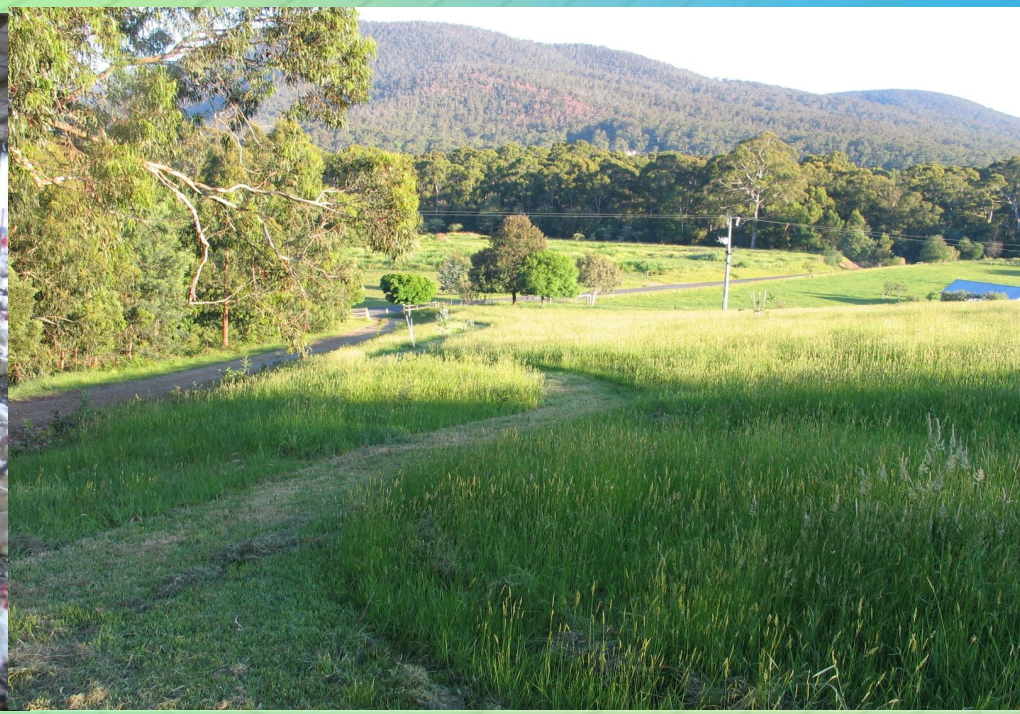
Discovering New Frontiers in Gut Health – Quo Vadis AGP?



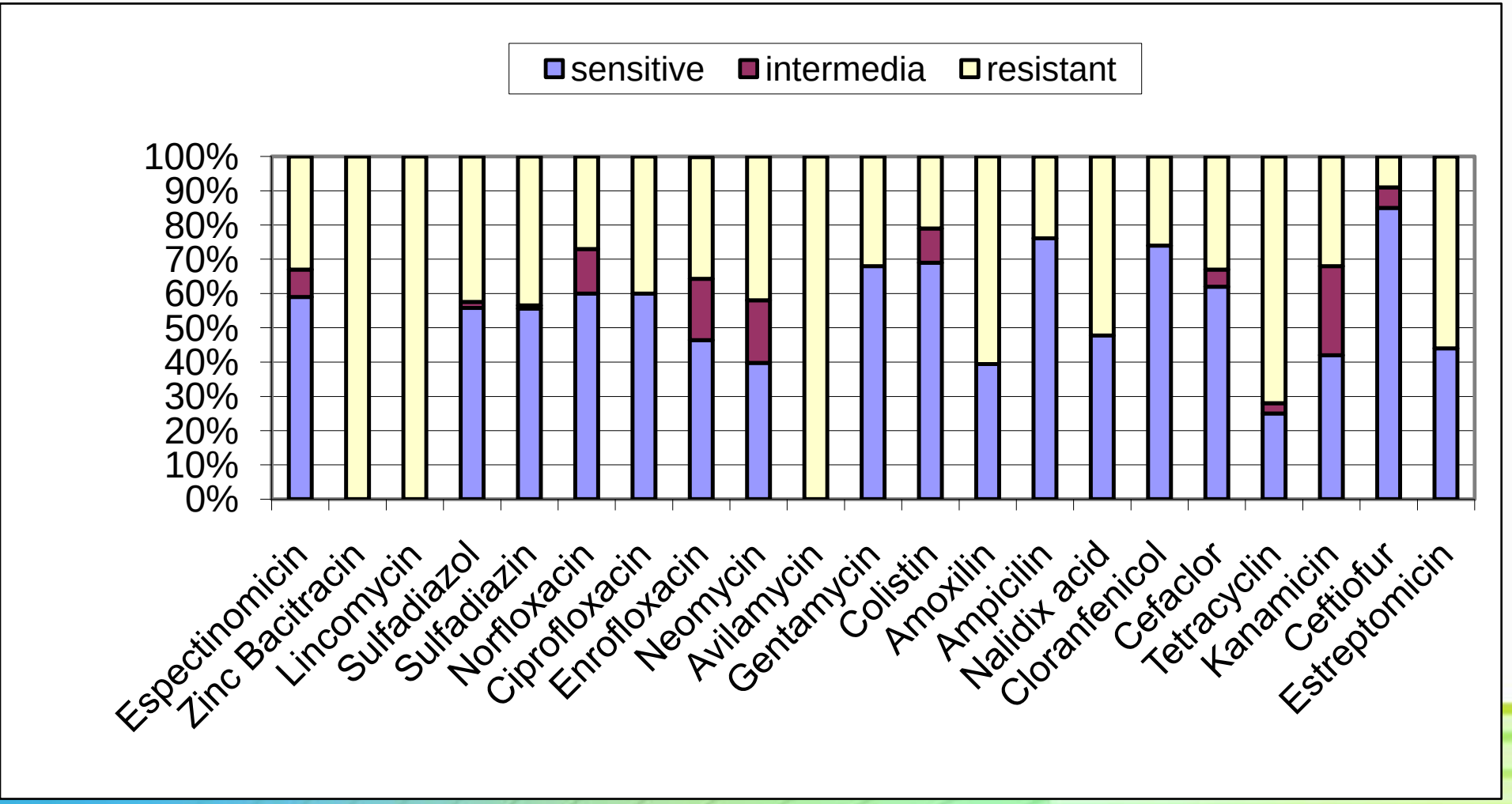


Andreas Kocher

Antibiotics – why banning there usage?

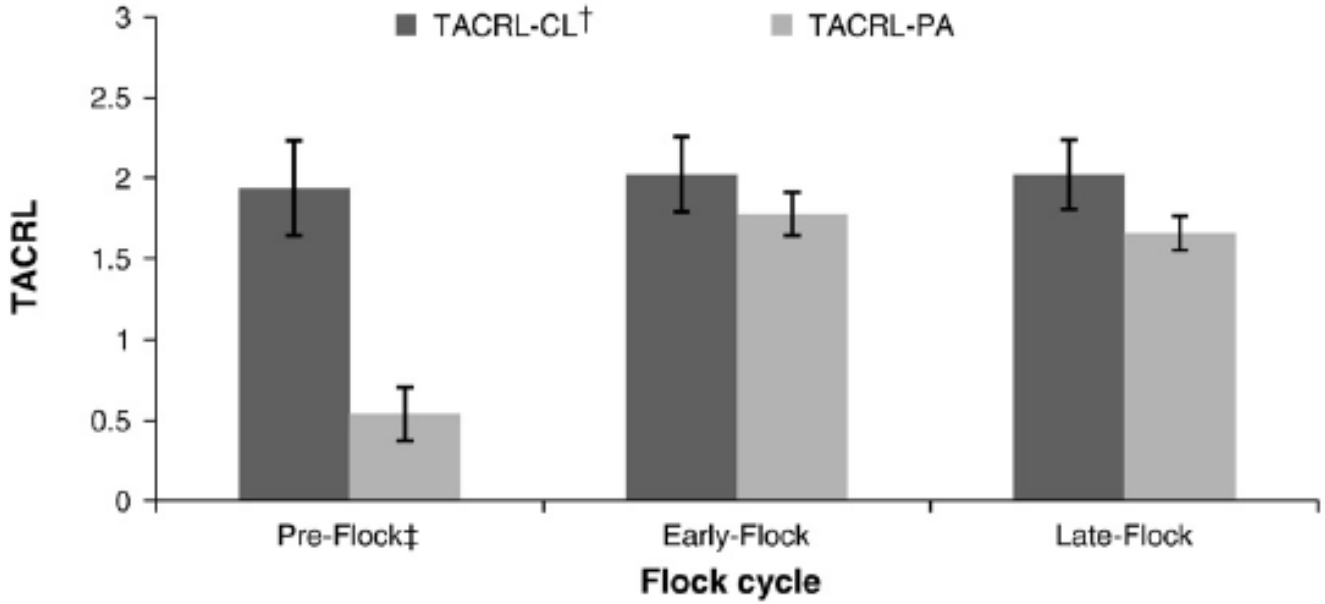
- Arguments for a ban:
  - Risk of developing multi resistant
    - Loss of real treatment options
  - Consumer demands
    - Food residues
- Arguments against a ban:
  - No relationship between AGPS use and resistance
  - Risk of serious human health issues (food borne diseases)
  - No credible alternatives

Resistance – reality of myth?



Swop samples from Brazil

Impact on the environment



TACRL =total antibiotic class resistance level
CL = chicken litter
PA = poultry aerosol

Brooks *et al.* 2010

Environment as a factor

- Carry over effect between flocks ***(da Costa et al. 2010)***
  - Change of phenotype of day-old birds to phenotype isolated from feed and environment
- Carry over to end product ***(Turkey: Kasimoglu-Dogru, 2010)***
  - 78% of samples tested had Enterococci at slaughter level (E. faecium, E. faecalis, E. gallinarum, E. durans and E. hirae)
  - 48% E.faecium (chloramphenicol, gentamicin and streptomycin) – not Vancomycin
- Carry over into sewage ***(Sahlström et al. 2009)***
  - *E. faecium* harbouring the vanB gene

Risk to human health

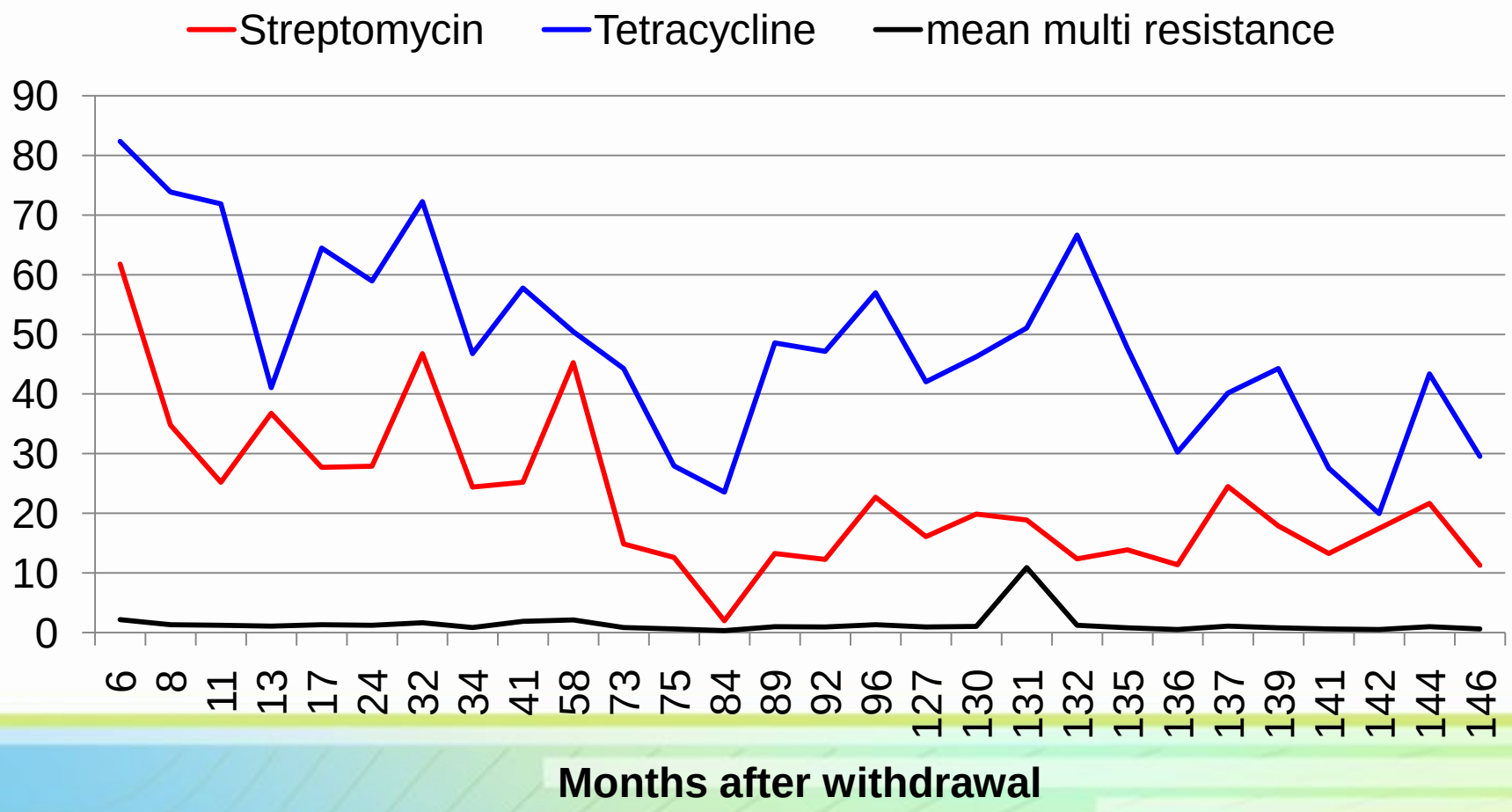
(Cox and Popken, 2006)

- RISK: additional illness days from continued of AGP and expected illness ***caused*** by increased antibiotic resistance to food borne pathogens
  - 57 days for enrofloxacin, 9 days for macrolides
- BENEFIT: reduced number of illness days - risk reduction expected illness days ***prevented*** by continued use of AGP by reduced animal disease
  - 40’050 days

✓ Benefit:Risk Ratio:

- 703 for enrofloxacin, 4500 for macrolides

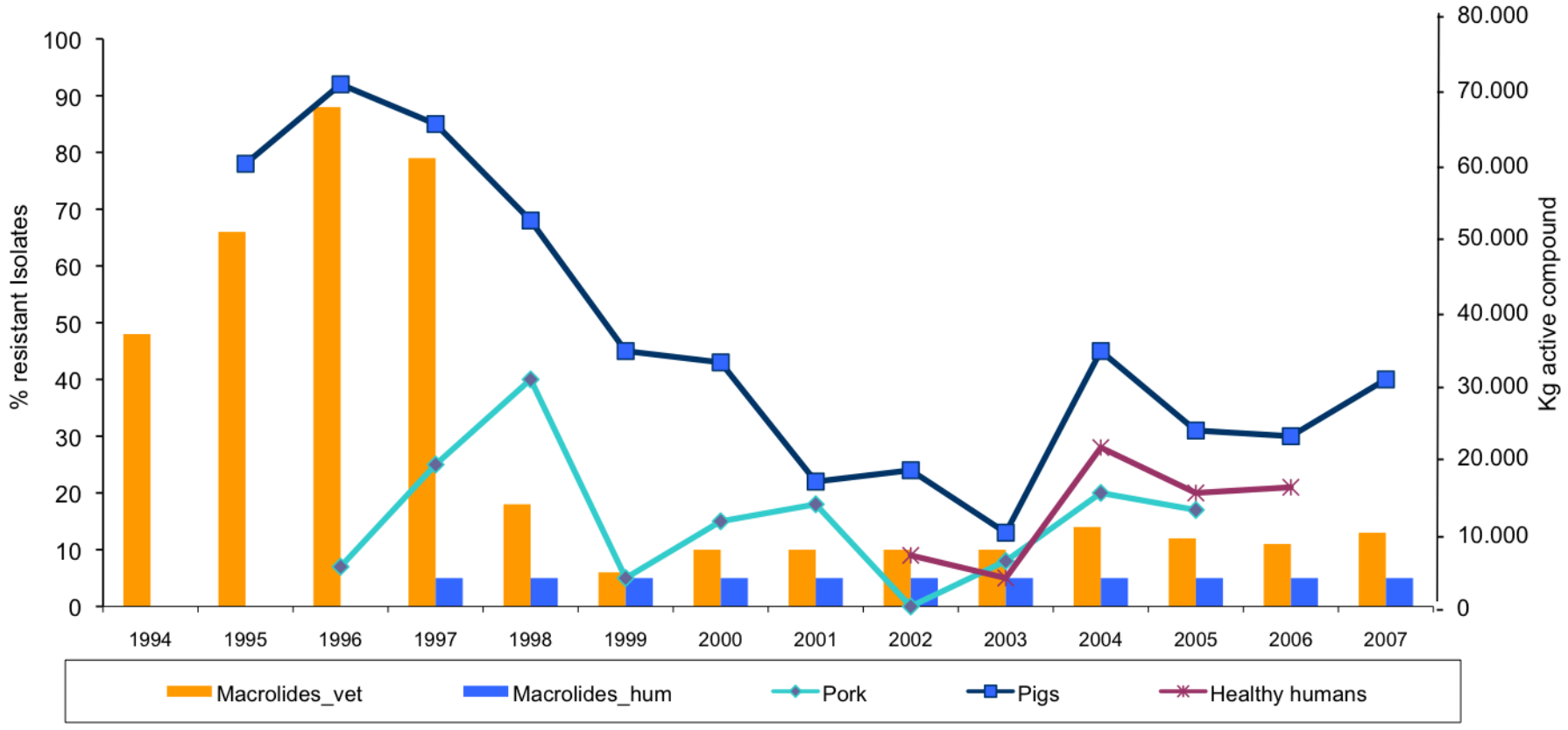
Resistant to streptomycin and tetracycline in pigs after AGP withdrawal – effect after 13 years



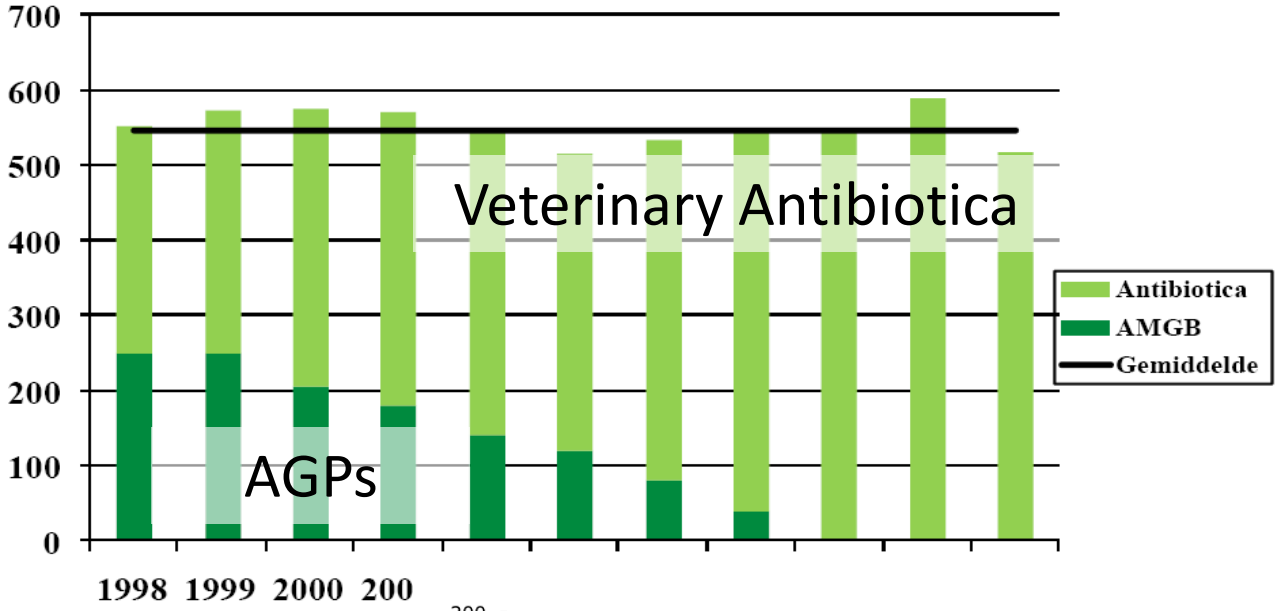
Langois et al. 1986

A total ban is the only answer ! / ?

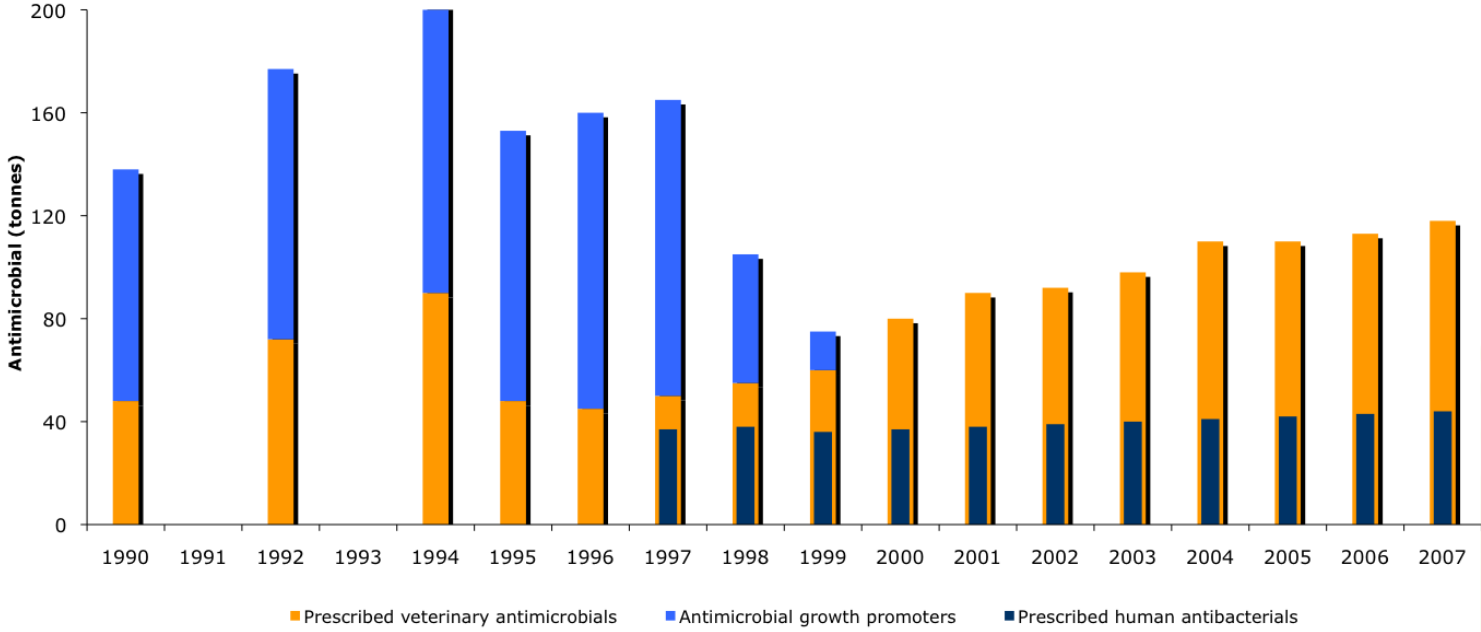
Erythromycin resistance in Enterococcus faecium from pigs, pork & healthy humans, & total consumption of macrolides: as AGPs & therapeutics in animals & humans



Does it work?


700
600
500
400
300
200
100
0
1998 1999 2000 200
Veterinary Antibiotica
AGPs
Antibiotica
AMGB
Gemiddelde




Antimicrobial (tonnes)
200
160
120
80
40
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007
Prescribed veterinary antimicrobials
Antimicrobial growth promoters
Prescribed human antibacterials

Costs of intestinal disorders

Effect ban	BWG	FCR
Healthy broilers	0 to -3%	+1 to +4%
Intestinal disorder	-3 to -6%	+4 to +7%

	Healthy broilers			Intestinal disorders	
	Amount	price/unit	total	amount	total
Sales profit					
Body wt (kg)	220	0.83	182.60	209	173.47
Costs chicks & feed					
Chicks	100	0.28	28.00	**-6.57**	28.00
Feed (kg)	352	0.32	112.64		110.08
Feed profit (€/100 birds)			**41.96**		**35.39**
Variable costs					
Housing, litter, manure			14.00	**-10.22**	15.65
Health care			2.00		4.00
Gross profit (€/100 birds)			**25.96**		**15.74**

Van der Klis, 2010

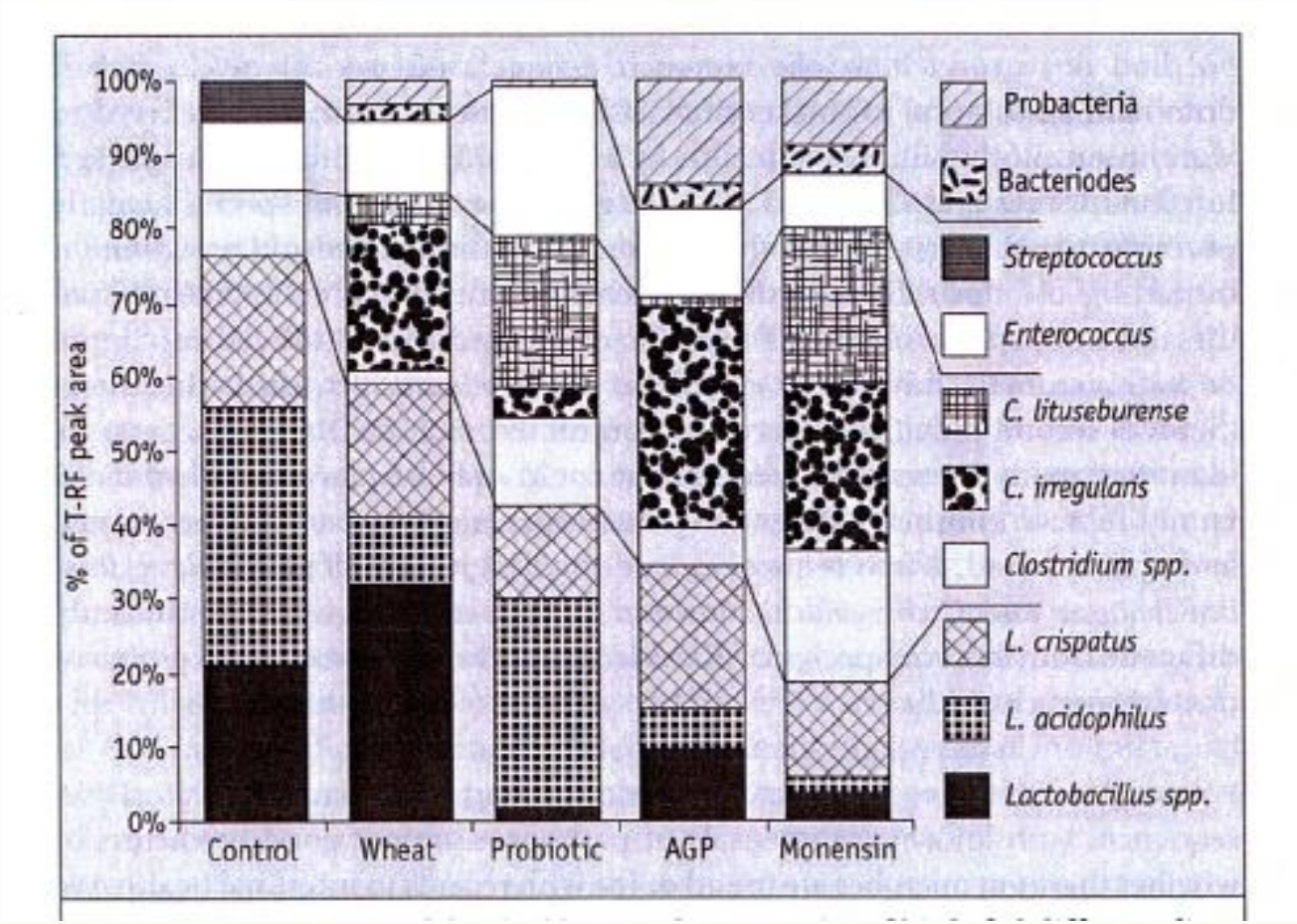
Animal production beyond in the next decade?



Credible alternatives to AGP

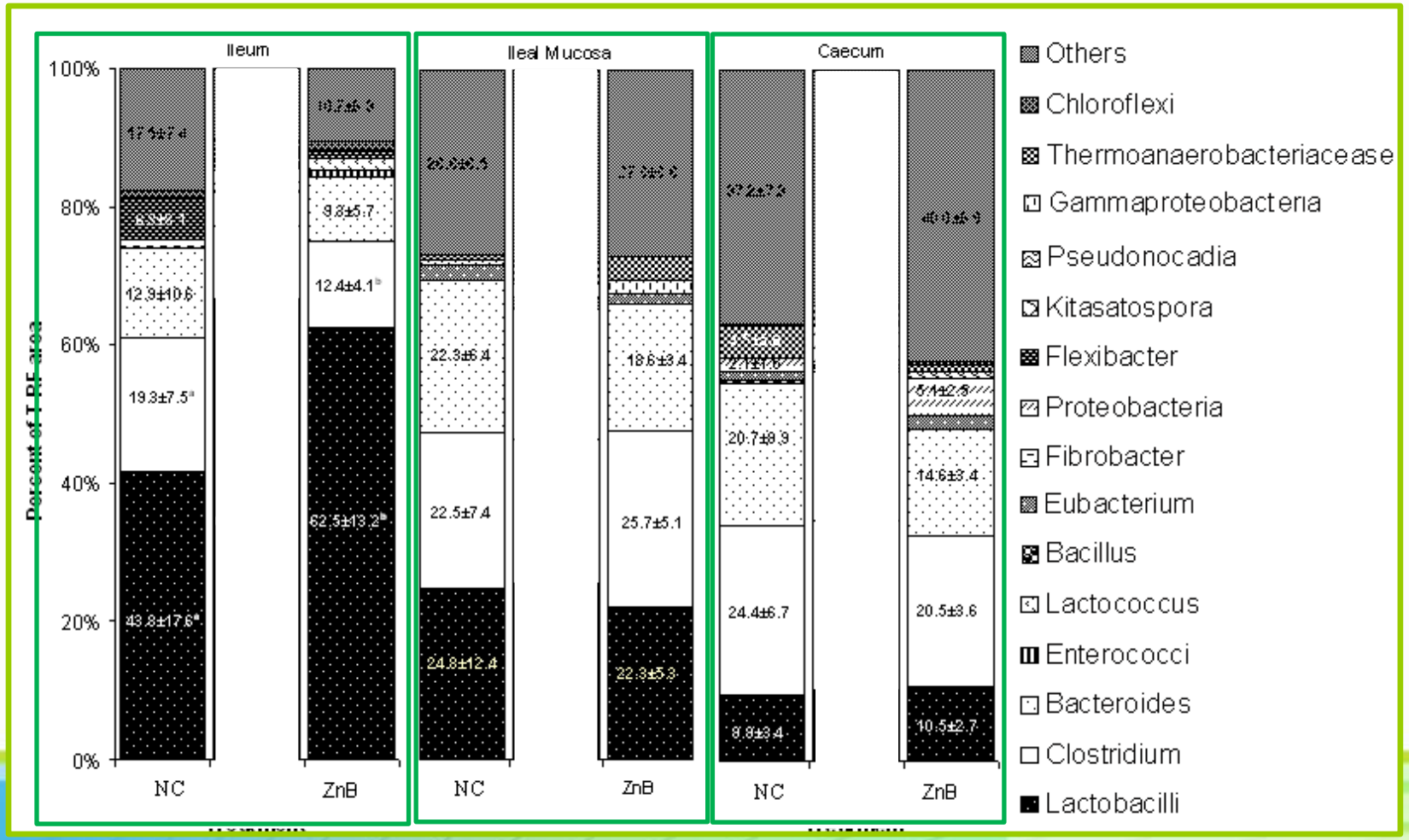
- Characterizing a GOOD alternative
  - Equal or better benefits than AGPs
  - Economic consideration
- Candidates (from Huyghebaert et al. 2010):
  - Enzymes
  - Organic acids
  - Probiotics
  - Prebiotic
  - Herbs and essential oils
  - Bactriophages
- Understanding the mode of action
  - Focus on microflora management

Understanding the mode of action



Composition of ileal bacterial communities depending on additive, pooled samples 0-42days (Lee, 2006)

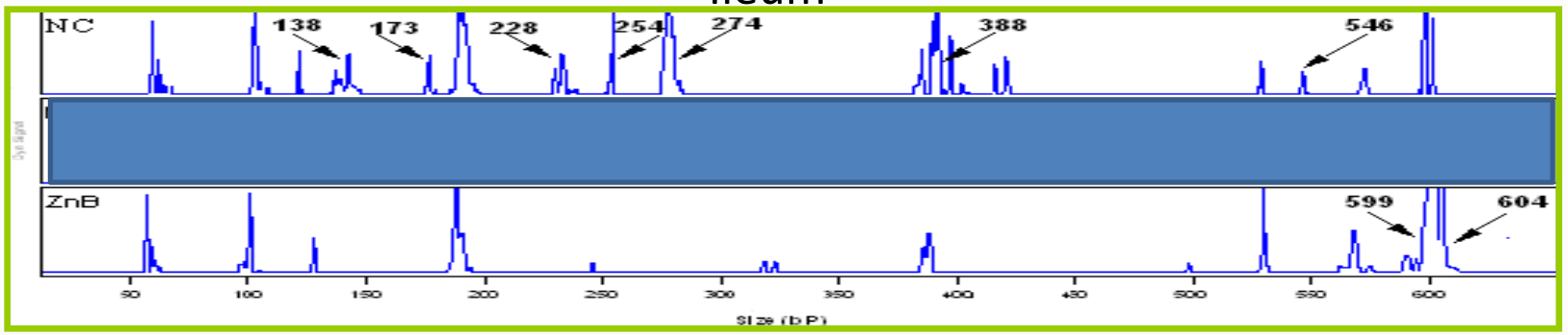
Understanding the mode of action



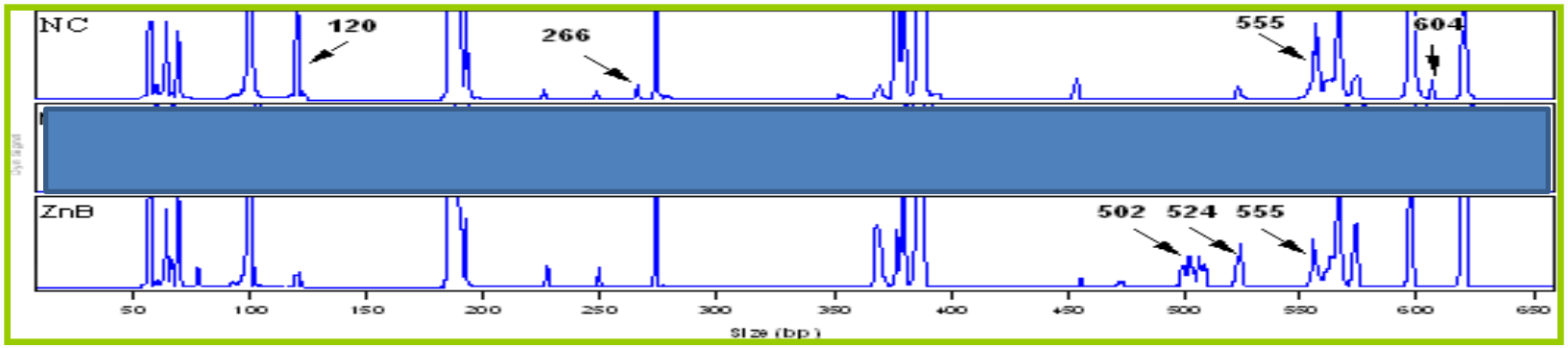
Chee 2009

Reduced diversity

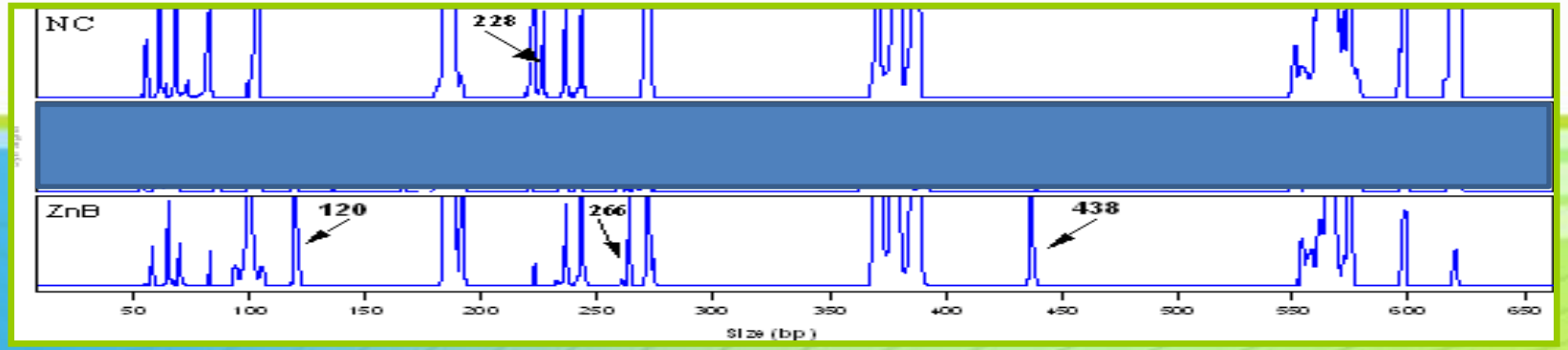
Ileum



Ileal Mucosa



Caecum



Chee 2009

Mode of Action of AGPs – Different schools of thought

For many years the use of antimicrobials to improve performance has been practiced widely but poorly understood why it is effective in 70% + of cases….

Microflora-Management Related Mechanisms of AGPs

1) Inhibition of endemic sub-clinical infection and thereby reduce the metabolic costs of the innate immune system,

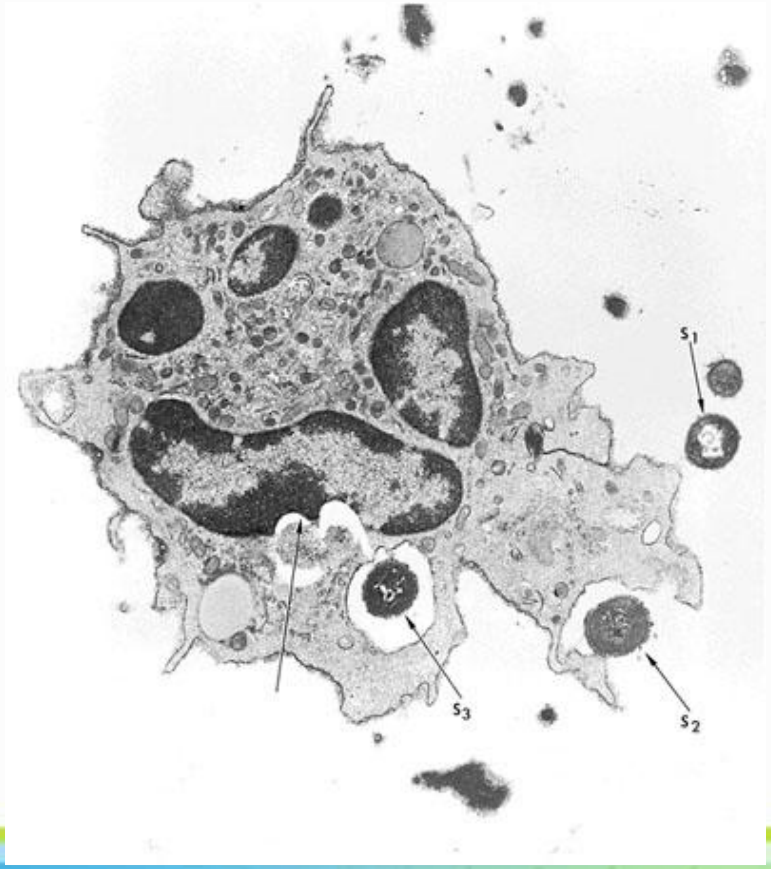
2) Reduction of concentrations of growth-depressing metabolites such as ammonia and bile degradation production generated by microbes,

3) Reduction of microbial consumption of nutrients in digesta,

4) Enhancement of the uptake and use of nutrients because the intestinal wall in AGP-fed animals is thinner.

Gaskins et al., 2002

Antibiotic anti-inflammatory effect



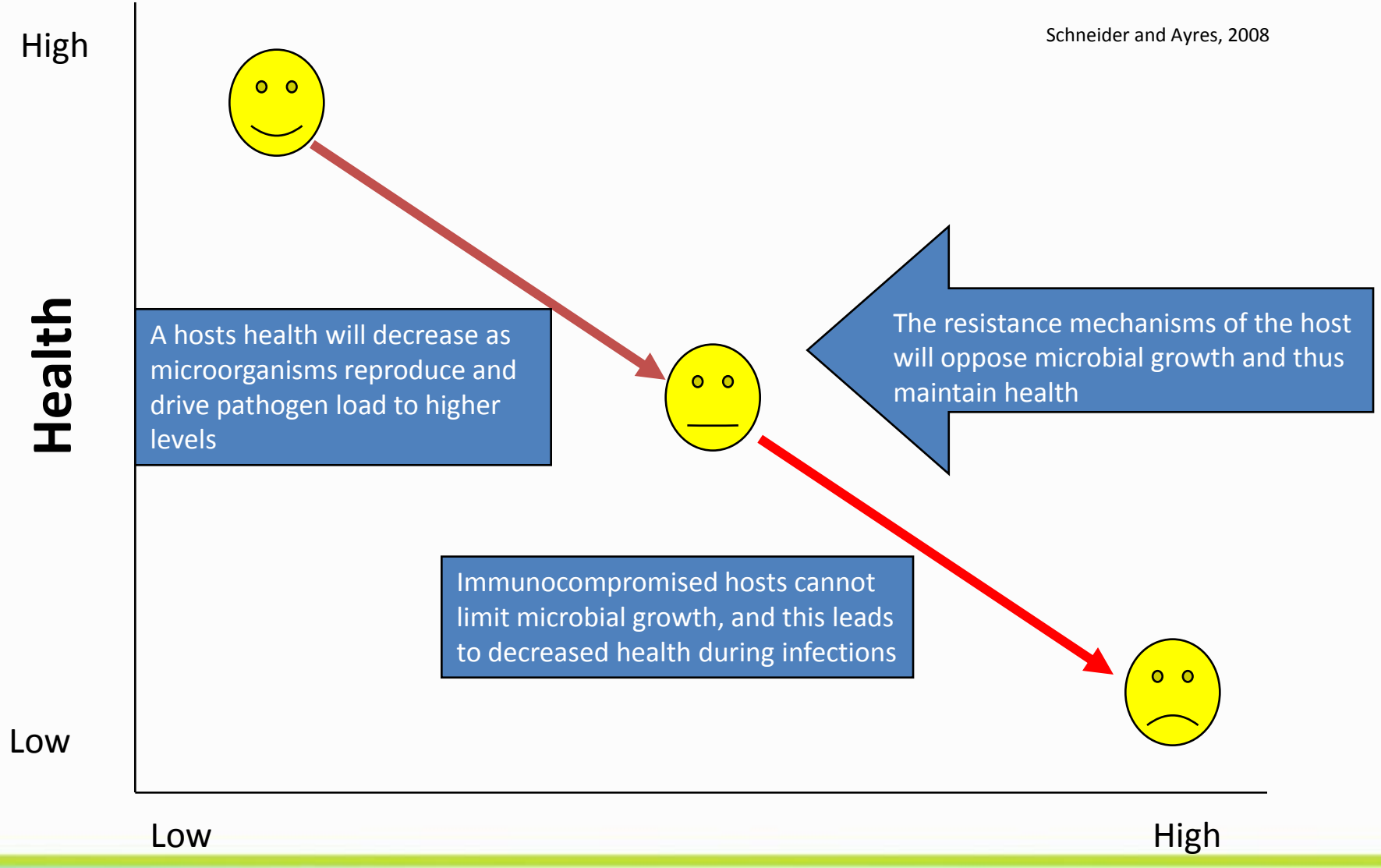
Phagocytic cells can accumulate antibiotics

Inhibition of one or more functions

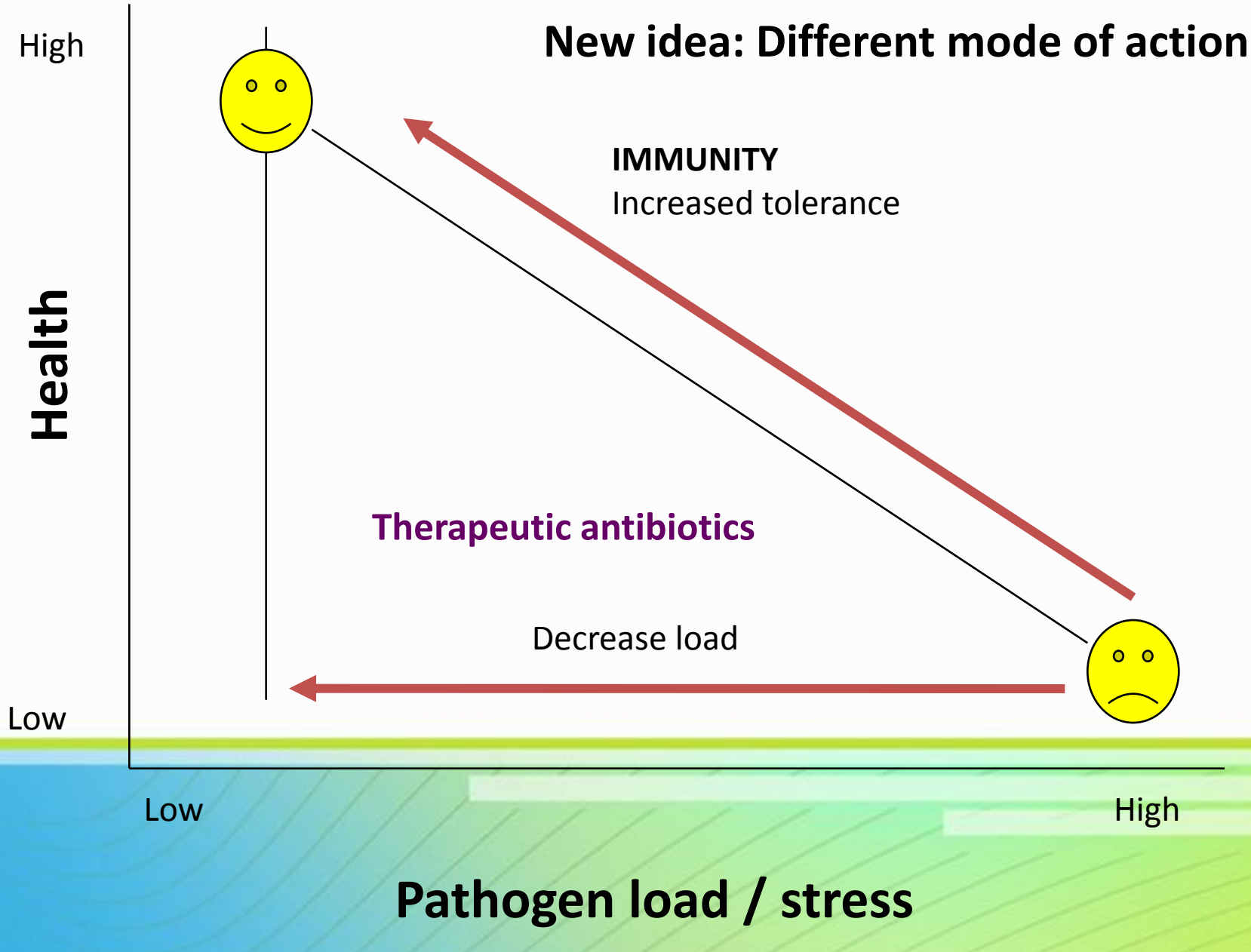
- Chemotaxis
- Production of reactive oxygen species
- Pro-inflammatory cytokine production

Altered immune status would have an effect on microbiota

Distinguished researchers such as Prof Kirk Klasing at UC Davis and Prof. Theo Niewold at University of Ghent believe that this mechanism is what is behind growth promotion.


High
Health
Low
Schneider and Ayres, 2008
A hosts health will decrease as microorganisms reproduce and drive pathogen load to higher levels
The resistance mechanisms of the host will oppose microbial growth and thus maintain health
Immunocompromised hosts cannot limit microbial growth, and this leads to decreased health during infections
Low
High
Pathogen load / stress

Schneider and Ayres, 2008



Why is this important ?

- 9% of the diet is used to fuel the pro-inflammatory response in the young animal !!!!!
- It takes time: 2-3 weeks for the immune system to learn ‘tolerance’ for non-commensal bacteria
- We can gain valuable FCR points by reducing this requirement

A new way of looking at AGPs and alternatives



DNA Microarray Technology

- Nutrigenomics tells us how nutrients affect genes, i.e. diet/gene interactions
- Evaluates the activity of thousands of genes in a single experiment.
- Tells us which genes are switched on, switched off or remain unchanged in response to a nutrient or diet.

Nutritional challenge model

Methods: 160 broilers divided into 3 treatment groups

Model: High viscosity wheat formulated to generate intestinal challenge & transcript analyses

Diets:
Corn Soy control
Wheat challenge (corn replaced with wheat)
Wheat challenge with Alternative 1
Wheat challenge with Alternative 2

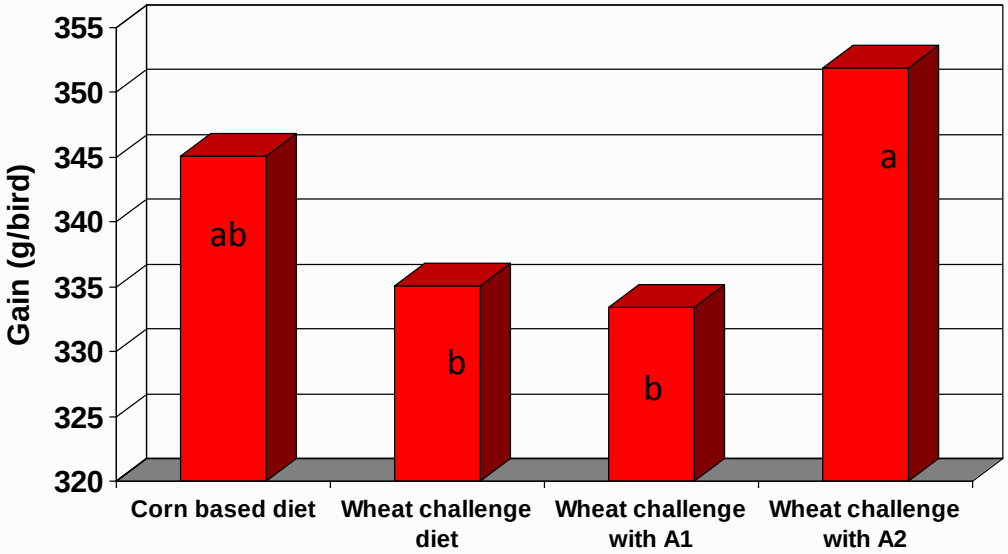
Measurements: Growth, Feed efficiency

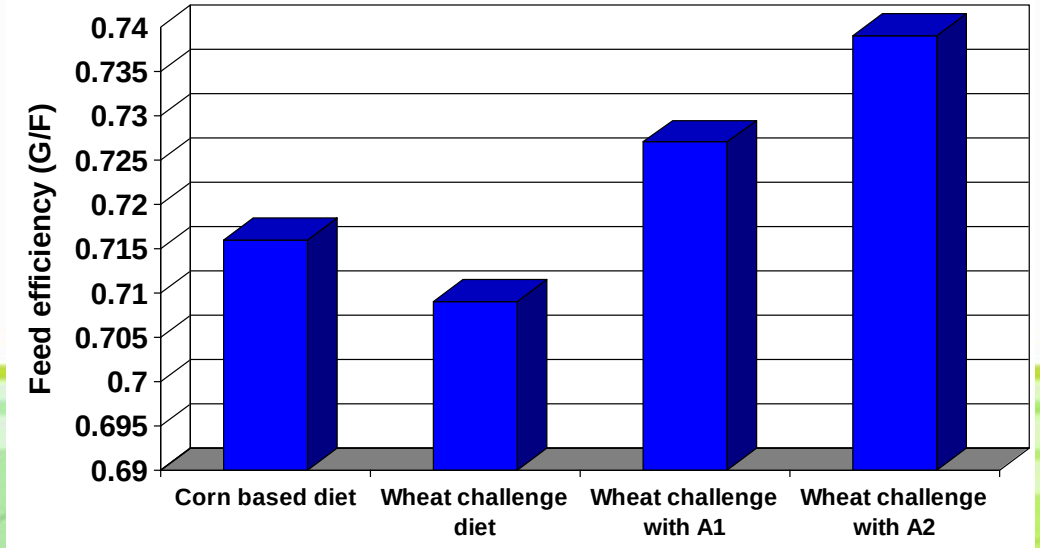
Nutrigenomics: Gene expression in jejunum measured at 21 days (7 birds per treatment)

Microarray “GeneChip Chicken Genome Array” with 37,703 probe sets representing 28,000 genes.

Dawson, unpublish

Growth performance (14days)

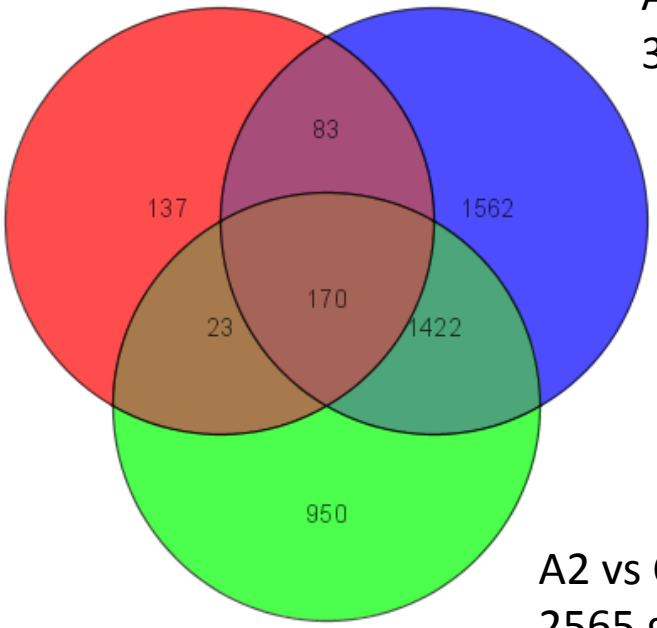




Dawson, unpublished

Some key observations from gene expression patterns

Wheat vs Corn
413 genes



A2 vs Corn
3237 genes

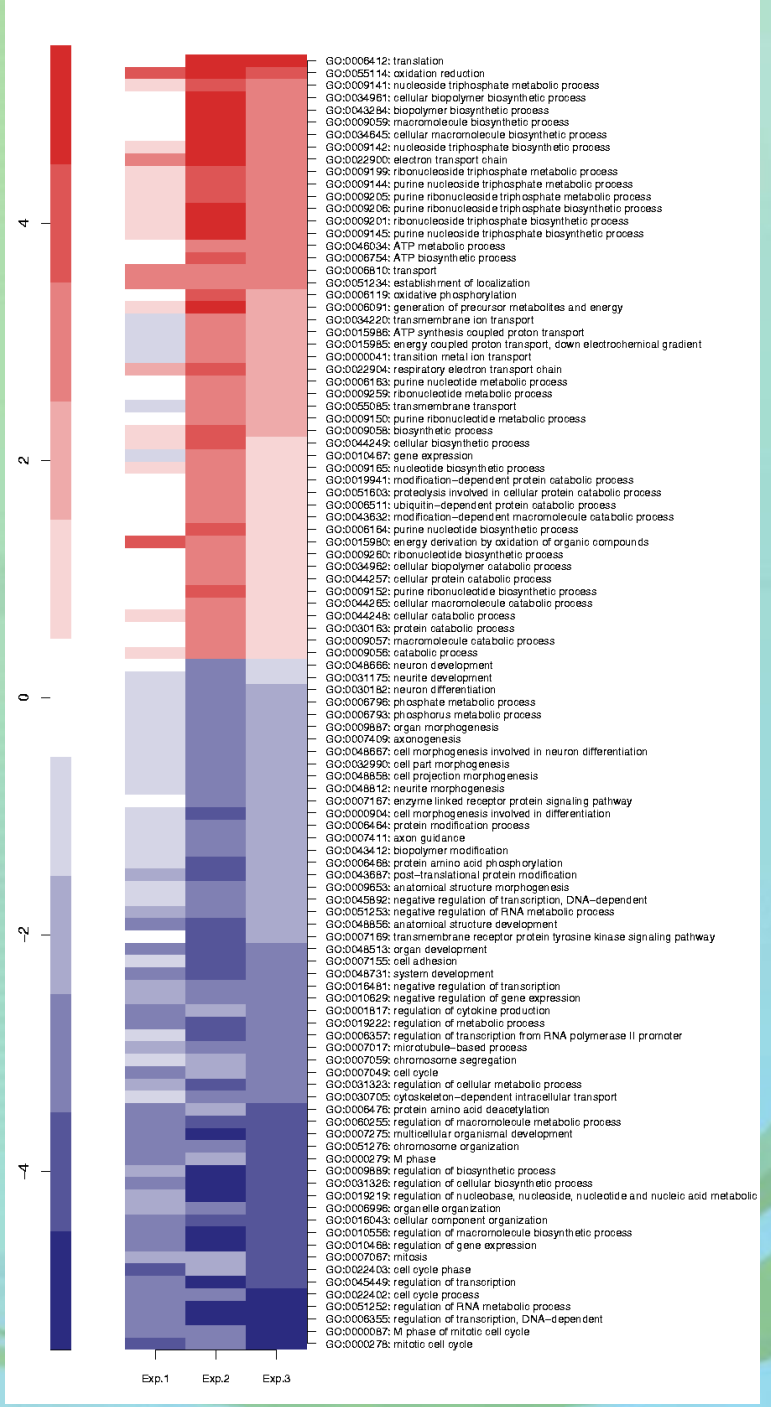
A2 vs Corn
2565 genes

- The wheat challenge modified the expression ($p<0.01$) of 413 genes (1.4%)
- A1modified the expression of 2565 genes (9.1%)
- A2 modified the expression of 3237 genes (11.5%)

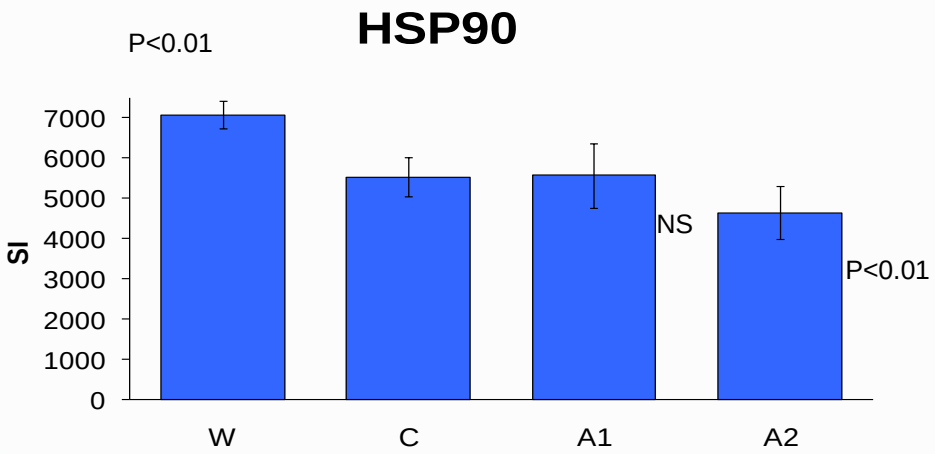
Key metabolic processes in the jejunum

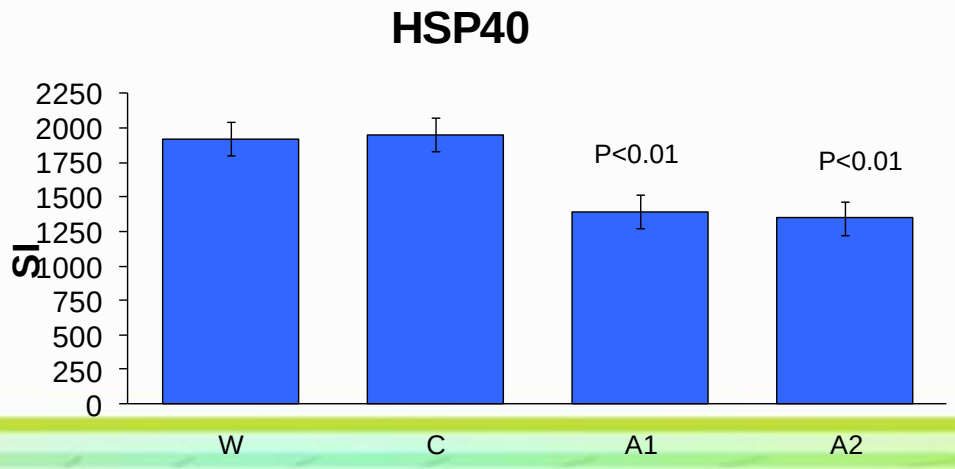
PAGE Biology processes evaluation

- Up-regulated
  - Protein translation
  - Energy production (e-transport and ATP production)
  - Transport systems
  - Digestive enzymes
  - Components of immune response
- Down-regulated
  - Stress responsive pathways
  - Protein degradation pathways



Decreased expression of stress protein genes





Practical application of a concept

- Commercial type diets (corn/soy)
- All birds vaccinated on day of hatch with coccidial vaccine using Spraycox machine
- Parameters: d21, 35, and 42 weight gain and adjusted feed conversions
- 3 treatments: Control, AGP, Alternative (A2)





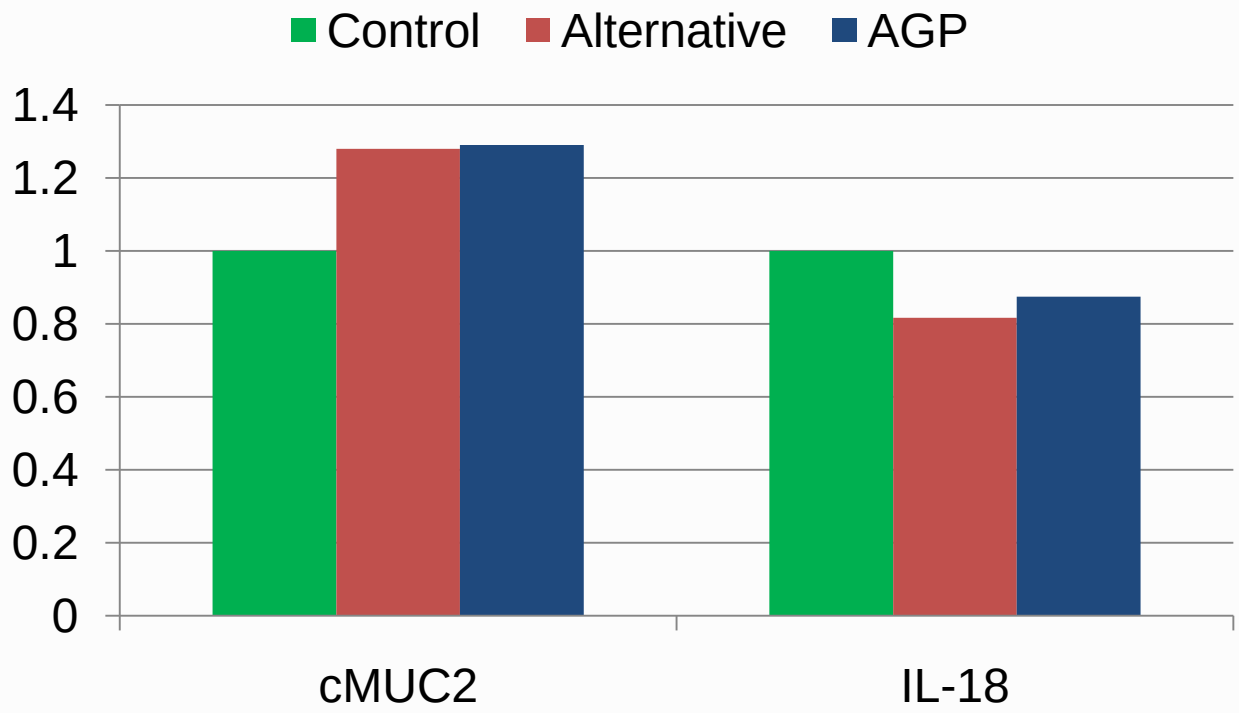
Treatment	Day 35 FCR	Avg. Live Weight (kg)	Day 42 FCR	Avg. Live Weight (kg)
Control	1.651 a	1.972 b	1.910 a	2.382 b
Alternative (A2)	1.593 b	2.063 a	1.820 b	2.502 a
BMD	1.598 b	2.085 a	1.815 b	2.529 a

Benefit	BWG	FCR
Alternative	plus 4 - 5%	minus 6 -9 points (5%)
AGP	plus 3 - 6%	minus 6 -9 points (5%)

$p<0.05$

Mathis 2010

Relative Quantification of cMUC2 and and IL-18 mRNA in chicken jejunum



Jejunum samples taken on D42: 7 birds /treatment

Mathis, 2010

Quo Vadis AGP?

- No conclusive evidence for either argument – ban or keep!
- Consumer pressure, Supermarket, fast food chain pressure, regulatory pressure
- **Discovering New Frontiers in Gut Health**

Thank you!

