Passive Immunity and IgG-like antibodies as an alternative to antibiotics

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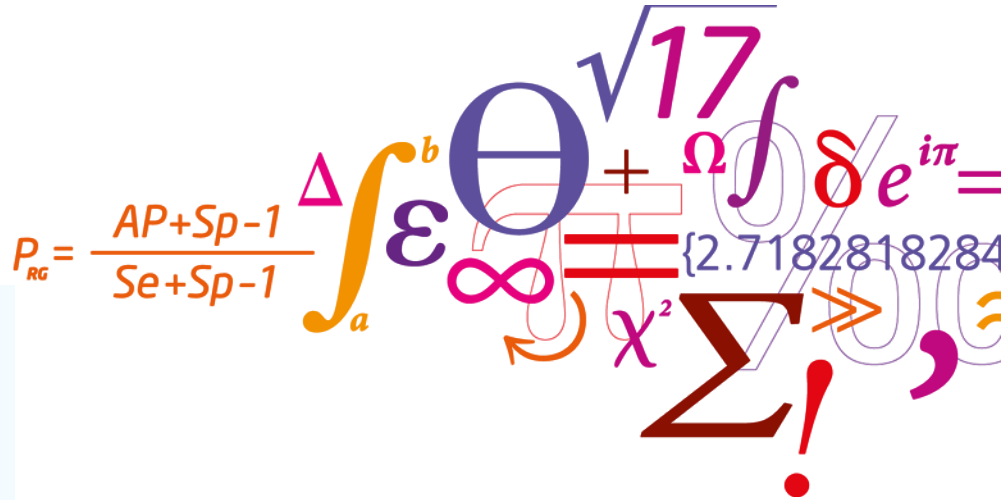
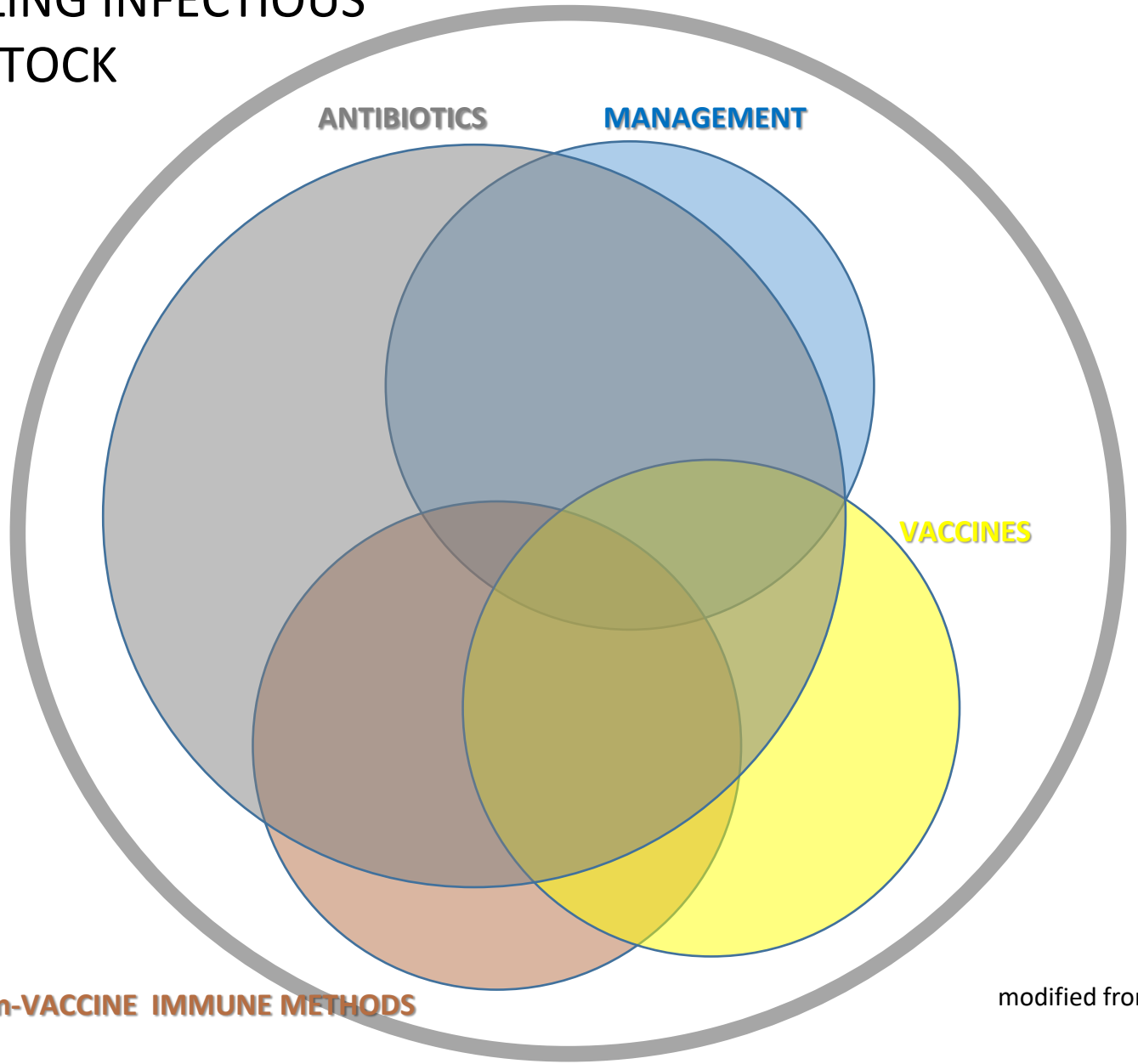


3rd International Symposium on Alternatives to Antibiotics (ATA)
Bangkok 16-18 December 2019

TOOLS FOR HANDLING INFECTIOUS DISEASES OF LIVESTOCK



modified from van Dijk et al. Vet Res. 49., 2018

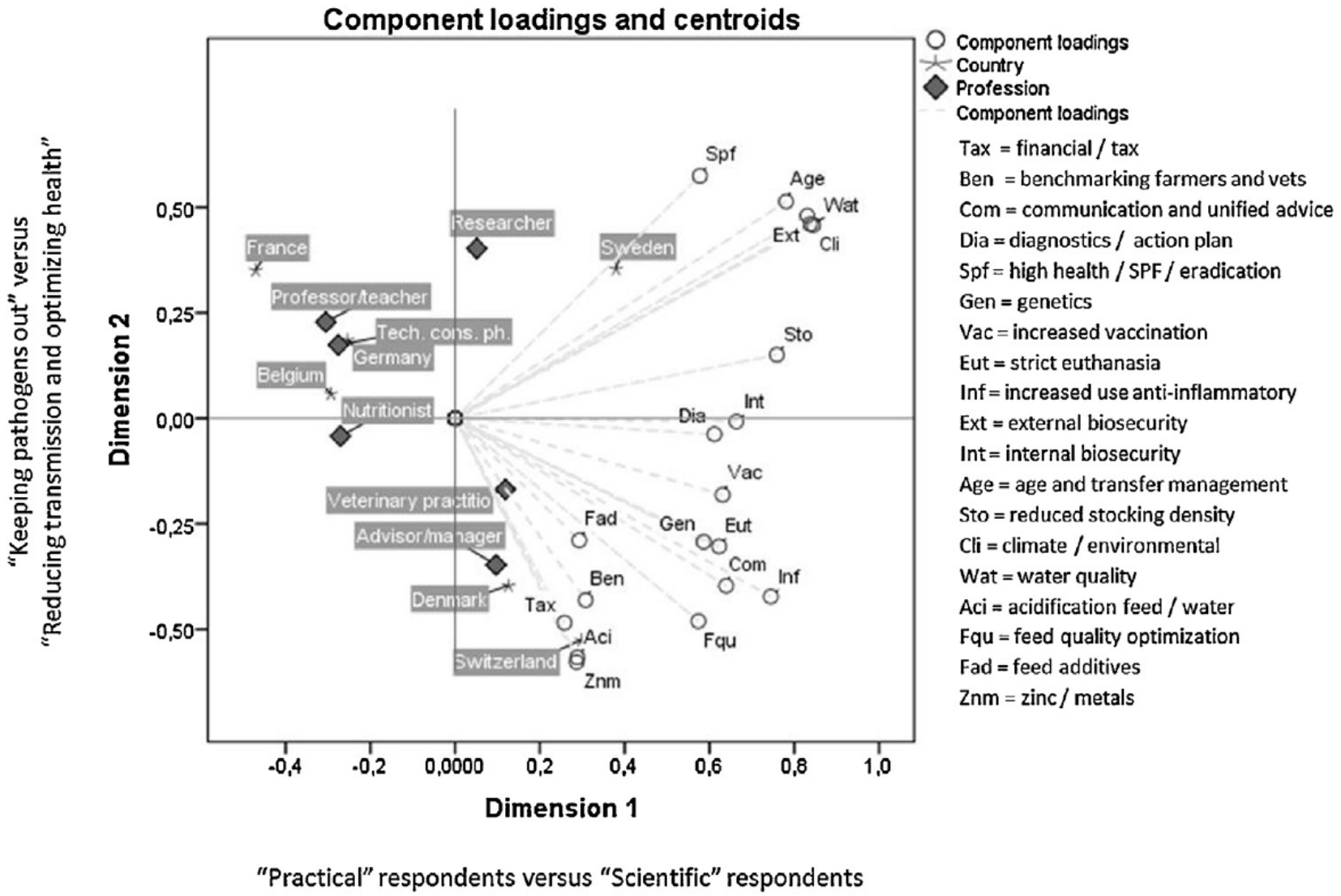
Perceived effectiveness, feasibility & ROI of ATAs

Table 2
Statistics of perceived effectiveness, feasibility and return on investment (ROI) for alternatives to antimicrobial usage as expressed by European experts ($n = 111$).

Alternative	Average of the three parameters				Effectiveness				Feasibility				ROI			
	Mean	Ranking[a]	SD	Mode	Mean	Ranking[a]	SD	Mode	Mean	Ranking[a]	SD	Mode	Mean	Ranking[a]	SD	Mode
Internal biosecurity	7.5	**1**	1.6	8.0	8.2	**1**	1.9	8.0	6.6	8	1.9	7.0	7.6	**1**	1.8	8.0
Increased vaccination	7.2	**2**	1.4	8.0	7.6	**5**	1.6	8.0	7.3	**1**	1.8	8.0	6.8	6	1.9	7.0
Zinc/metals	7.2	**3**	1.9	6.0	7.5	8	1.9	8.0	7.1	**5**	2.9	8.0	7.0	**2**	2.4	8.0
Feed quality/optimization	7.2	**4**	1.7	8.0	7.5	7	1.9	8.0	7.1	**4**	2.0	8.0	6.9	**4**	2.3	8.0
Diagnostics/action plan	7.0	**5**	1.6	7.0	7.4	9	1.7	7.0	6.8	7	2.0	8.0	6.9	**3**	2.1	8.0
External biosecurity	7.0	6	1.5	8.0	7.8	**2**	1.8	8.0	6.5	9	1.9	7.0	6.7	7	2.1	7.0
Climate/environmental	7.0	7	1.4	6.7	7.7	**3**	1.6	8.0	6.4	12	1.7	5.0	6.9	**5**	2.0	8.0
Communication/unified advice	6.6	8	1.7	7.3	7.1	11	2.1	8.0	6.4	13	2.3	5.0	6.2	11	2.5	8.0
Water quality	6.5	9	1.8	6.0	6.3	14	2.4	7.0	7.2	**3**	2.1	8.0	6.1	12	2.3	5.0
Age and transfer management	6.5	10	1.8	7.3	7.2	10	1.8	8.0	5.9	16	2.1	5.0	6.4	9	2.3	8.0
Strict euthanasia	6.3	11	1.8	5.0	6.4	13	2.3	5.0	6.2	15	2.6	8.0	6.4	10	2.2	7.0
High health/SPF/eradication	6.3	12	1.7	6.0	7.6	**4**	2.1	8.0	4.6	18	2.3	5.0	6.6	8	2.5	8.0
Reduced stocking density	6.3	13	1.9	6.0	7.5	6	2.0	8.0	5.6	17	2.8	5.0	5.7	13	2.5	8.0
Increased use anti-inflammatory	6.2	14	2.0	6.0	5.9	15	2.4	5.0	7.3	**2**	2.1	8.0	5.4	16	2.6	5.0
Benchmarking farmers/vets	6.2	15	1.6	7.0	6.8	12	2.1	8.0	6.4	14	2.1	5.0	5.3	17	2.5	5.0
Acidification feed/water	6.0	16	1.6	6.0	5.7	17	1.9	6.0	6.8	6	2.2	9.0	5.5	15	2.0	5.0
Financial/tax	5.3	17	1.8	5.0	5.9	16	2.5	5.0	6.4	11	2.7	5.0	3.6	19	3.0	0.0
Genetics	5.2	18	1.8	5.0	5.6	18	2.0	5.0	4.5	19	2.4	3.0	5.5	14	2.3	5.0
Feed additives	5.1	19	1.8	5.0	4.6	19	2.1	5.0	6.4	10	2.4	5.0	4.1	18	2.4	2.0

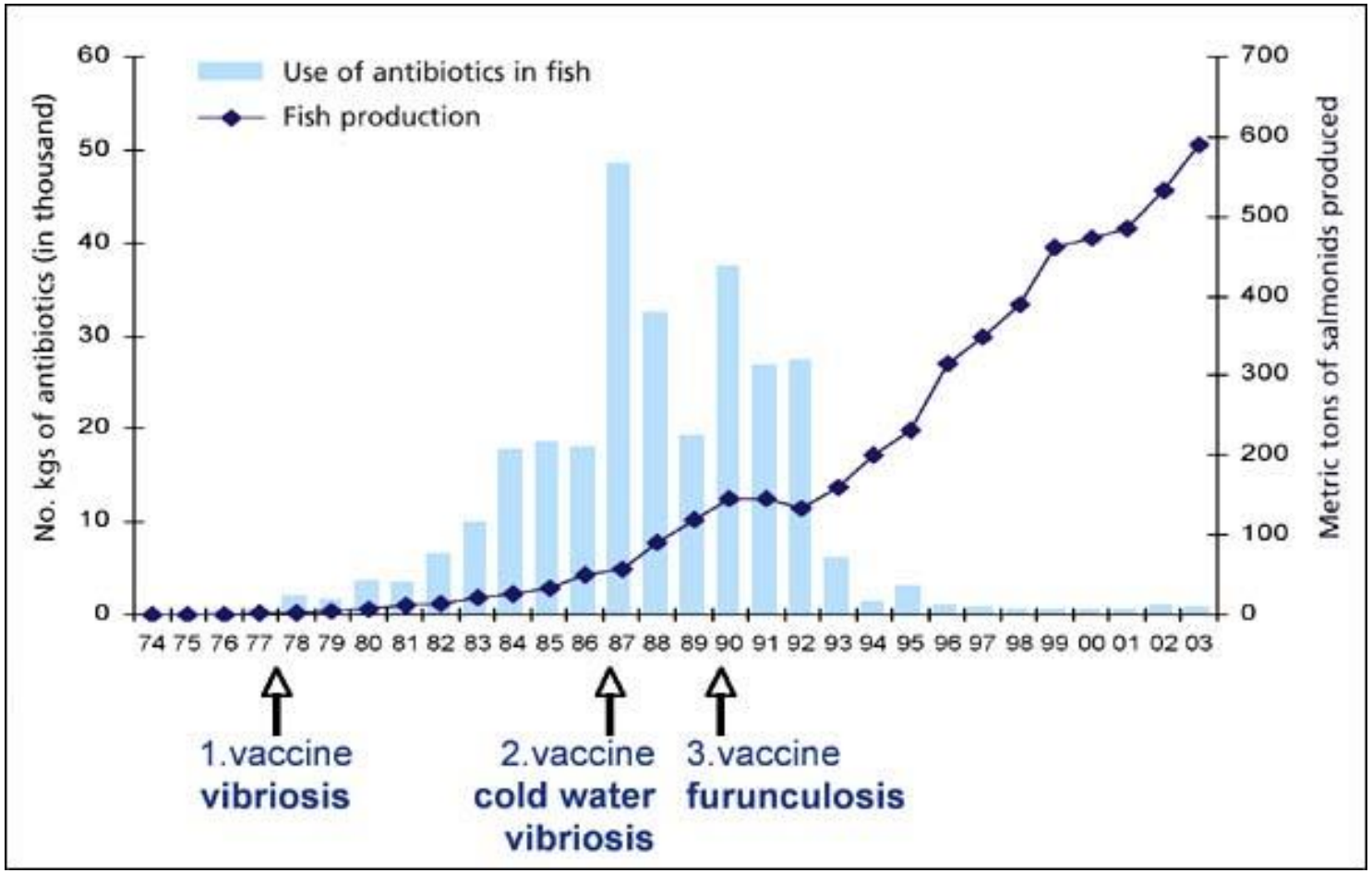
[a] The ranking is provided for each measure and presented in bold for the top 5.

M. Postma et al. / Preventive Veterinary Medicine 118 (2015) 457–466



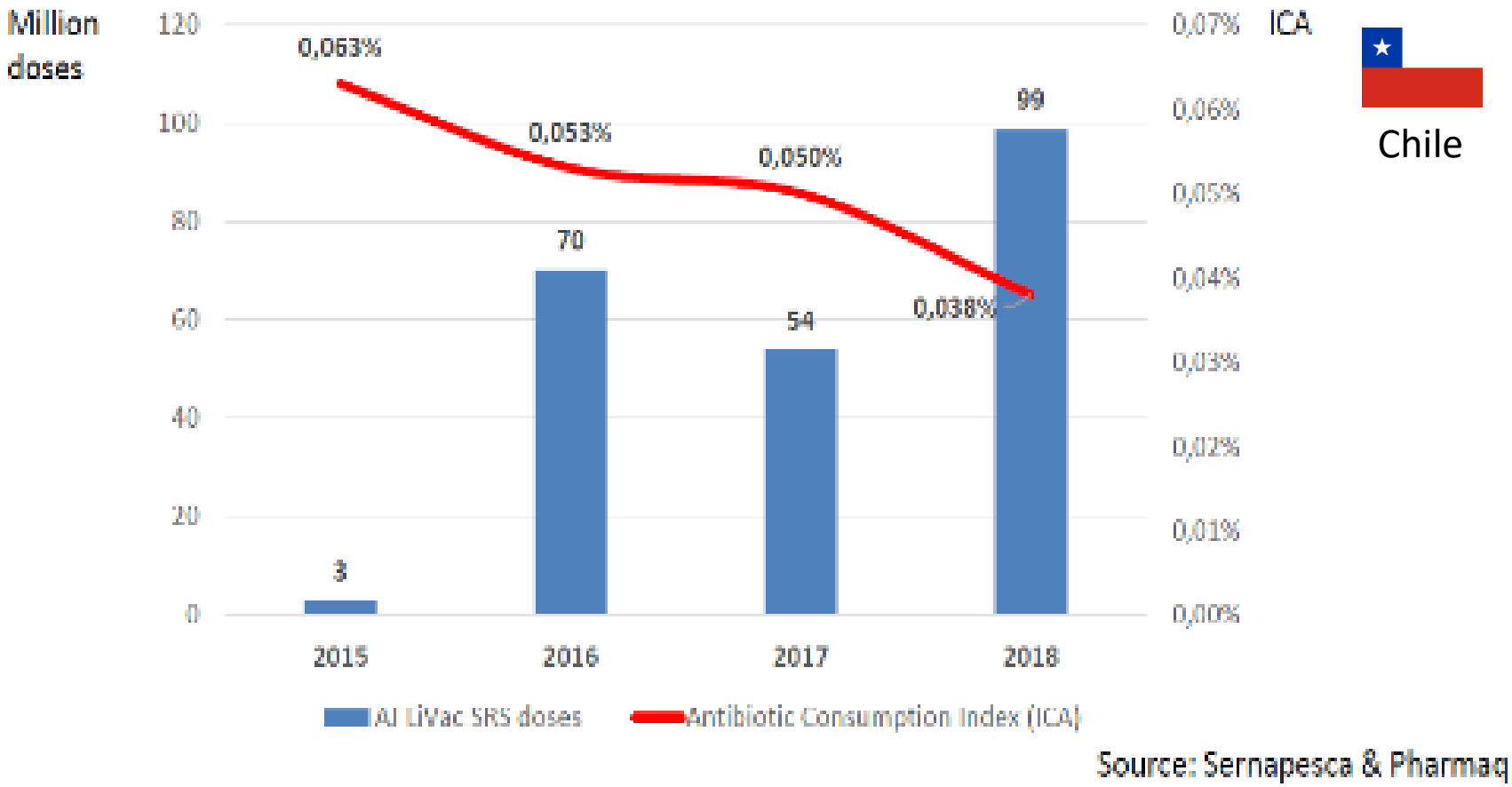
M. Postma et al. / Preventive Veterinary Medicine 118 (2015) 457–466

ATA: vaccination succes: marine aquaculture



Norway

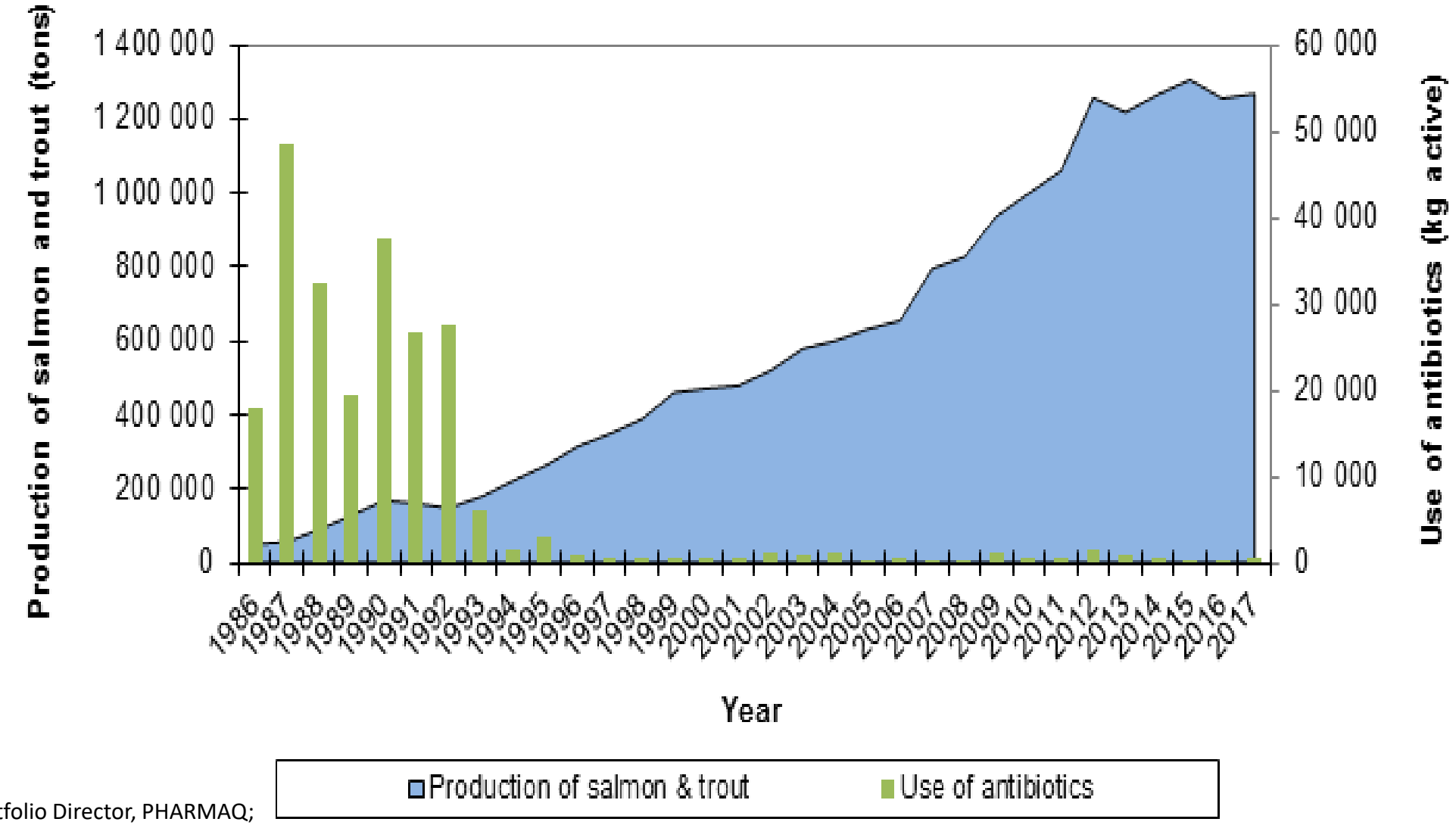
http://www.fao.org/3/A0192E09.htm



Salmon Rickettsial Septicemia(SRS)

https://www.oie.int/aquatic-conference2019/wp-content/uploads/2019/04/3.Ben_North_OIE_Santiago_short_final.pdf

1987: 50t antibiotics/50kt salmon (1g/kg); 2017: 300kg antibiotics/1,3mill t salmon(0,0002g/kg).



Ben North: R&D Portfolio Director, PHARMAQ;
https://www.oie.int/aquatic-conference2019/wp-content/uploads/2019/04/3.Ben_North_OIE_Santiago_short_final.pdf

Veterinary Record (2016) doi: 10.1136/vr.103406

Influence of porcine circovirus type 2 vaccination on the level of antimicrobial consumption on 65 Austrian pig farms

J. Raith, M. Trauffler, C. L. Firth, K. Lebl, C. Schleicher, J. Köfe

"The estimated impact of PCV-2 vaccination revealed a **highly significant (P<0.001) decline** in total antimicrobial drug use from 1.72 ADDkg/kg/year to 0.56 ADDkg/kg/year on finishing farms"

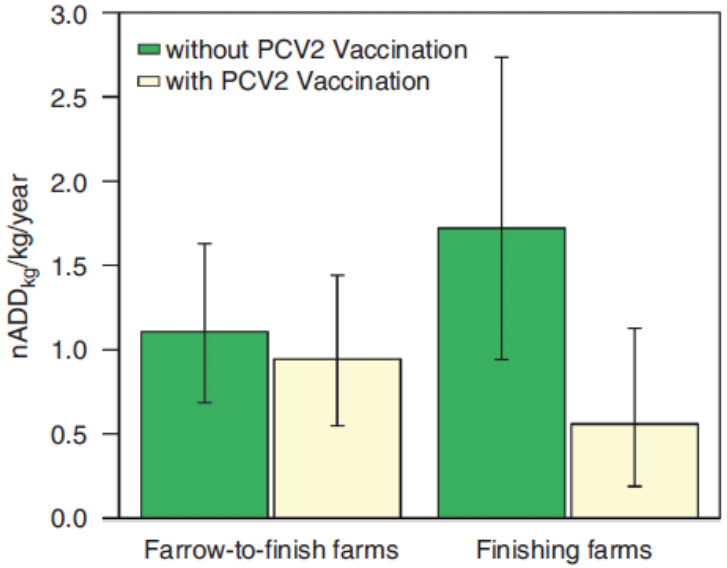


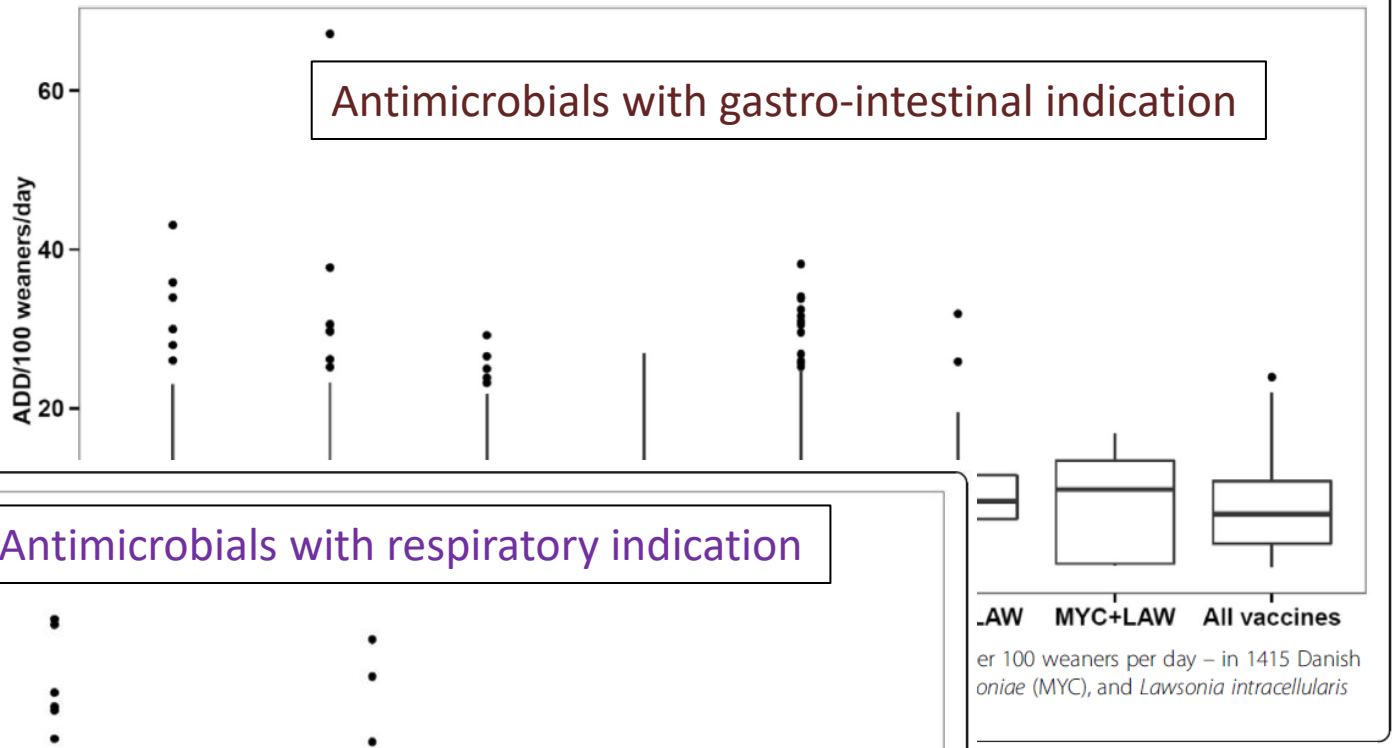
FIG 3: Expected antimicrobial consumption at farm level (expressed in $nADD_{kg}$/kg/year with 95 per cent CIs) in dependence of the interaction between the respective farm type and porcine circovirus type 2 (PCV-2) vaccination according to the linear mixed effects model. Treatment frequency: nADD, number of animal daily doses

frontiers in Veterinary Science

No Clear Effect of Initia Vaccination against Co Endemic Infections on of Prescribed Antimicr Danish Weaner and Fin during 2007–2013

Amanda Brinch Kruse[1], Leonardo Victor de Knegt[1], Liz Lis Alban[2]*

Antimicrobials with gastro-intestinal indication



er 100 weaners per day – in 1415 Danish
oniae (MYC), and *Lawsonia intracellularis*

Antimicrobials with respiratory indication

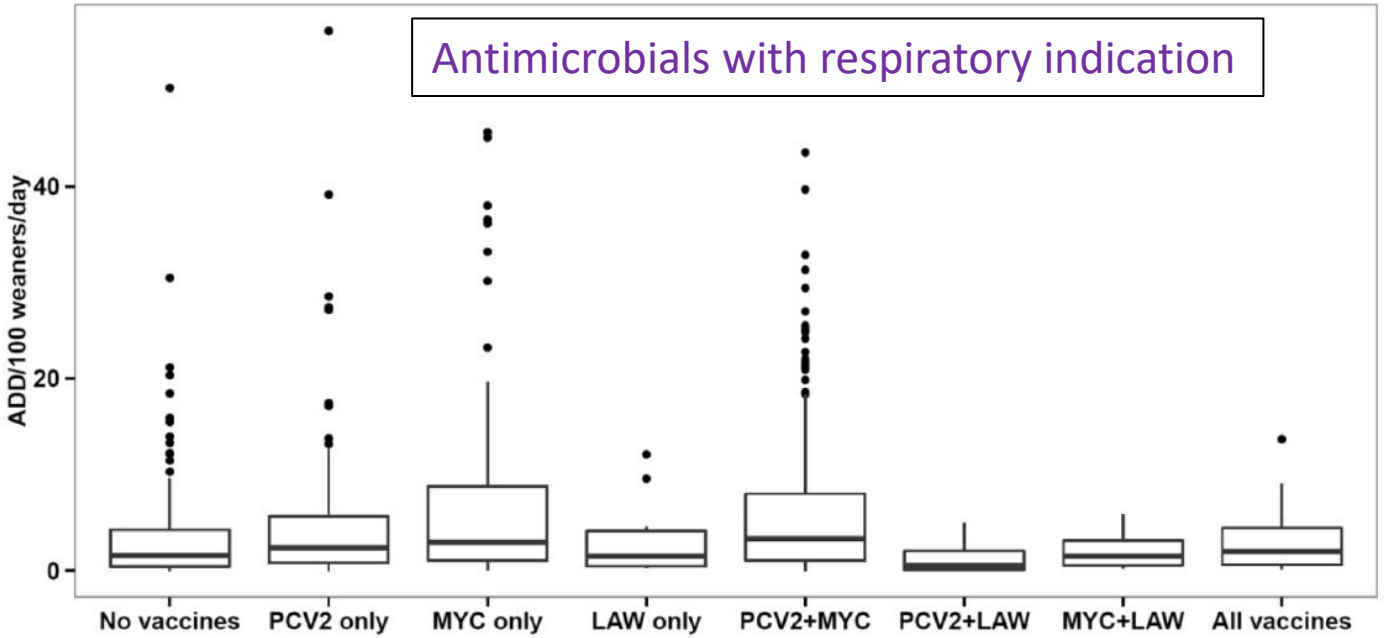


Fig. 3 Use of antimicrobials with respiratory indication – measured as Animal Daily Doses (ADD) per 100 weaners per day – in 836 Danish sow herds, divided according to the combined use of vaccination against PCV2, *Mycoplasma hyopneumoniae* (MYC), and *Lawsonia intracellularis* (LAW), 2013

The hard ones….

- Hard to target complex infections (multiple pathogens, including virus/bacteria combinations)
- Hard to target management/infection combinations
- Hard to target infections: unknown/many pathogen variants/ and/or unknown mechanisms
- Chronic disease states increasing susceptibility to infection/decreasing vaccine response
- Mucosal infections
- Neonatal/young animal vaccination: reduced vaccination responses

Challenges for the use of veterinary vaccines in animal production

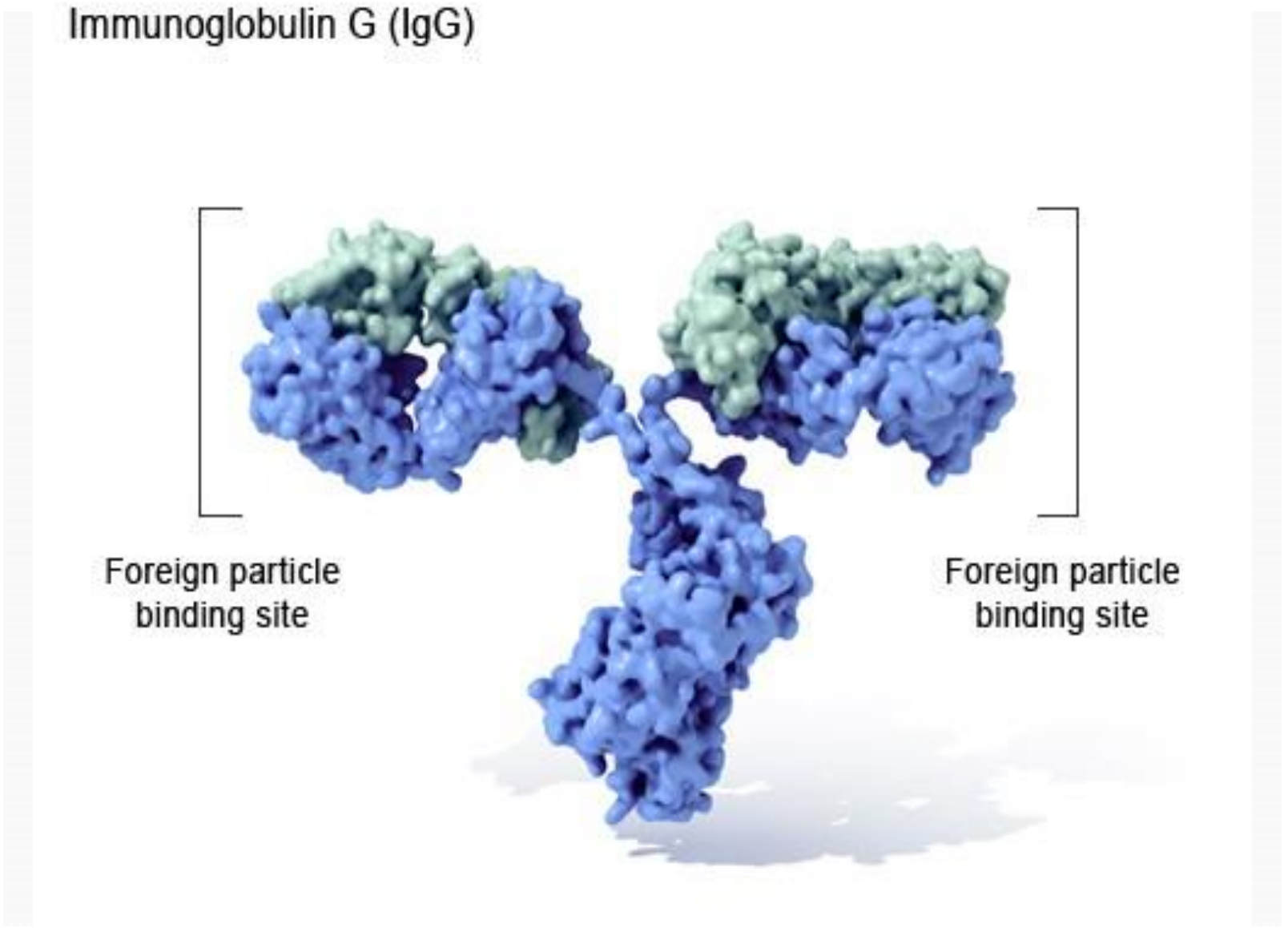
- Inexpensive (sustainable cost/benefit balance)
- Ease of use/large populations
- Safe (pathogen transmission/reversion)
- Shelf life/non-demanding storage
- No interference with serological monitoring of infection status
- Minimal off-target negative effects
- Measurable positive effect on production parameters
- Consumer concerns

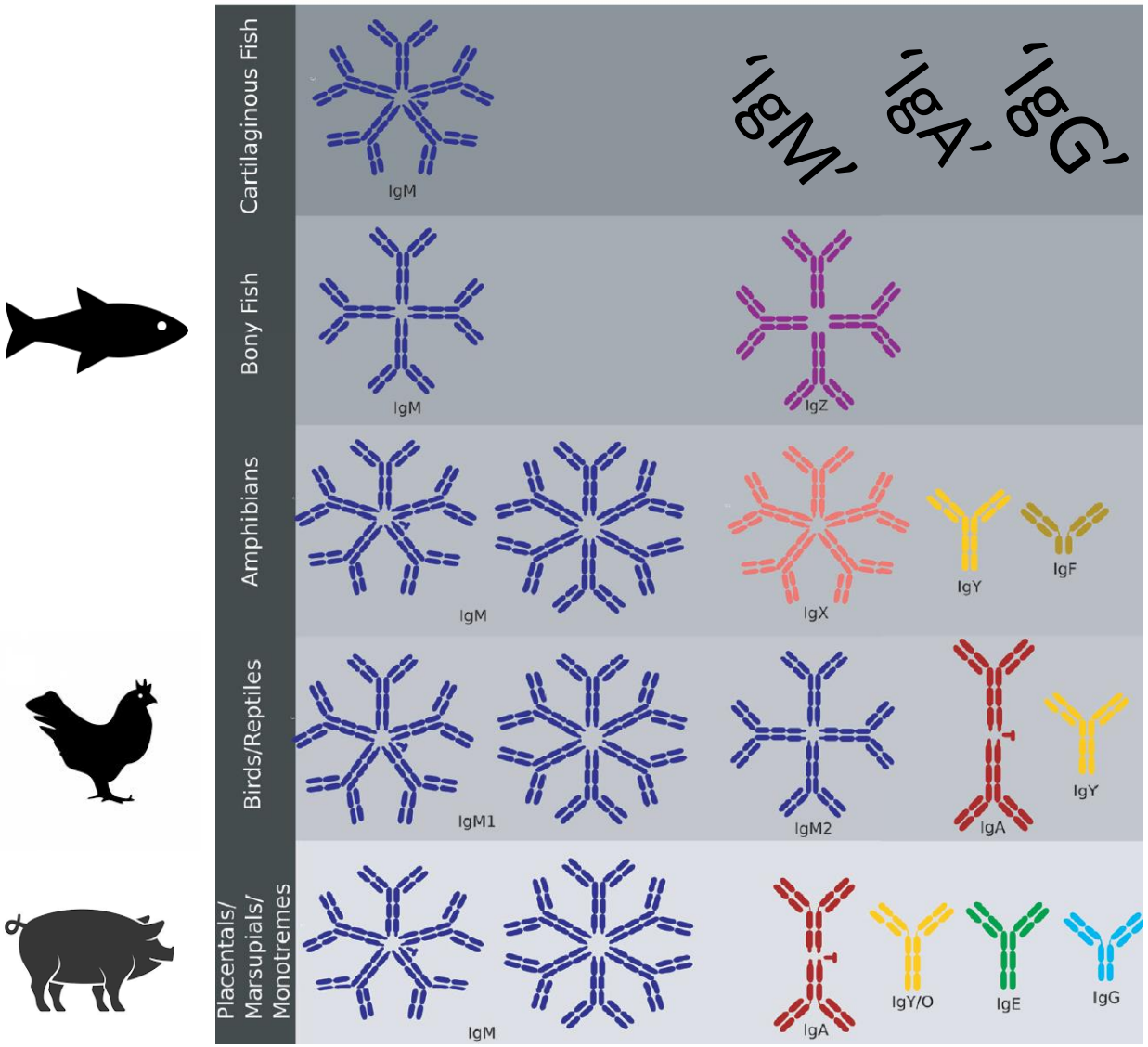
NEW IMMUNE BASED STRATEGIES SHOULD:

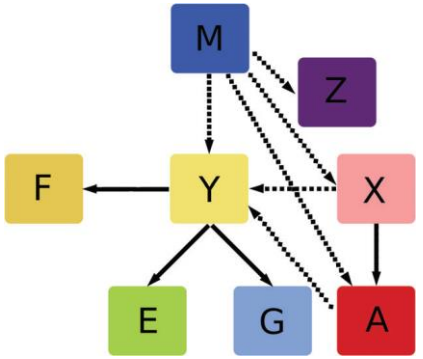
- Inexpensive (sustainable cost/benefit balance)
- Ease of use/large populations
- Safe (pathogen transmission/reversion)
- Shelf life/non-demanding storage
- No interference with serological monitoring of infection status
- Minimal off-target negative effects
- Measurable positive effect on production parameters
- Consumer concerns

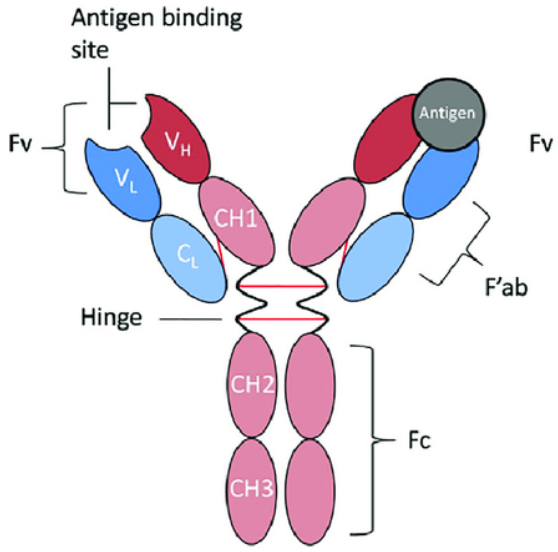
Non-antibiotic non-vaccine immunization approaches

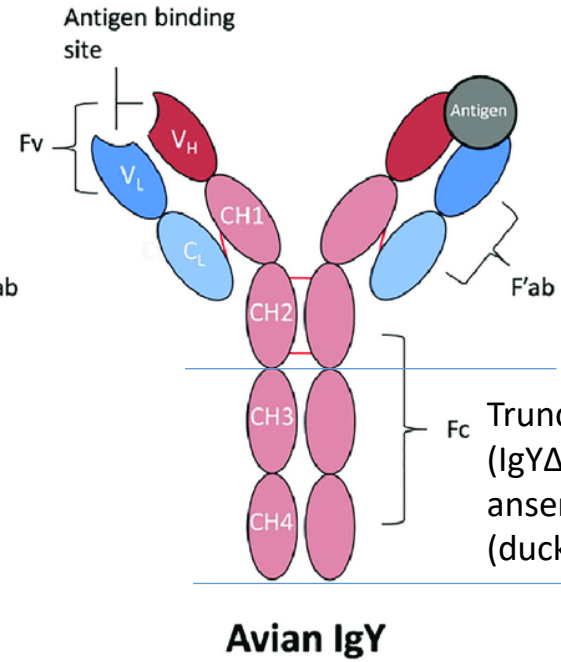
PASSIVE IMMUNIZATION: IMMUNOGLOBULIN EFFECTORS











Truncated IgY (IgYΔFc): anseriform birds (duck, goose)

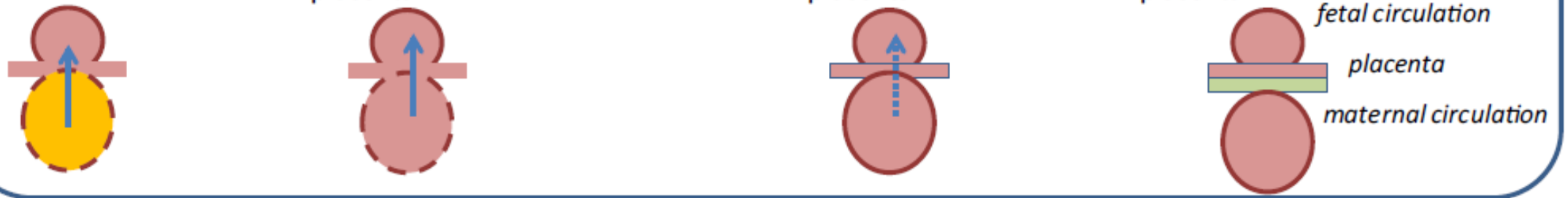
Zhang, X., *et al., Biol. Rev.* (2017), **92**, pp. 2144–2156. doi: 10.1111/brv.12325

https://www.researchgate.net/figure/The-canonical-strutures-of-IgG-and-IgY

Passive immunization in Nature:
Transfer of maternal immunity perinatally

Fetal stage – mother to embryo immunoglobulin transport

FISH & BIRDS	PRIMATES & RODENTS	DOG, CAT, MINK	RUMINANTS, PIGS, HORSES
Active transport /yolk sac	Active transport Hemochorial placenta	Limited transport Endotheliochorial placenta	No transport Epitheliochorial placenta

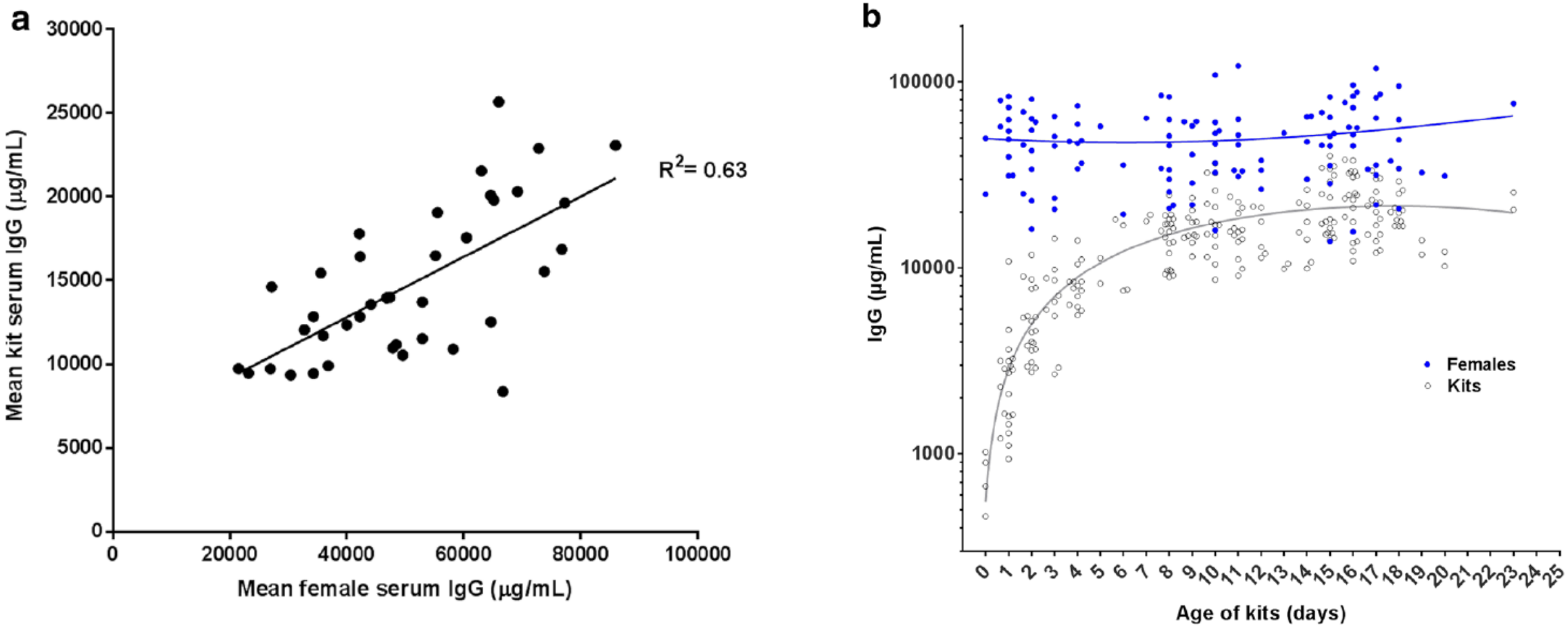


Neonatal stage – circulating immunoglobulins

IgM (fish) **IgY** (birds)	**IgG**	**IgG** (low levels)	No circulating Ig's
Gut uptake: (open gut)			
No	**No**	**Yes** (< 36 h after birth)	**Yes** (< 24 h after birth)

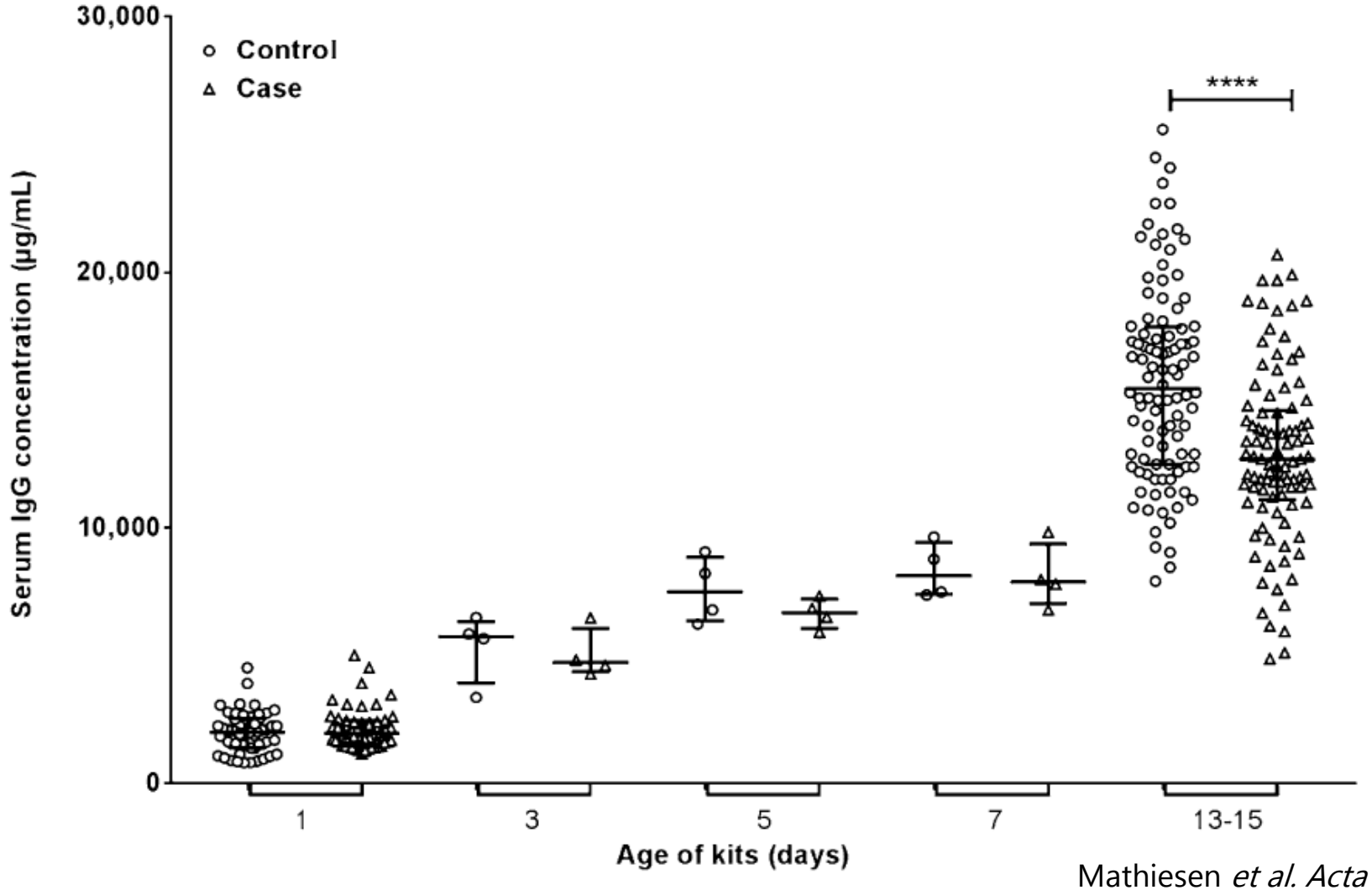
van Dijk *et al. Vet Res (2018) 49:68*

IgG uptake after birth: Mink example



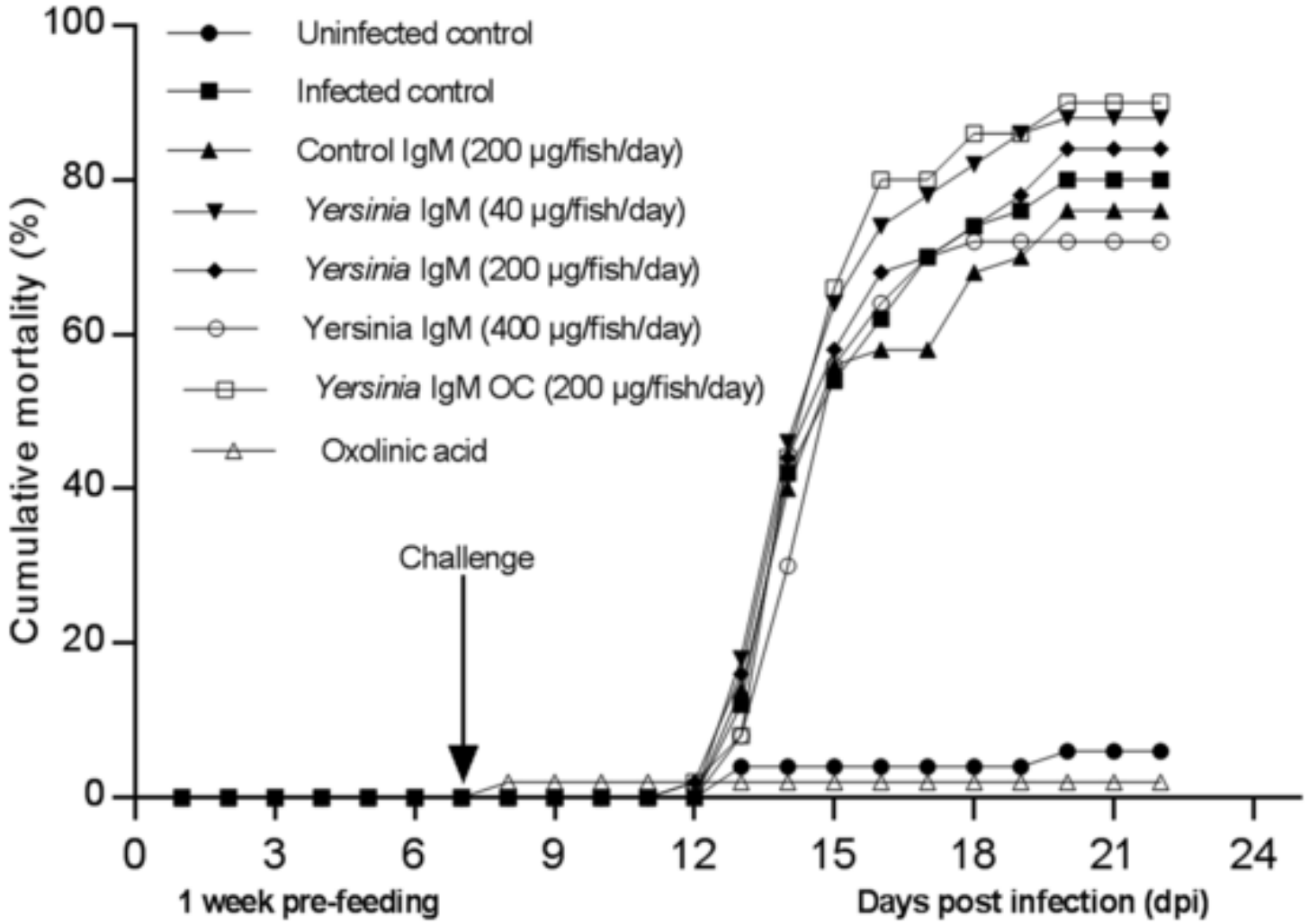
Mathiesen *et al. Acta Vet Scand (2018) 60:36;* https://doi.org/10.1186/s13028-018-0391-7

Mink pre-weaning diarrhea: association with decreased IgG concentration at day 13-15 of age

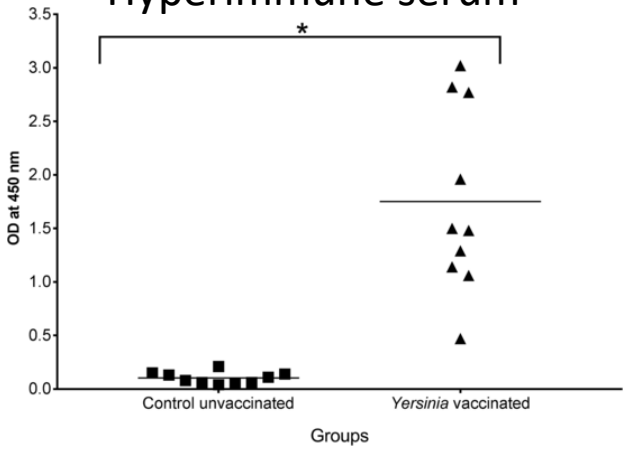


Mathiesen *et al. Acta Vet Scand (2019) 61:26.*

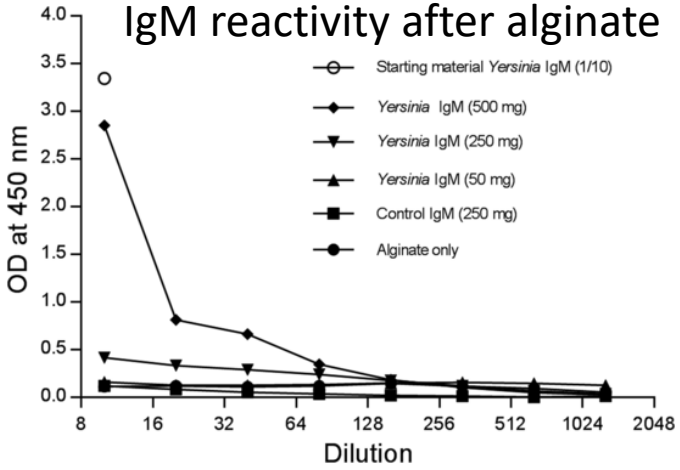
Rainbow trout IgM immunization



Hyperimmune serum



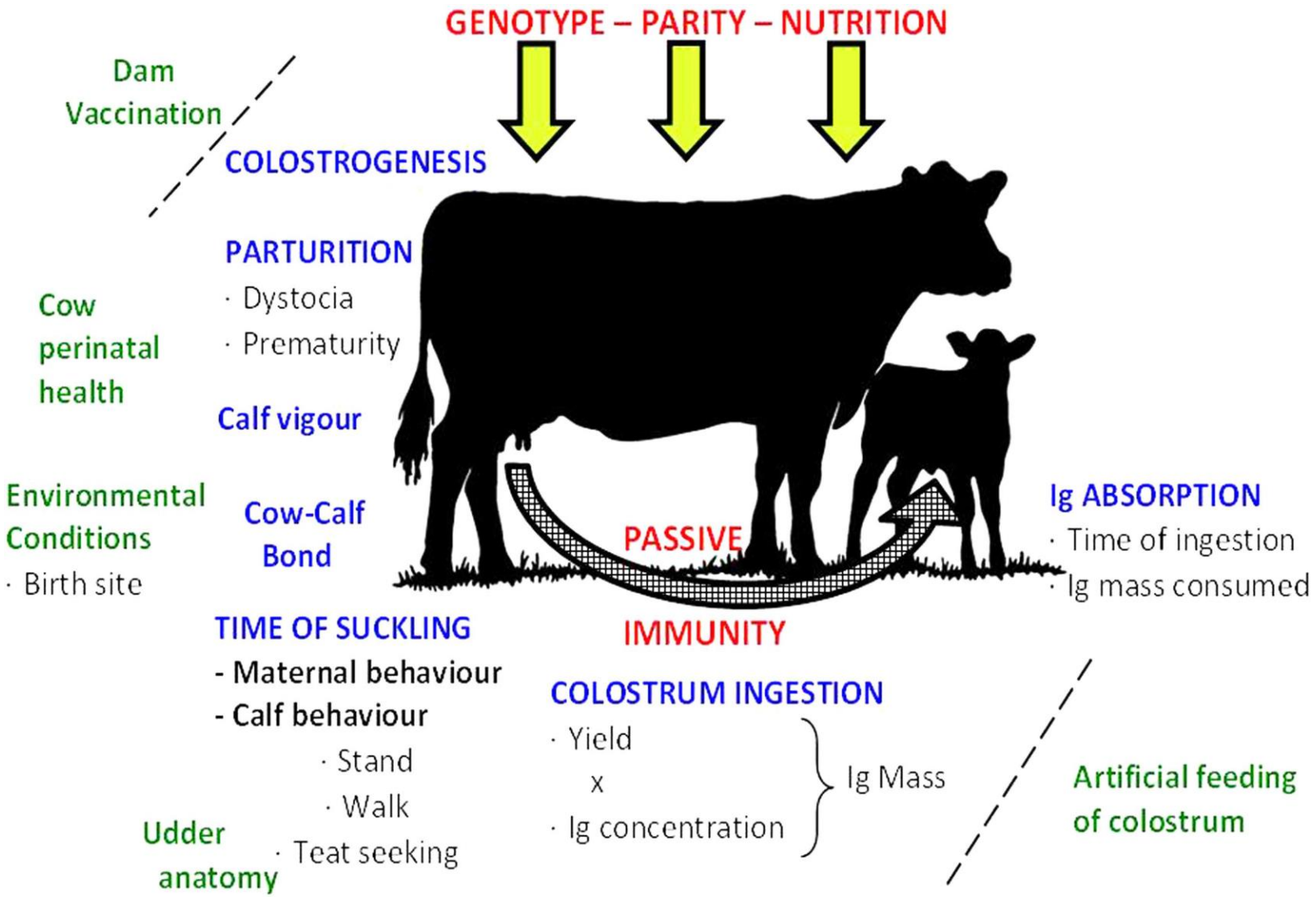
IgM reactivity after alginate



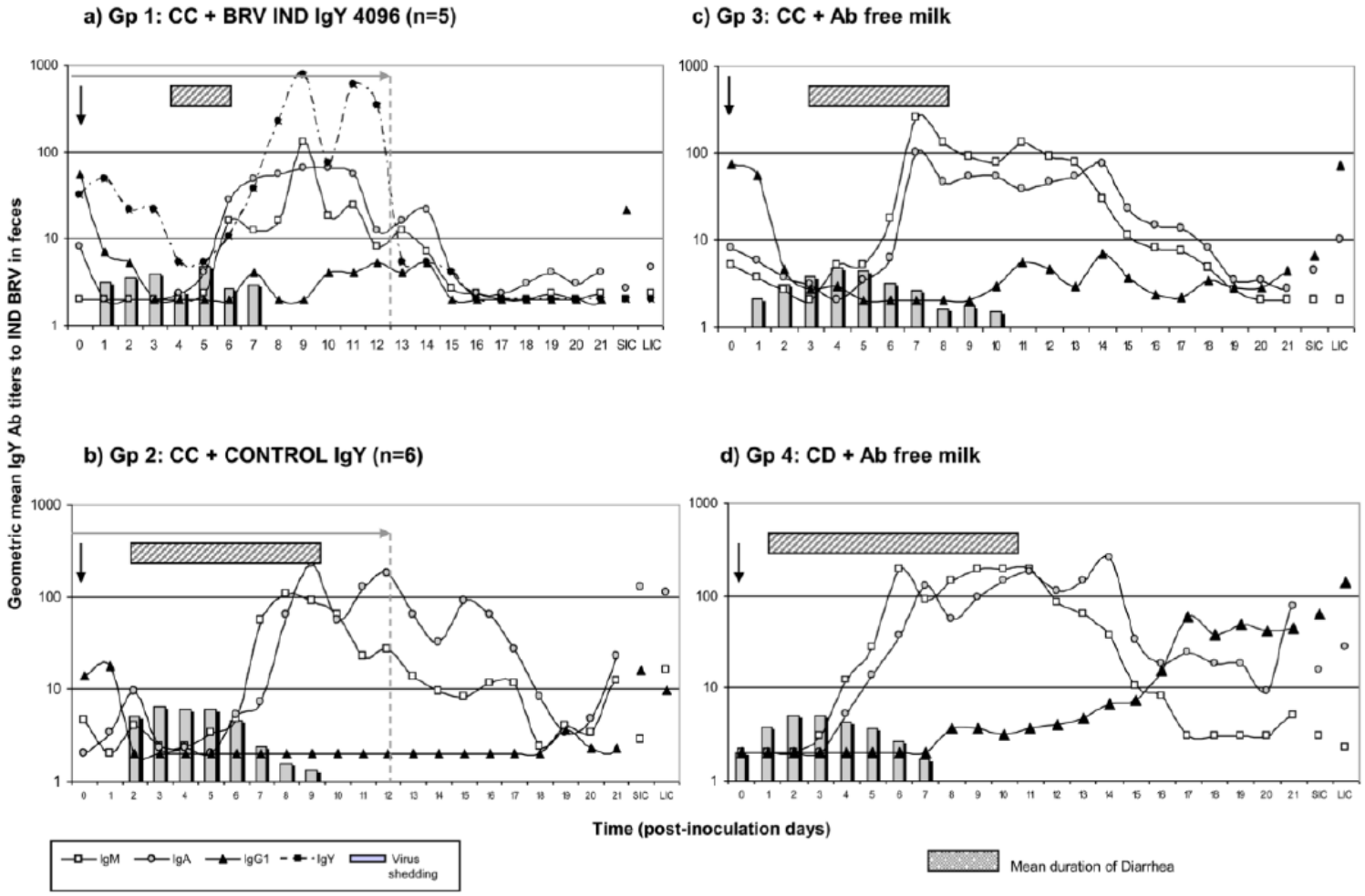
Chettri, JK., et al., 2019, Fish and Shellfish Immunology

Key factors affecting passive immunity in beef-suckler calves

McGee & Early, 2019, Animal (2019), 13:4, pp 810–825



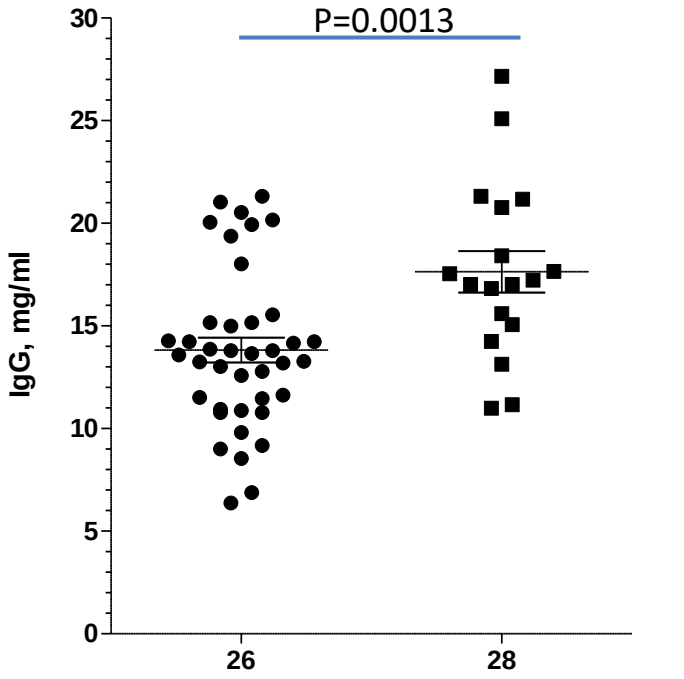
Bovine rotavirus, exp. infection: effect of IgY (hyperimmune egg yolk supplementation)

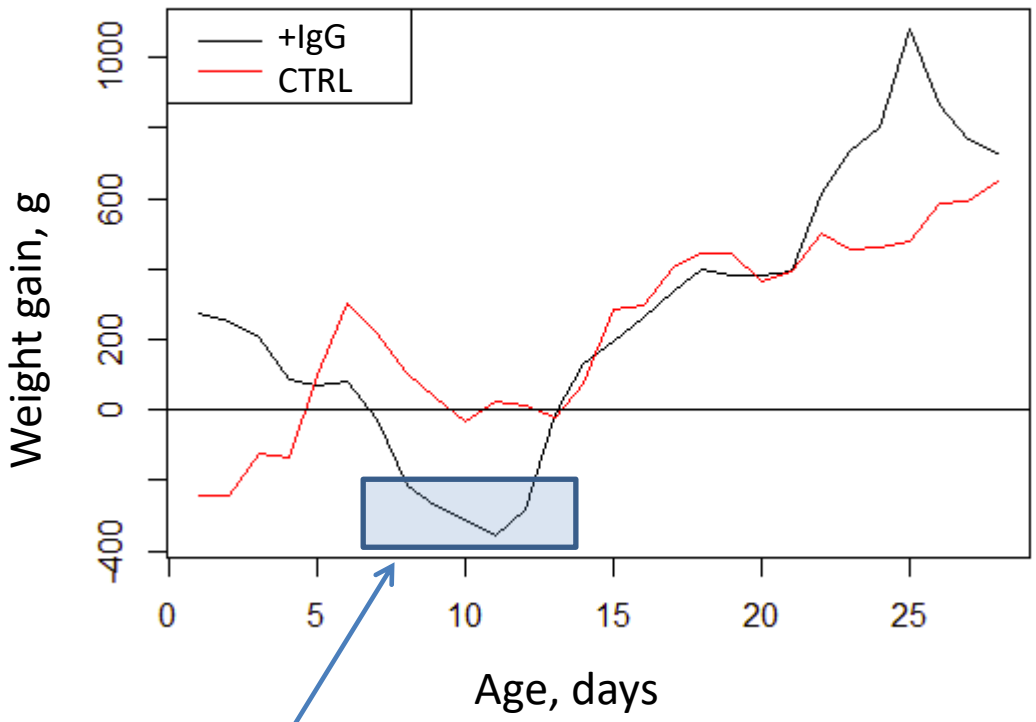


Vega et al., Vet Immunol Immunopathol. 2011 August 15; 142(3-4): 156–169

Bovine IgG supplementation: natural IgG from whey

Final IgG concentrations

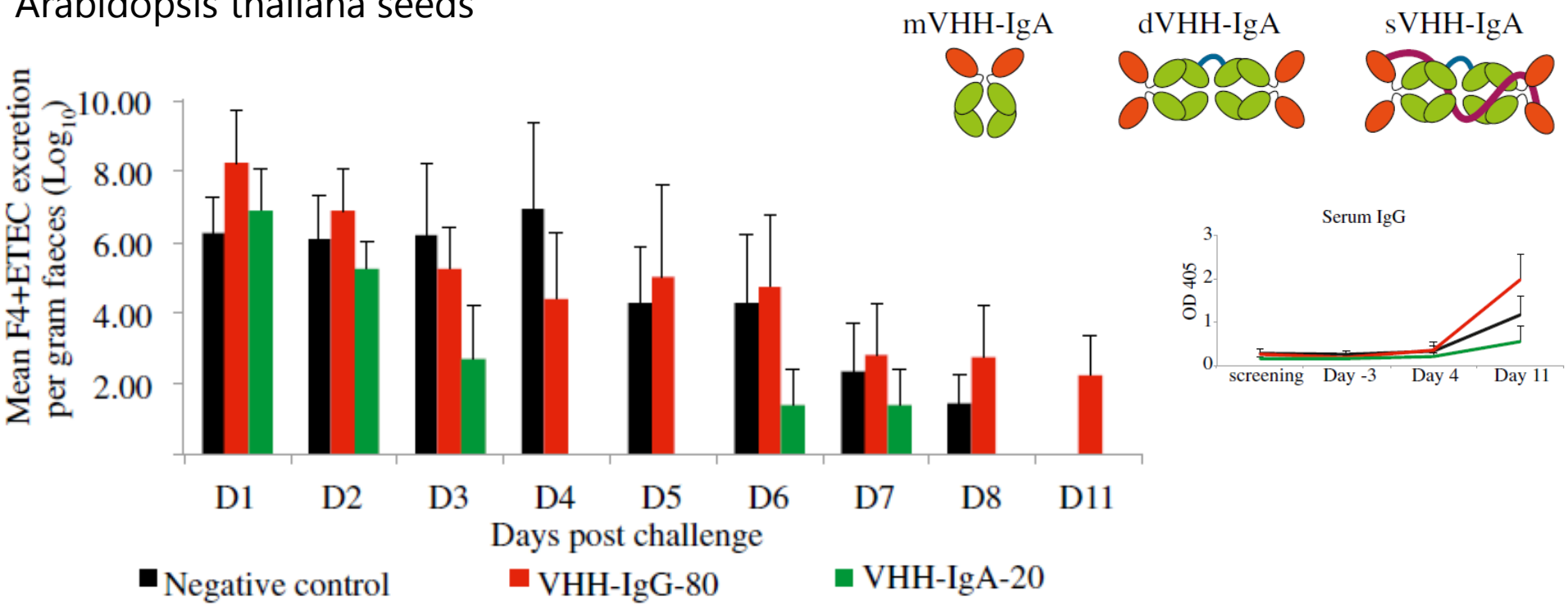




Pneumonia in IgG group!

Plant produced immunoglobulin A and G for prevention of experimental E.coli infection in piglets (F4 specific)

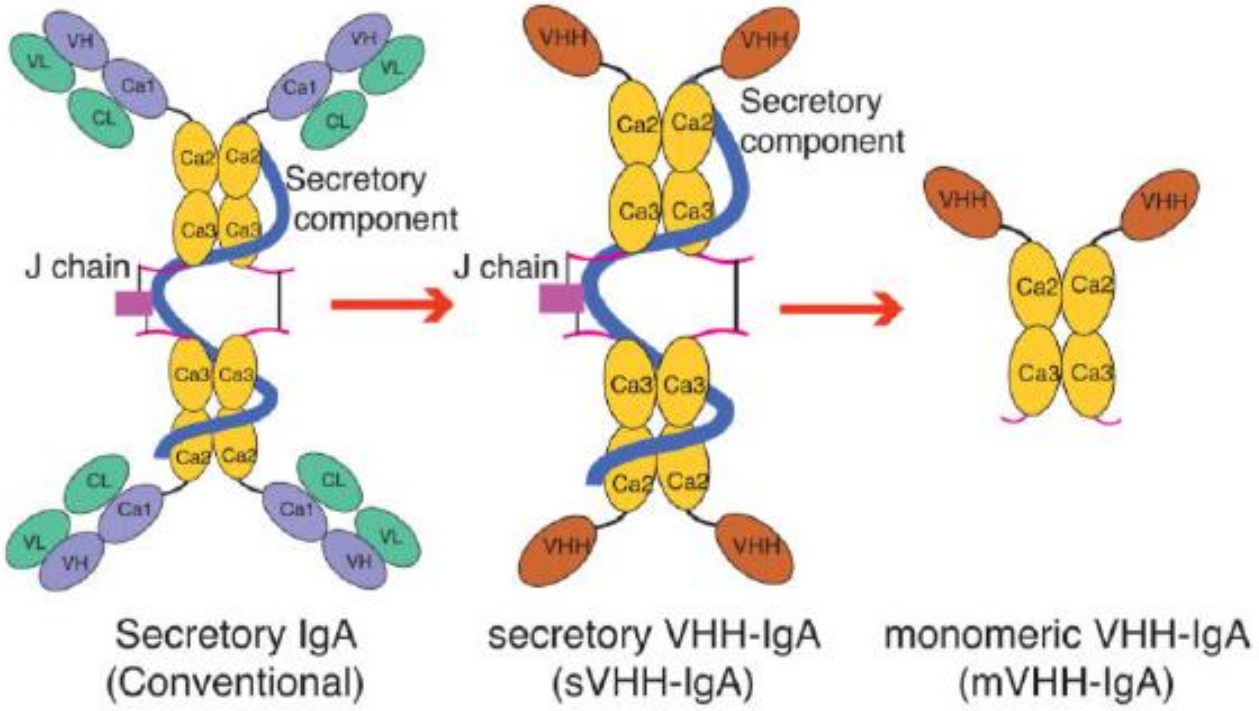
Arabidopsis thaliana seeds



Virdi et al., 2013, www.pnas.org/cgi/doi/10.1073/pnas.1301975110

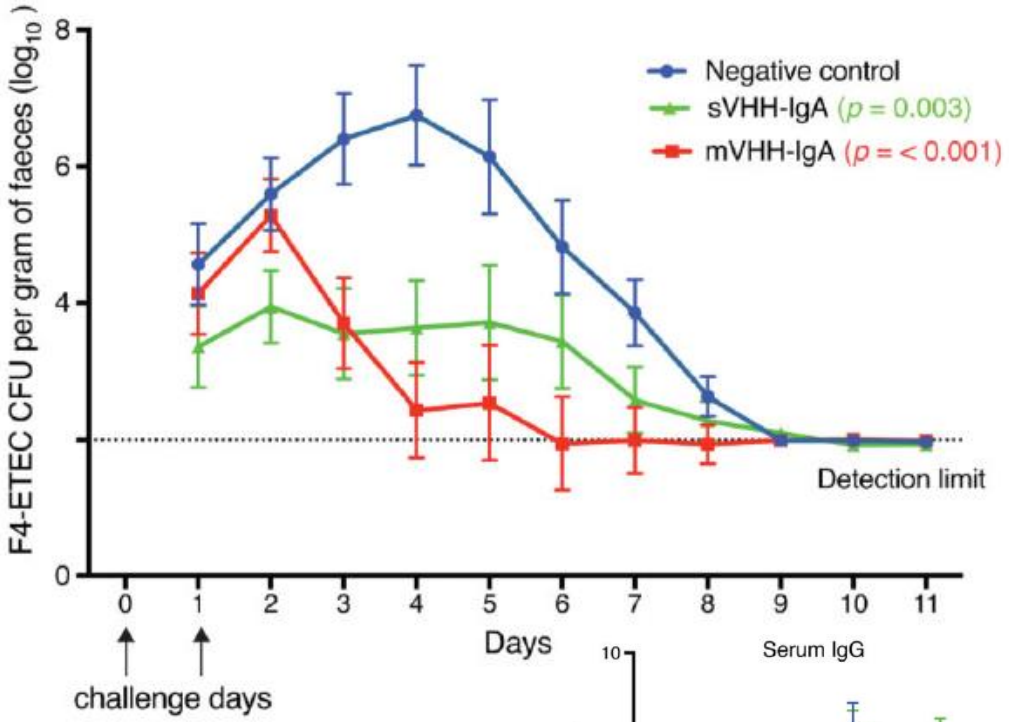
IgG: FcNR interaction?Less stable than IgA?

Plant and yeast produced monomeric IgA for prevention of experimental E.coli infection in piglets (F4 specific)

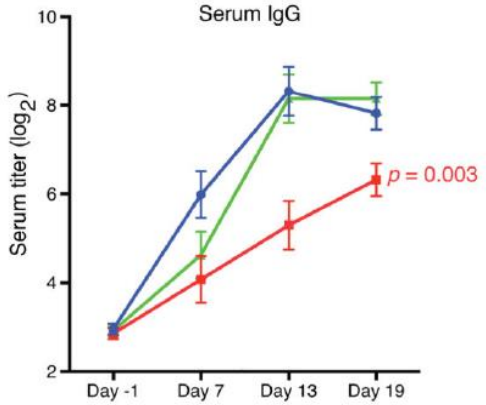


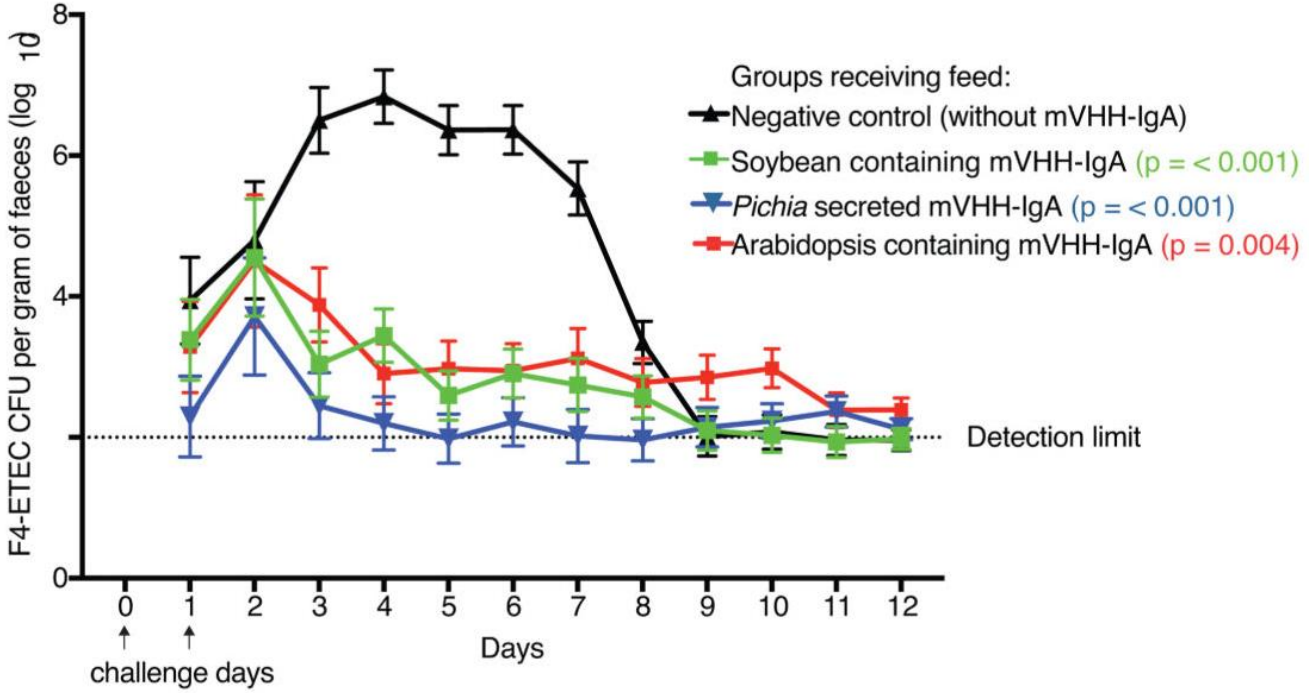
Virdi, V., et al., Nat Biotechnol. 2019 May ; 37(5): 527–530.

Plant and yeast produced monomeric IgA for prevention of experimental E.coli infection in piglets (F4 specific)

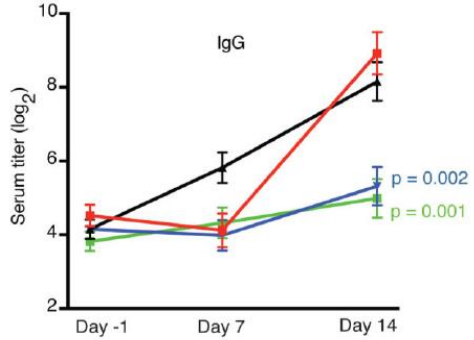


Arabidopsis
sVHH-IgA
mVHH-IgA



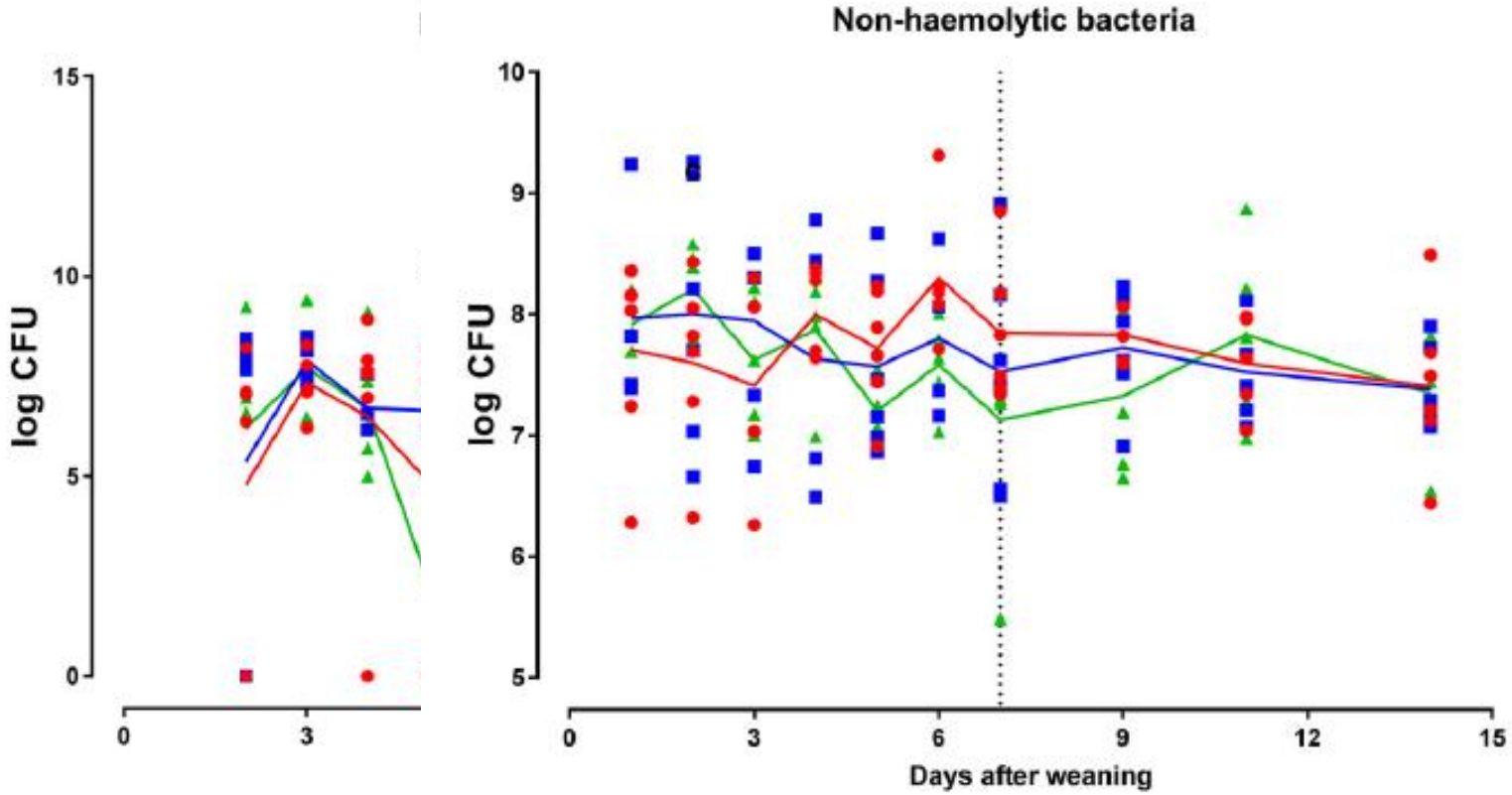


Pichia pastoris
Soybean
Arabidopsis
mVHH-IgA



Virdi, V., et al., 2019

Zinc and ppIgG compared, *E.coli* O149:F4 challenge model. Faecal bacterial counts



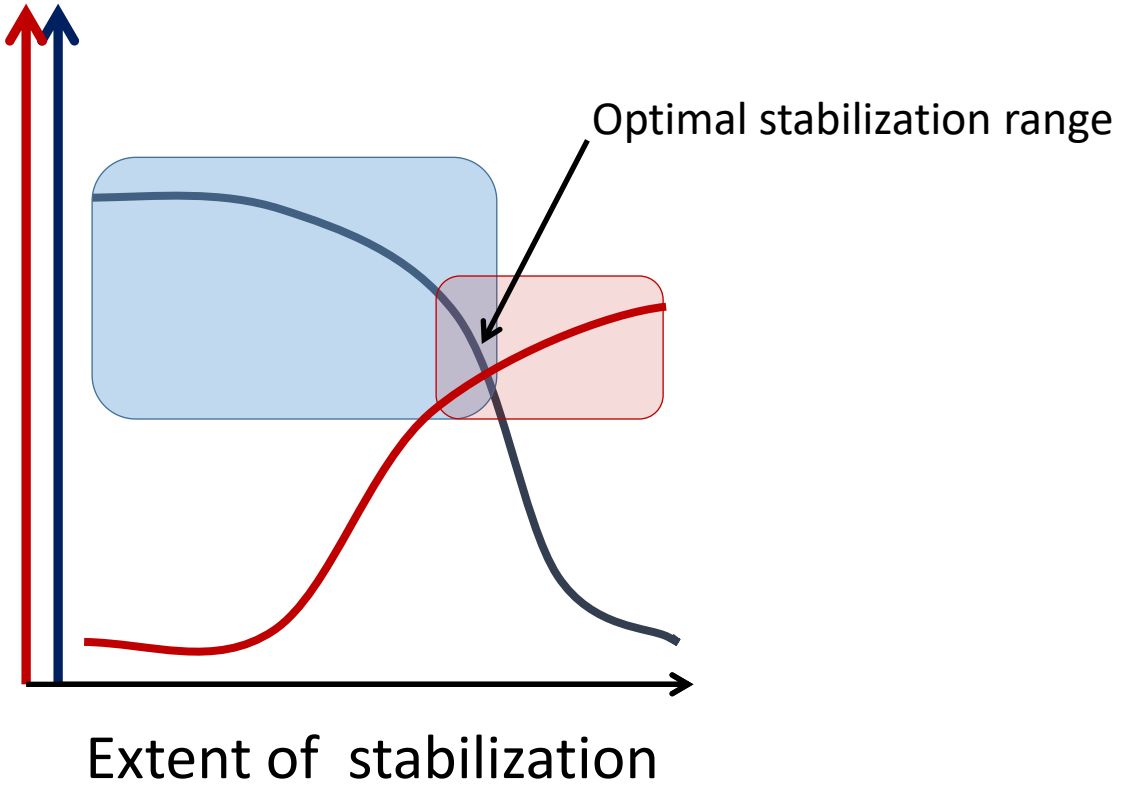
Hedegaard et al. 2017

Unstabilized

Heavy chain

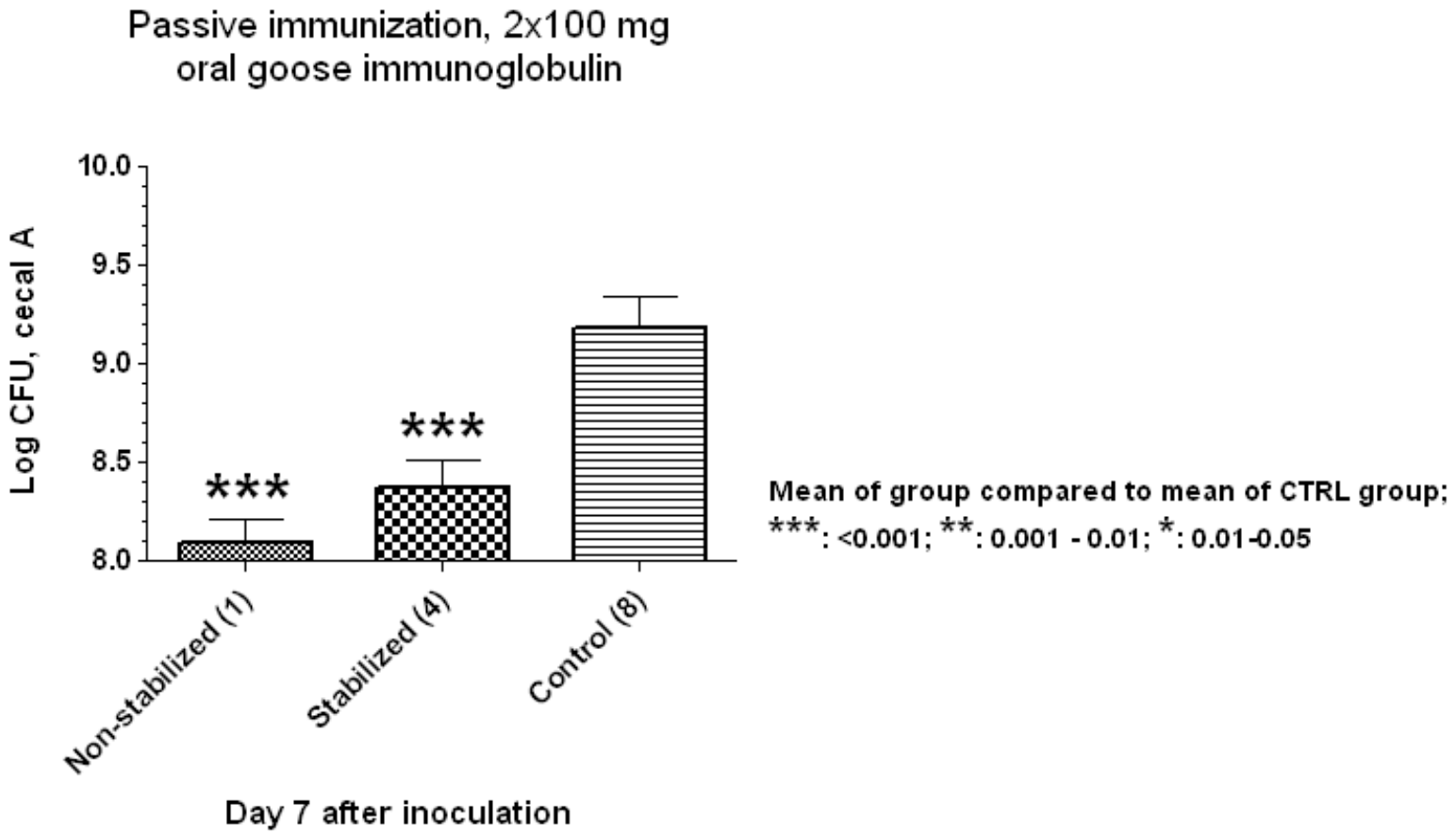
Light chain

Pepsin	-	+
Activity	+++	+



Chettri and Heegaard, unpublished

Cecal CFU *C. jejuni* (inoculation strain)



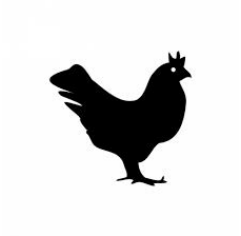


Table 2. Effect of hyperimmune egg-yolk IgY on bacterial infections of poultry

Pathogen	Donor hens immunized with	Experiment: Prevention/ therapeutic	Experiment: *In vitro*/ *in vivo*	Mode of IgY treatment	Outcome	Reference
E. coli	Live or killed *E. coli*, lipopolysaccharide (LPS), FimH, PapG, IutA	Prevention	*In vivo*	IgY 100 mg I/M	Protection from homologous challenge	Kariyawasam *et al.* (2004)
E. coli	*E. coli* and Freund's complete adjuvant (FCA)	Prevention	*In vivo*	IgY 3 ml orally	Reduced symptoms, lesions	Tamilzarasan *et al.* (2009)
E. coli O78:K80	*E. coli* O78:K80	–	*In vitro*	IgY powder 50–150 mg ml^{-1}	Reduced growth	Mahdavi *et al.* (2010a)
E. coli O78:K80	*E. coli* O78:K80	Prevention	*In vivo*	Lyophilized IgY powder in diet (0.1–0.4%)	↓ileal *E. coli* counts ↓H:L ratio	Mahdavi *et al.* (2010b)
E. coli, S. enterica	*E. coli, S. enterica* whole cell antigen (Ag)	–	*In vitro*	IgY solution	Reduced growth rate	Diraviyam *et al.* (2011a)
C. jejuni	*C. jejuni* and *Campylobacter coli*	Prevention and therapeutic	*In vivo*	IgY preparation oral	↓fecal bacterial counts	Tsubokura *et al.* (1997)
C. jejuni	*C. jejuni* and FCA	Prevention	*In vivo*	IgY 3 ml orally	↓morbidity, mortality	Tamilzarasan *et al.* (2009)
C. jejuni	*C. jejuni* colonization-associated proteins	–	*In vitro*	Lyophilized egg yolk powder	↓adherence to cells	Al-Adwani *et al.* (2013)
C. jejuni	*C. jejuni* whole cell lysate or hydrophobic fraction	Prevention and therapeutic	*In vivo*	Egg yolk 5% (W/W) in feed	↓cecal *C. jejuni* counts ↑binding to mucus	Hermans *et al.* (2014)
C. perfringens	*C. perfringens* bacterin	Prevention	*In vivo*	IgY solution sprayed onto feed (0.05%, 0.065% V/W)	No effect on colonization	Wilkie *et al.* (2006)
C. perfringens	*C. perfringens* and FCA	Prevention	*In vivo*	IgY 3 ml orally	↓morbidity, mortality	Tamilzarasan *et al.* (2009)
S. pullorum	*S. pullorum killed antigen* with FCA	–	*In vitro*	Reconstituted freeze-dried IgY powder	Generated antibodies specific to *S. pullorum* Ag	Diraviyam *et al.* (2011b)
S. pullorum	*S. pullorum* with FCA	Prevention	*In vivo*	IgY 3 ml orally	↓morbidity, mortality	Tamilzarasan *et al.* (2009)
S. enteritidis or S. typhimurium	Formalin-inactivated *S. enteritidis* or *S. typhimurium* with *FCA*	–	*In vitro*	Reconstituted freeze-dried IgY powder	↓growth	Lee *et al.* (2002a)
S. enteritidis	Formalin-inactived whole-cell Ag of *S. enteritidis*	Prevention	*In vivo*	Whole egg powder in feed (3 g day^{-1} $bird^{-1}$)	↓rate of contamination of eggs	Gürtler *et al.* (2004)
S. enteritidis	*S. enteritidis* whole-cell Ag with FCA	Prevention	*In vivo*	15 ml of antibody in drinking water	↓reduced fecal shedding ↓cecal colonization ↓isolation from liver, spleen, ileum	Rahimi *et al.* (2007a)
S. enteritidis and *S. typhimurium*	Outer membrane proteins (OMP) of *S. enteritidis* and *S. typhimurium* with FCA	–	*In vitro*	Reconstituted freeze-dried IgY powder	Inhibitory effect on bacterial growth	Chalghoumi *et al.* (2009b)
S. enteritidis, S. typhimurium, S. heidelberg	Killed *S. enteritidis, S. typhimurium, S. heidelberg*	Prevention	*In vivo*	Spray vaccination and in water	↓cecal colonization ↓organ invasion	Tellez *et al.* (2001)
S. enteritidis and *S. typhimurium*	OMP of *S. enteritidis* and *S. typhimurium* with FCA	Prevention	*In vivo*	Egg yolk powder in feed (5%)	No effect on cecal colonization	Chalghoumi *et al.* (2009c)

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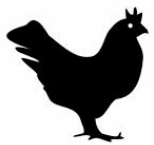

Table 3. Effect of hyperimmune egg-yolk IgY on viral infections of poultry

Pathogen	Hens immunized with	Experiment: Prevention/ therapeutic	Experiment: *In vitro/ in vivo*	Mode of IgY treatment	Outcome	Reference
IBDV	Oil-based IBDV vaccine	Therapeutic	*In vivo*	Diluted yolk with antibodies	Birds recovered	Muhammad *et al.* (2001)
IBDV	Inactivated oil-based vaccine	Therapeutic	*In vivo*	Hyperimmune yolk solution in drinking water 1 l day^{-1}	↓mortality Shift in morbidity to a milder syndrome	Yousif *et al.* (2006)
IBDV	Oil-based vaccine	Therapeutic	*In vivo*	IgY solution injected I/P	↑recovery rate	Malik *et al.* (2006)
IBDV	Live intermediate strain IBDV vaccine and Inactivated IBDV vaccine	Prevention	*In vivo*	IgY solution orally 0.5 ml $bird^{-1}$	↓morbidity, mortality, lesions	Abd El-Ghany (2011)
NDV		Prevention and therapeutic	*In vivo*	Egg yolk I/M	Prevented ND and protected from challenge	Phillips (1956)
NDV	Commercial wing-web NDV vaccine	Prevention	*In vivo*	Egg yolk S/C	Protected 80% of birds	Wills and Luginbuhl (1963)
NDV	Natural infection	Prevention	*In vivo*	Egg yolk I/M 1 mL	Conferred passive immunity	Box *et al.* (1969)

IBDV, infectious bursal disease virus; NDV, Newcastle disease virus.

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Conclusions

- LOTS OF EXAMPLES – HOW TO ENABLE USE?

- CHALLENGES REMAINING/oral immunoglobulins:
- Formulation issues for ease of administration and optimal gut stability
- Sourcing: Sustainable ‘natural’ sources (slaughter blood, whey, etc.) and securing absence of unwanted agents
- Dosing (stabilized/non-stabilized)?
- Non-enteric infections?

Thank you for your attention