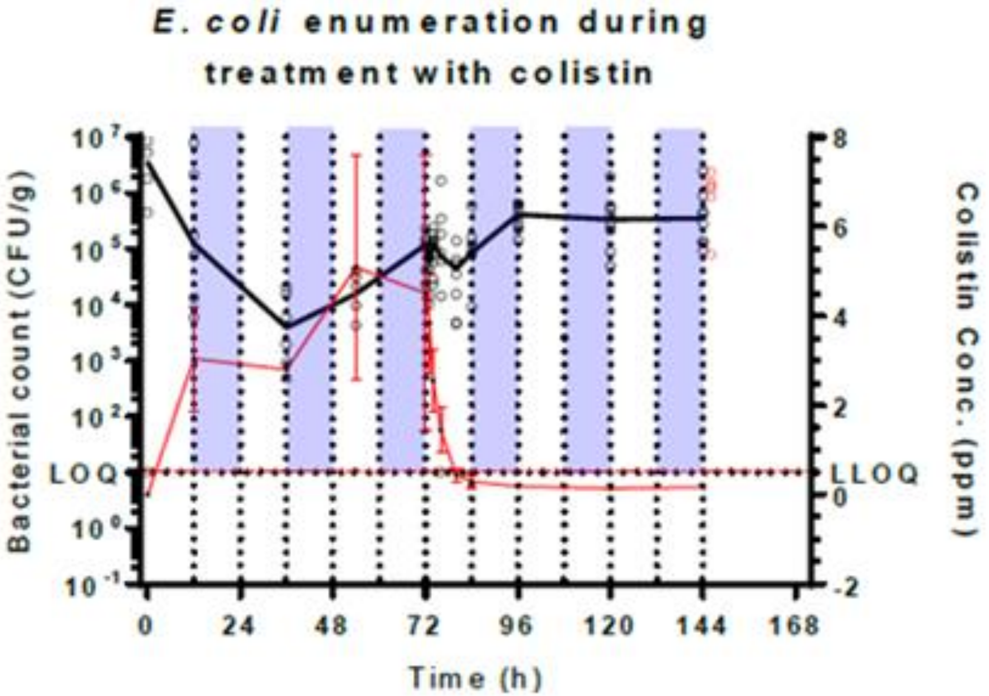


Mead A. PK/PD-informed clinical break-point determination for colistin in the chicken to limit the emergence of resistance and enhance One Health antimicrobial sustainability. London: Royal Veterinary Collegae; Interim Report, 26 June 2020

B. Practical measures to reduce AM's use

6. Rationalization of AB-treatment





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B. Practical measures to reduce AM's use

6. Rationalization of AB-treatment

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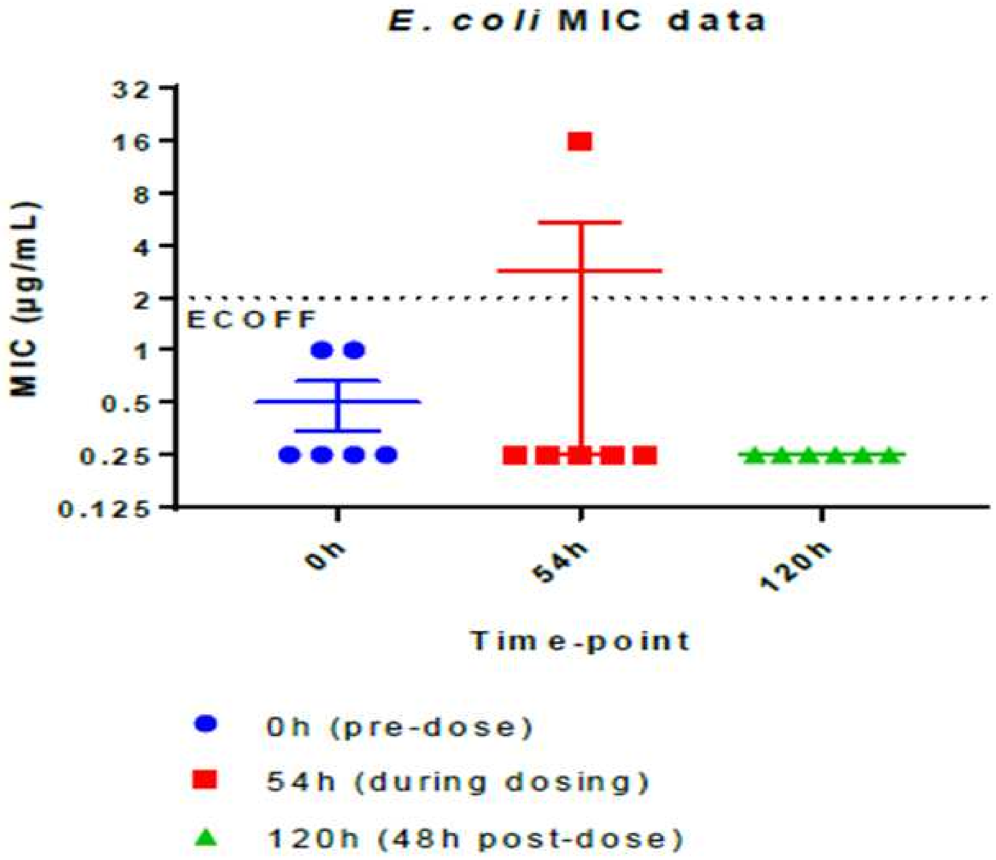

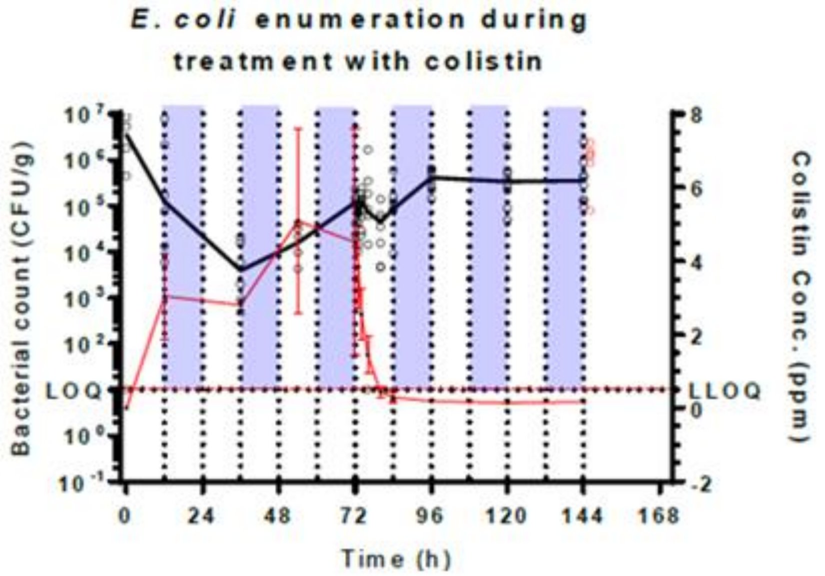

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B. Practical measures to reduce AM's use

6. *Rationalization of AB-treatment*

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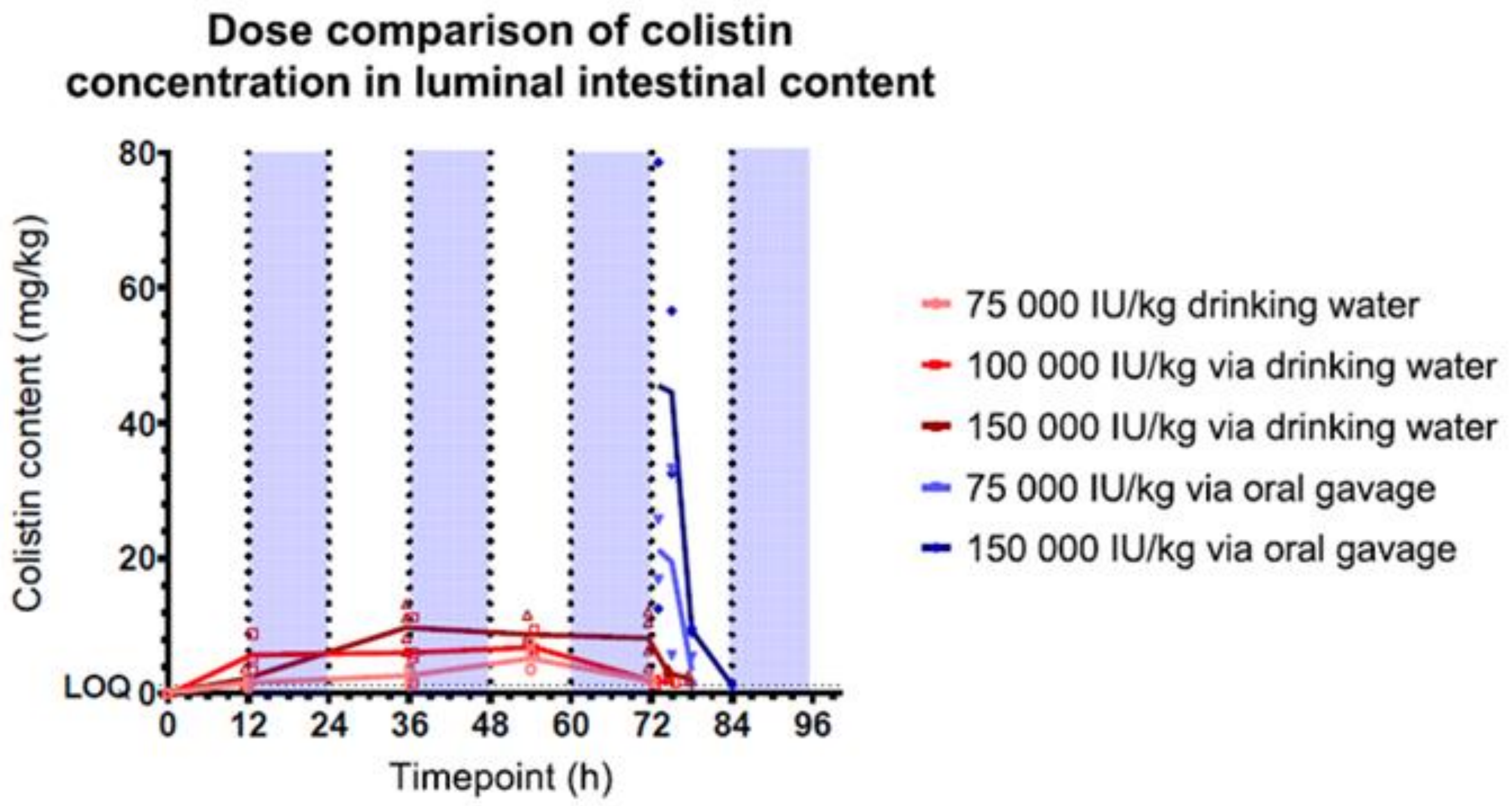

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7. *Supportive therapies – anti-inflammatory drugs*

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Supportive therapies known benefits:

- Increased welfare
- Quicker recovery of diseased animals → retainment of production level
- Aid in reduction of AM's use

B. Practical measures to reduce AM's use

7. *Supportive therapies – anti-inflammatory drugs*

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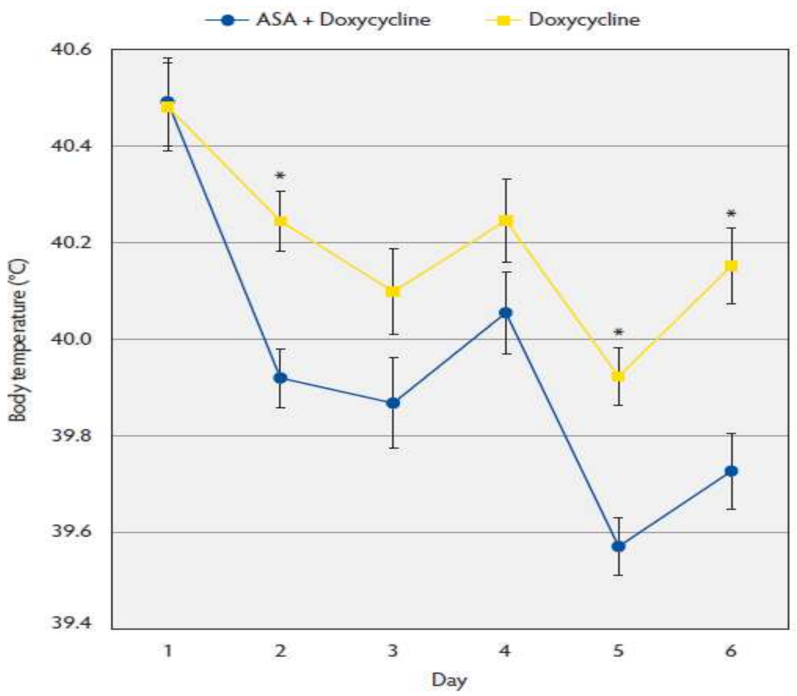
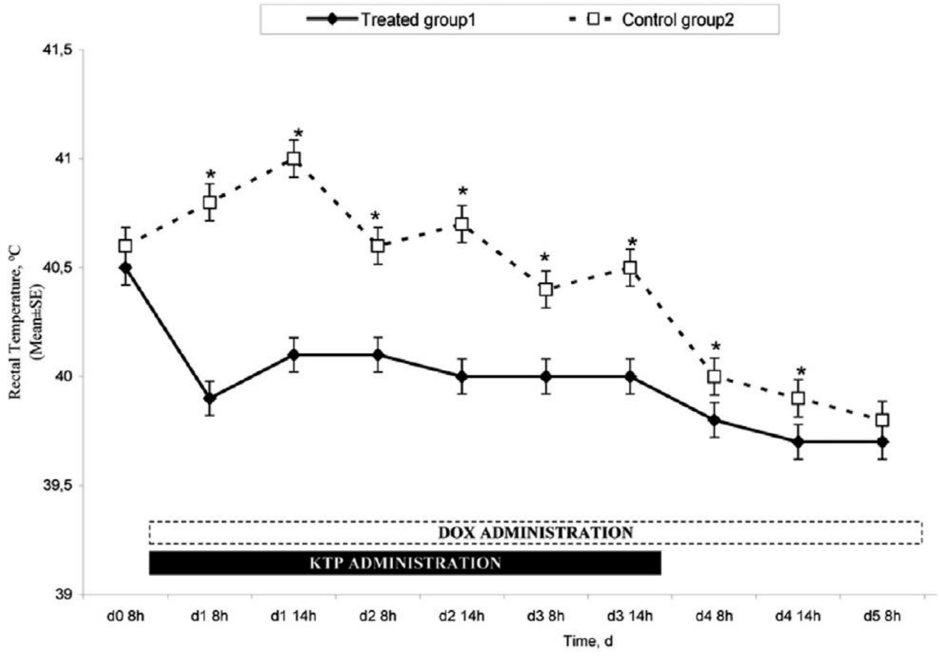
Practical application of oral products

Most important for respiratory disease

- Classical combination of antibiotic and anti-inflammatory treatment



Vilalta C. et al. Clinical efficacy of acetylsalicylic acid as an adjunct to antibacterial treatment of porcine respiratory disease complex. Journal of Swine Health and Produtio 2012;20(1):10-16



Salichs M et al. Efficacy of ketoprofen administered in drinking water at a low dose for the treatment of porcine respiratory complex. J. Anim. Sci. 2013;91:4469-4475

B. Practical measures to reduce AM's use

7. Supportive therapies – anti-inflammatory drugs

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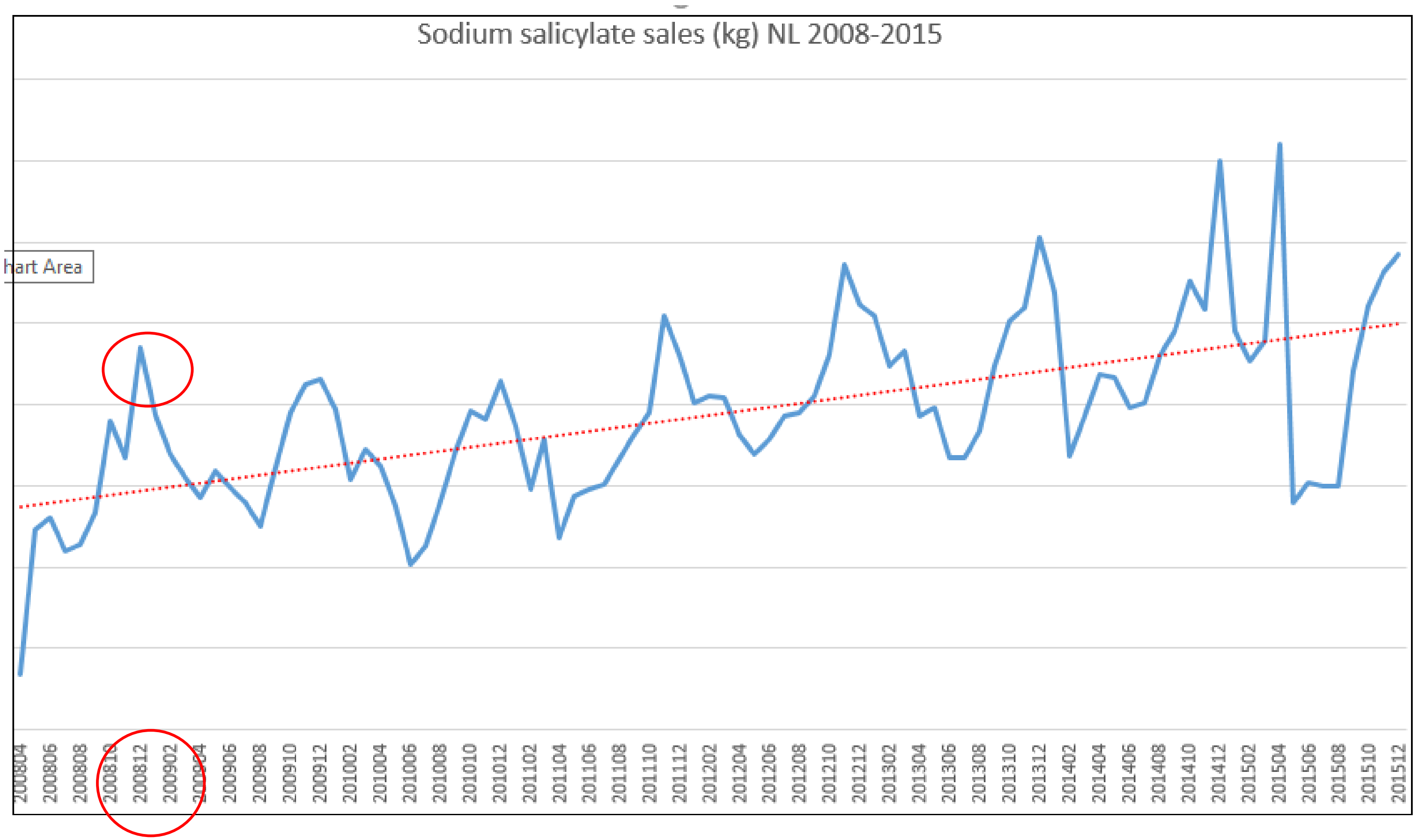
Practical application of oral products



Data: Dopharma BV

7. Supportive therapies – anti-inflammatory drugs

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Practical application of oral products

Most important for respiratory disease

- Combination of antibiotic and anti-inflammatory treatment
- Mono-treatment with anti-inflammatory drug
  - Better management/biosecurity → higher health status → more mono-infections
  - Diagnosis key for precision treatment

- **Early treatment with NSAID in viral respiratory infections e.g. recurrent swine influenza → often sufficient!**
- **If complication with secondary bacterial infection → early enough to start antibiotic treatment (+NSAID)**

B. Practical measures to reduce AM's use

7. *Supportive therapies – anti-inflammatory drugs*

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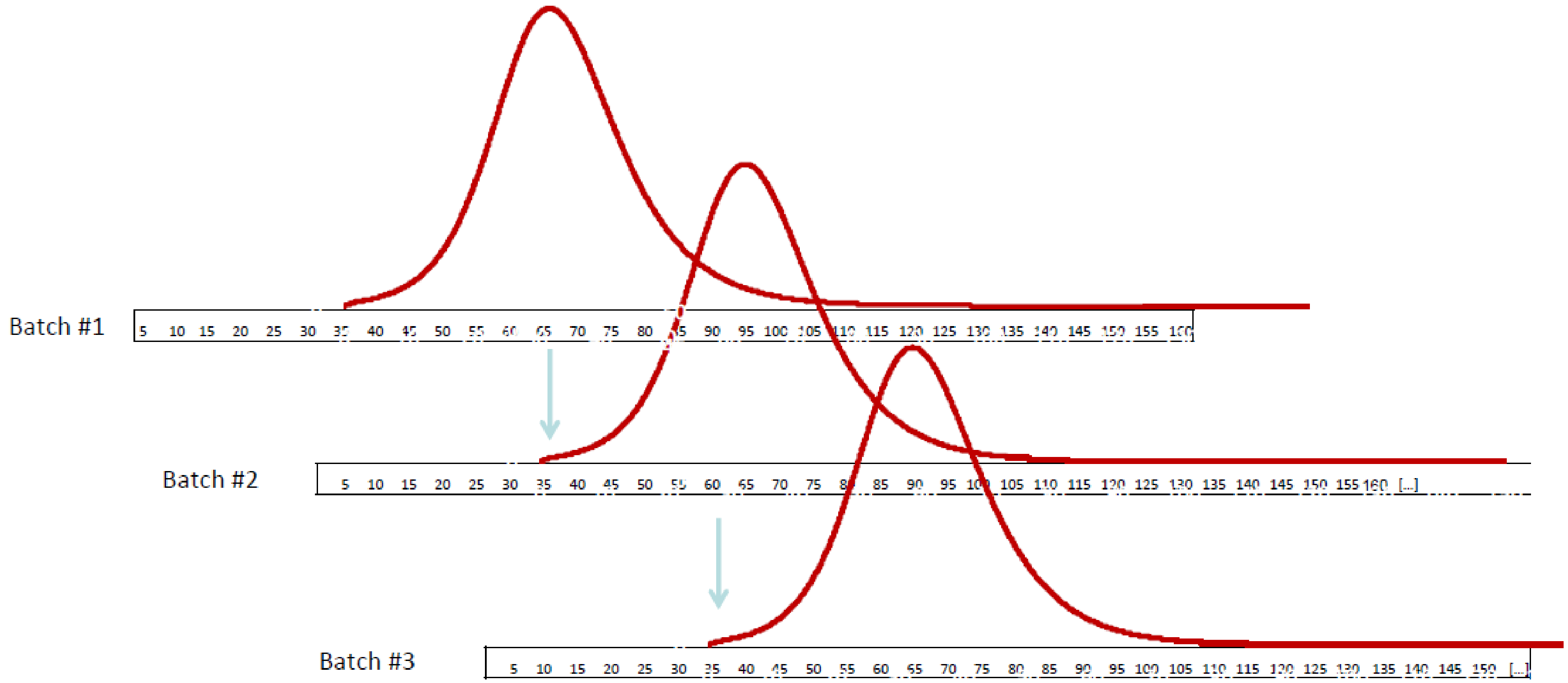
Practical application of oral products

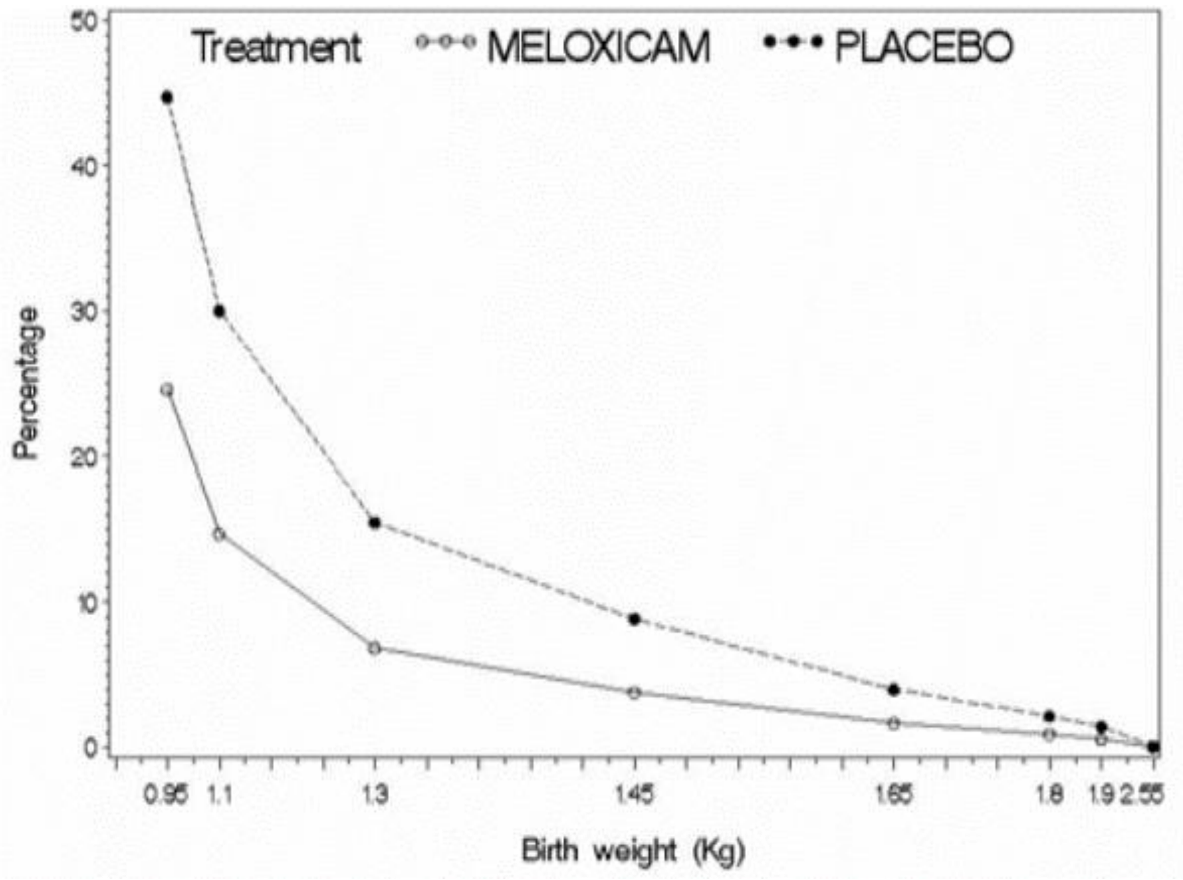
- Treatment at strategic moments in recurrent swine influenza infections



Rose N. Recurrent Influenza infections in pig farms and associated epidemiological characteristics. Presented at VGV, 2016

Practical application of injectable products

- Post Partum Dysgalactiae Syndrome (PPDS)
  - Usually no bacterial infection involved (mastitis)
  - **Start early treatment with NSAID + oxytocin → often sufficient!**
  - **If symptoms worsen → early enough to start treatment with antibiotics (+ NSAID)**



Revilla E et al. Pos-farrowing treatment of sows with meloxicam on the preweaning weight gain and mortality rate of the low birth weight piglets in subclinical MMA. In International Pig Veterinary Society Congress. 2006. Copenhagen

B. Practical measures to reduce AM's use

7. *Supportive therapies – mucolytic*

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Internal and Emergency Medicine
https://doi.org/10.1007/s11739-020-02383-3

IM - REVIEW

Check for updates

Potential new treatment strategies for COVID-19: is there a role for bromhexine as add-on therapy?

Markus Depfenhart[1,2] · Danielle de Villiers[3] · Gottfried Lemperle[4] · Markus Meyer[5] · Salvatore Di Somma[6,7]

Received: 19 April 2020 / Accepted: 18 May 2020

Abstract
Of huge importance now is to provide a fast, cost-effective, safe, and immediately available pharmaceutical solution to curb the rapid global spread of SARS-CoV-2. Recent publications on SARS-CoV-2 have brought attention to the possible benefit of chloroquine in the treatment of patients infected by SARS-CoV-2. Whether chloroquine can treat SARS-CoV-2 alone and also work as a prophylactic is doubtful. An effective prophylactic medication to prevent viral entry has to contain, at least, either a protease inhibitor or a competitive virus ACE2-binding inhibitor. Using bromhexine at a dosage that selectively inhibits TMPRSS2 and, in so doing, inhibits TMPRSS2-specific viral entry is likely to be effective against SARS-CoV-2. We propose the use of bromhexine as a prophylactic and treatment. We encourage the scientific community to assess bromhexine clinically as a prophylactic and curative treatment. If proven to be effective, this would allow a rapid, accessible, and cost-effective application worldwide.

Keywords SARS-CoV-2 · COVID-19 · Prophylactic · Treatment · Bromhexine · Protease inhibitor

B. Practical measures to reduce AM's use
7. *Supportive therapies – mucolytic*

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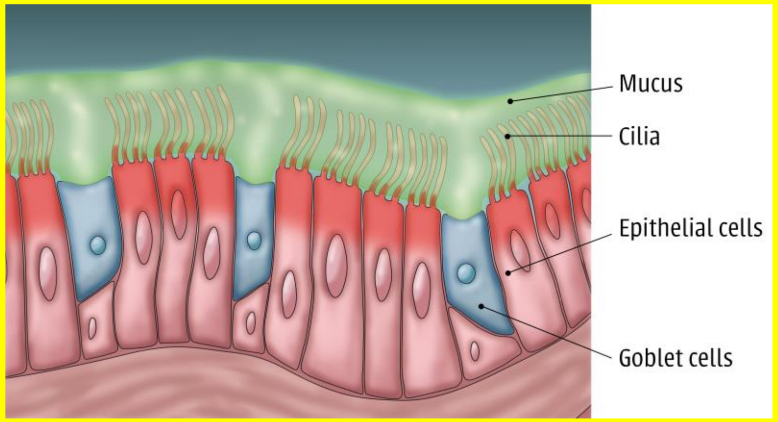
Mucoregulator in respiratory disease

- Effective mucus clearance is essential for lung health; airway disease is a typical consequence of poor clearance
  - ➢Physiologic mucus: low viscosity and elasticity → easy transport by cilia
  - ➢Pathologic mucus: high viscosity and elasticity → impaired clearance



B. Practical measures to reduce AM's use

7. *Supportive therapies – mucolytic*

Mucoregulating effect of bromhexine

- Activates and increases secretion of seromucous glands (Globet cells)
  - ➢ Reduction of viscosity and elasticity
- Increases ciliary activity

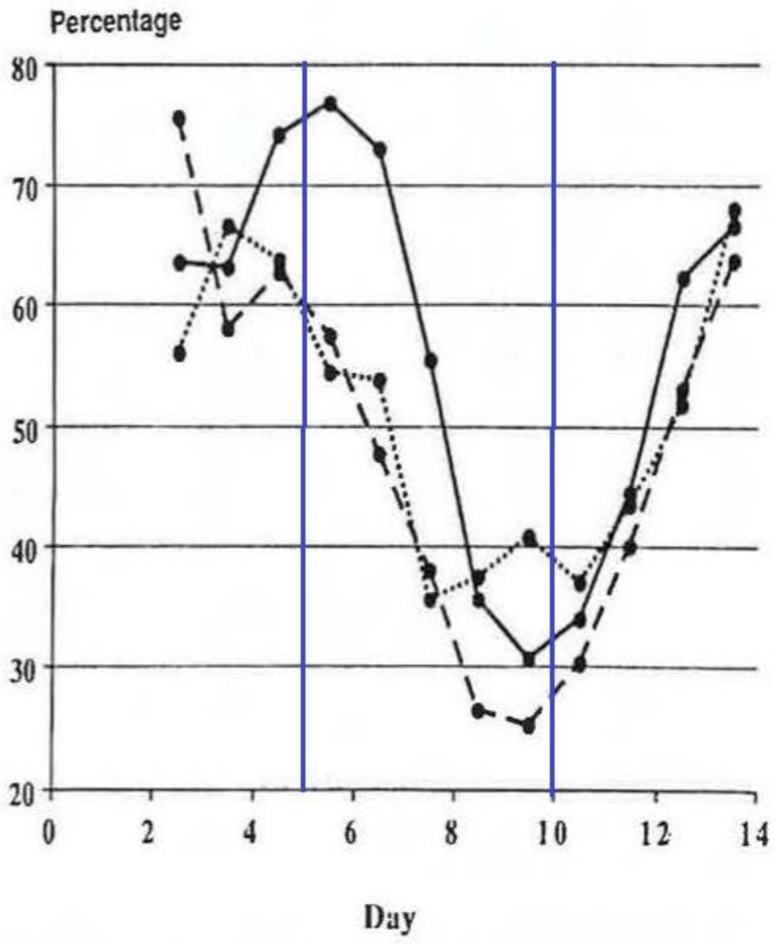


Fig. 1. – Mean percentage change in four day running means of residual shear viscosity (ηo) (normalized to highest value. —●— : 0.5 mg·kg⁻¹ BHCl; ·····●····· : 1.0 mg·kg⁻¹ BHCl; ---●--- : 2.0 mg·kg⁻¹ BHCl.

Martin GP et al. The effect of bromhexine hydrochloride in the viscoelastic properties of mucus from the min-pig. Eur. Respir. J 1990;3:392-396

Dopharma

Mucoregulator in respiratory disease

- **Secondary** effect of bromhexine
  - Increases concentration of antibiotics in bronchopulmonary secretion
  - Increases production of surfactant
  - Anti-oxidant effect
  - Reduces release of cytokines
  - Local anesthetic effect

Practical application – oral products

Group treatment of (secondary) bacterial infection respiratory tract

1. Antibiotic + bromhexine
2. **Bromhexine only** as **follow-up treatment** of antibiotic treatment

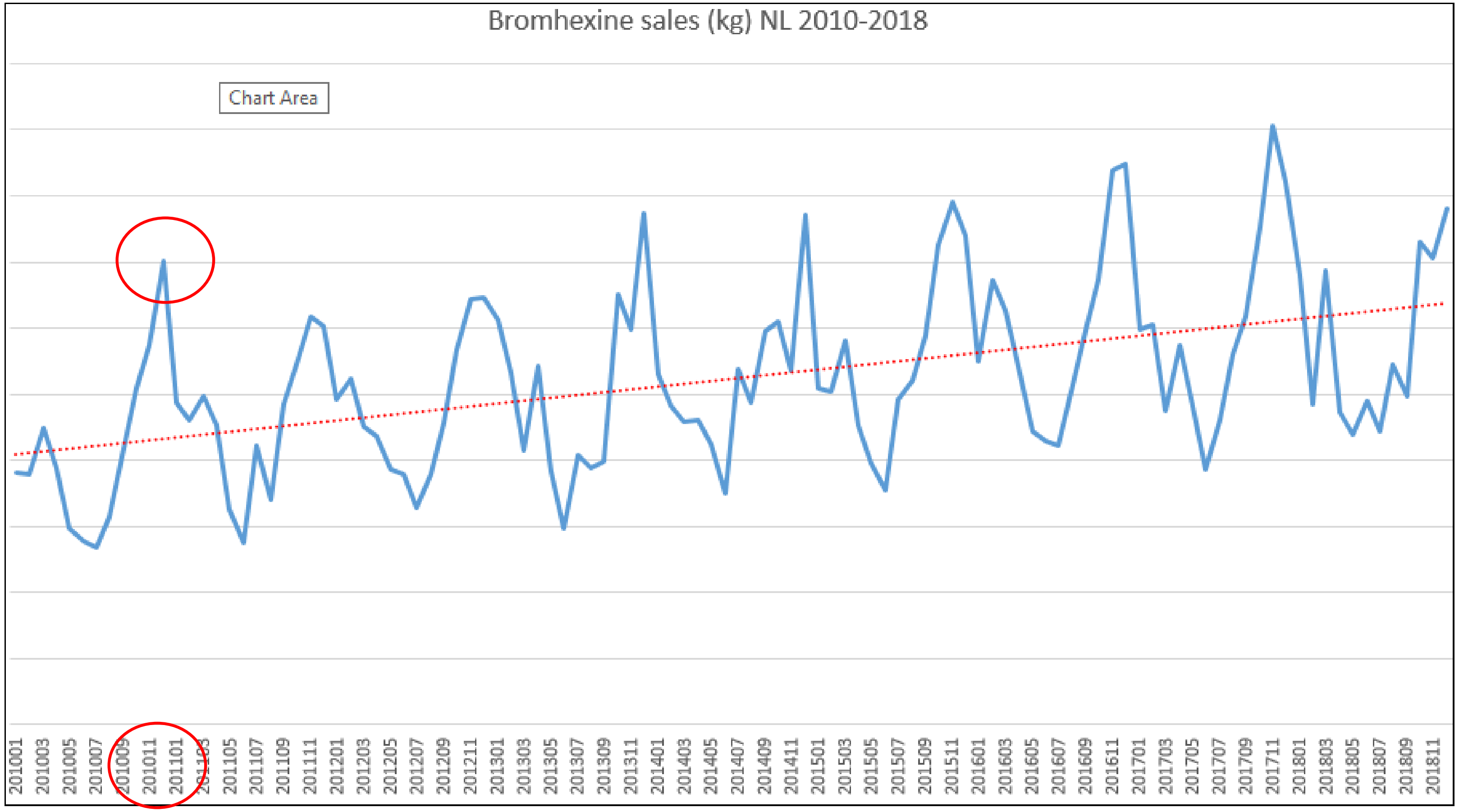
- Pigs recover after antibiotic treatment but often still residual coughing.
  - Prolonged or second antibiotic treatment NOT necessary
  - Follow-up treatment with bromhexine only

B. Practical measures to reduce AM's use

7. Supportive therapies – bromhexine

Dopharma

Practical application – oral products



Data: Dopharma BV

Example of Supportive Therapies application

(N)SAID	MUCOLYTIC
Early mono-treatment NSAID	Combination with antibiotic treatment
Combination with antibiotic treatment	Follow-up mono-treatment Bromhexine

Flow

Summary

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- Epidemiology of resistance in animals and humans is very complex: are we doing the right thing to limit AM resistance in humans?
- Pressure on veterinary AM use will stay... more focus on real impact / welfare
- At what extent 2022 Regulations will impact Medicated Premix usage? And on autogenous vaccines?
- In-depth knowledge of rational antibiotic use can contribute to its reduction
- Supportive and alternative treatments can be a viable, “accessible” and effective tools to reduce usage of antibiotic.