IABS: Avoiding Antimicrobial Resistance: Veterinary Use of Phages for Prevention, Therapy and Control of Bacterial Infections
19th November 2024

Phage therapy in pigs:

Observations on the control of zoonotic pathogens in pork production.

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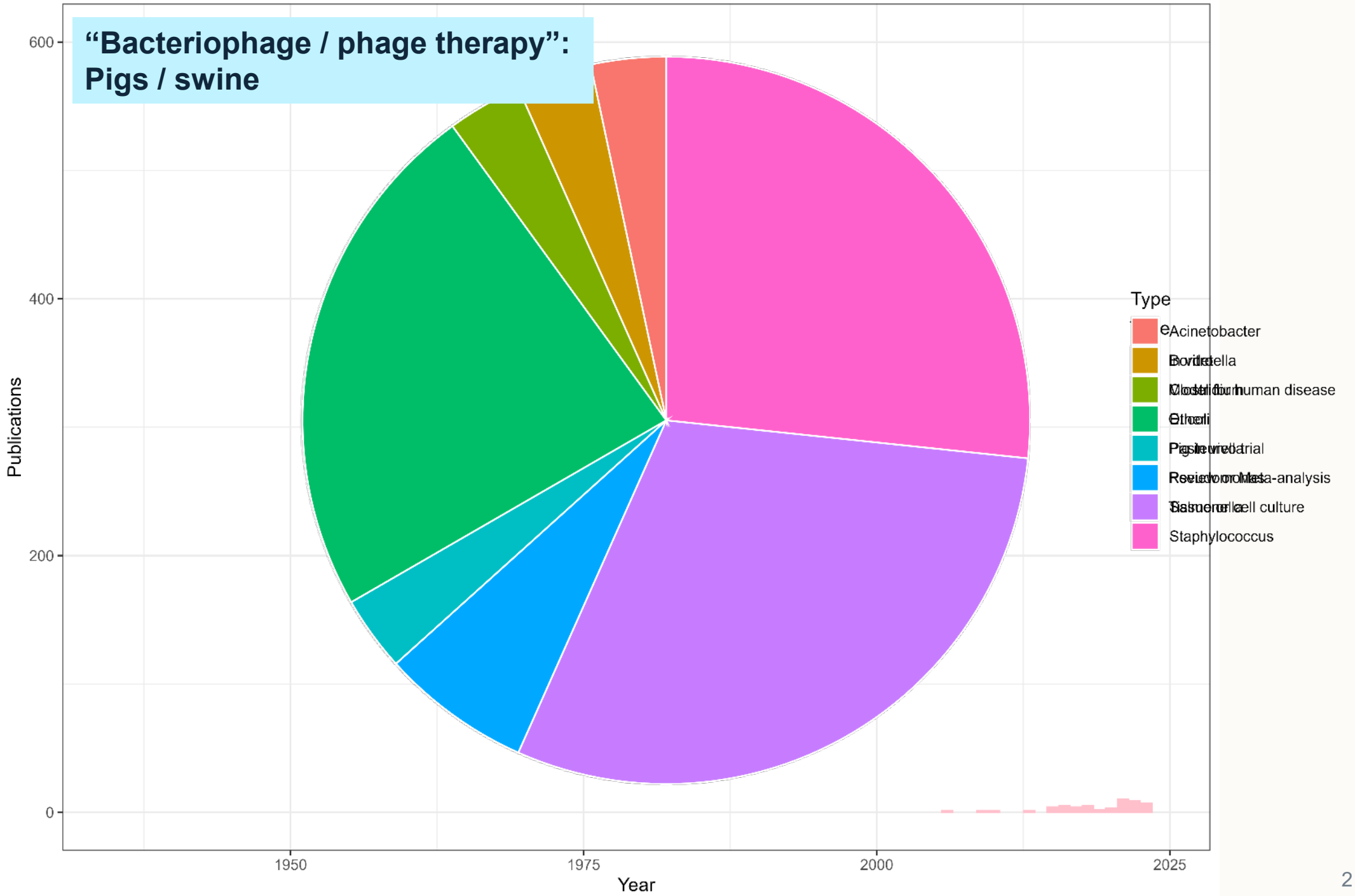
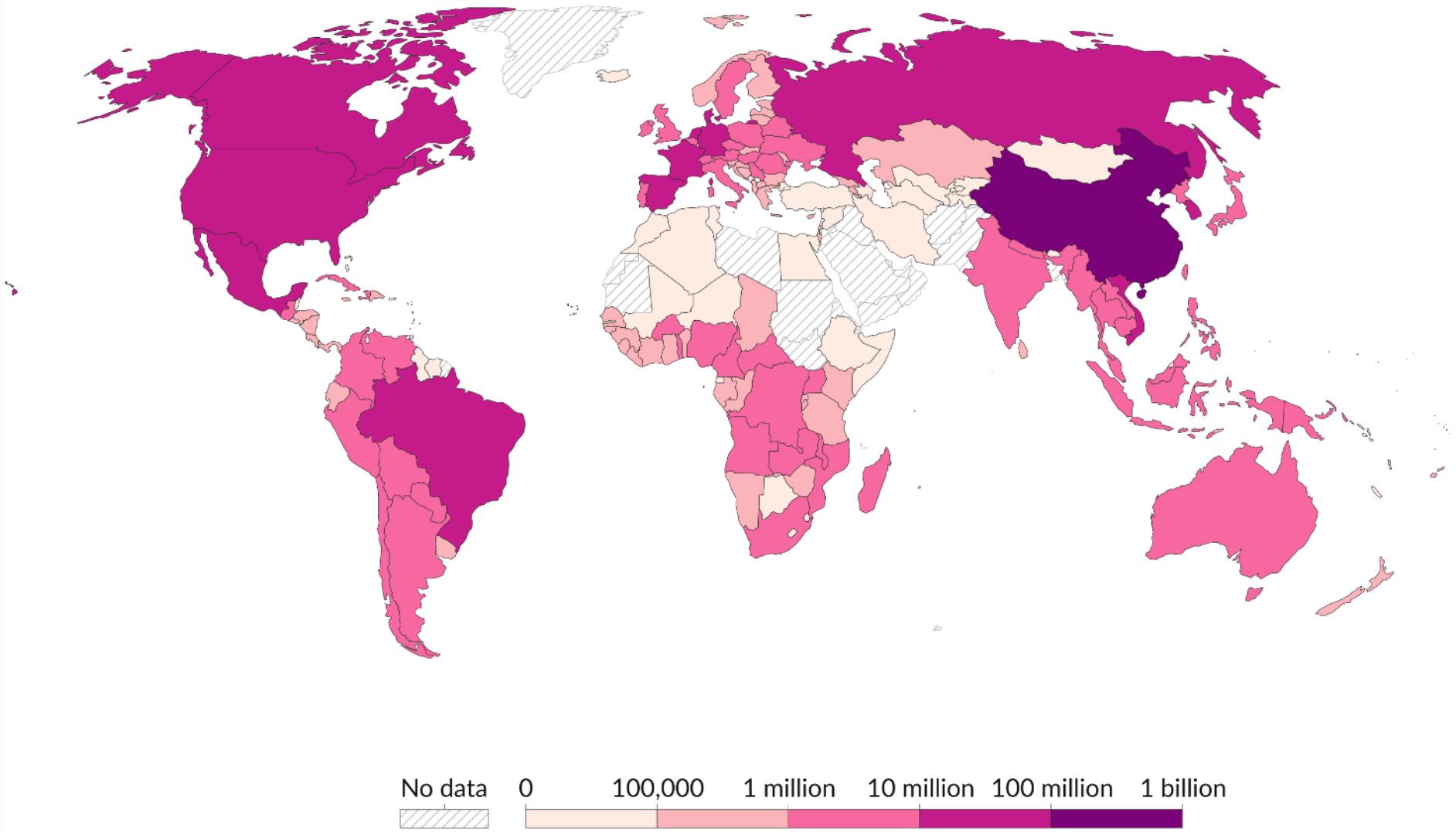
“Bacteriophage / phage therapy”: Pigs / swine



Number of pigs, 2022

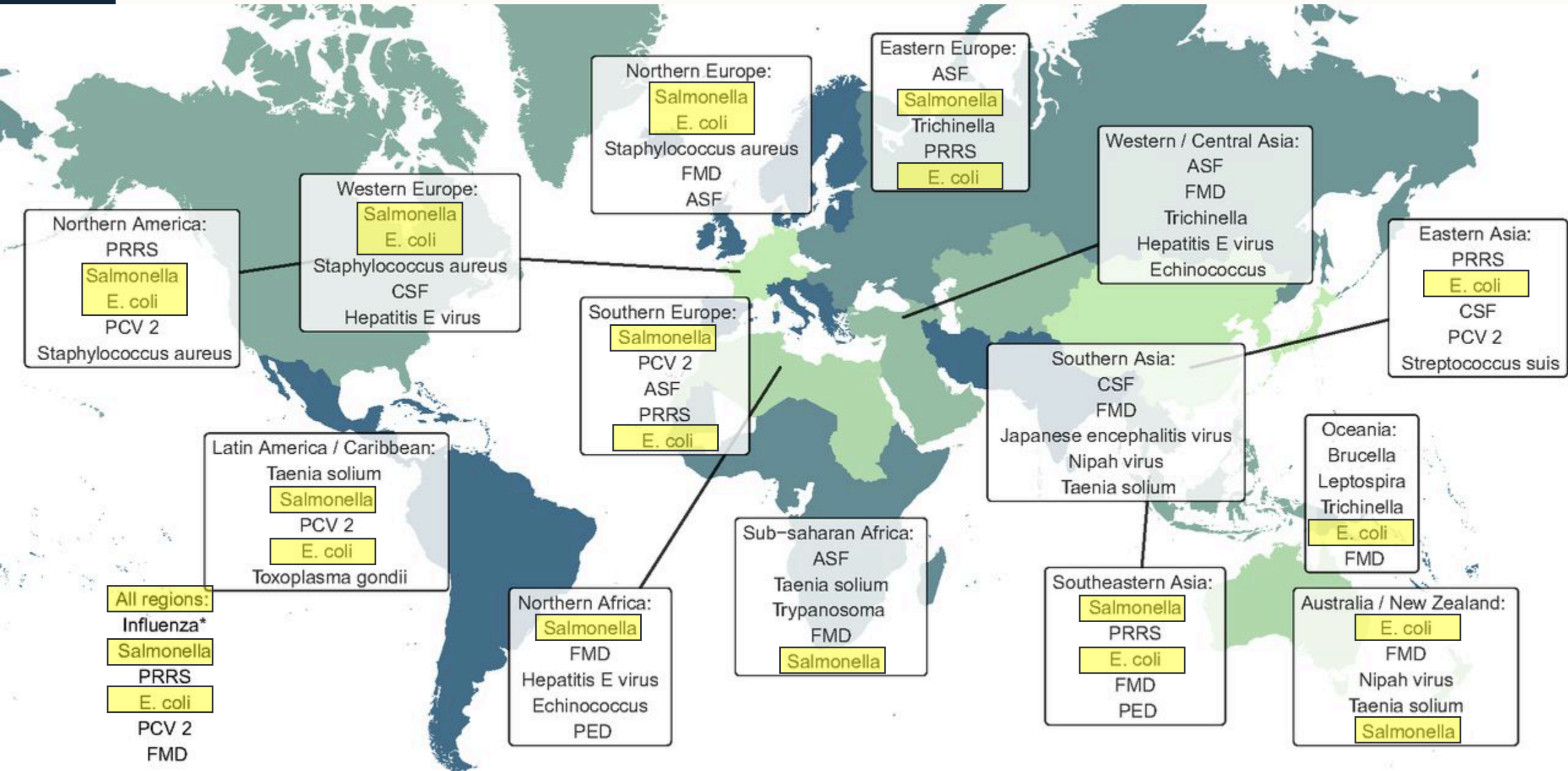
Our World in Data



Data source: Food and Agriculture Organization of the United Nations (2023)

OurWorldinData.org/meat-production | CC BY

Priority pig pathogens



Background

- Weaning ~3/4 weeks of age
- Farrowing crates w/ sow
- Vulnerable 1-2 weeks post-wean
- No/poor growth
- Diarrhoea
- Dehydration
- Mortality can increase by 20%

Post-weaning diarrhoea

- Multifactorial disease
- *E. coli* major challenge (ETEC)
- *Salmonella* and *Campylobacter*
- Controlled with ZnO (~3,000 ppm)
- Environment contamination
- Antimicrobial resistance
- Banned in EU/UK

ETEC phage therapy in neonates

- Smith and Huggins (1983)
- 10^8 CFU ETEC 6h after birth
- Phage treatment (10^{10} PFU)

- High mortality in untreated (4/7)
- No mortality in treated
- Rapid return to normal health
- ETEC decreased markedly in faeces

- Difference in phage recovery

Piglets	No.	No. that died	Approx. duration of diarrhoea* (h)
Treated	7	0	7, 9, 10, 11, 13 (3)
Untreated	7	4	26†, 28†, 33†, 44 (2), 65†, 84

* The number of piglets, when this was >1, is given in parentheses.
† Until death.

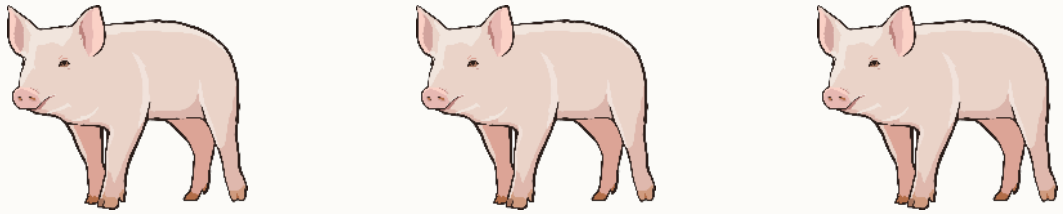
Time after onset of diarrhoea* (h)	Treated piglet			Untreated piglet
	E. coli P433	Phage P433/1	Phage P433/2	*E. coli* P433
0	8·5	N	N	8·4
3	6·9	8·6	7·5	9·0
7	5·0	9·2	8·3	9·0
11	5·8	9·2	8·3	9·2
15	4·0	8·2	6·3	9·4
24	4·6	6·7	5·5	9·6
48	6·5	8·9	5·0	8·4
72	5·4	6·5	3·3	8·9
96	5·0	6·0	N	7·7

Smith HW, Huggins MB. J Gen Microbiol. 1983. 129(8):2659-75. doi: 10.1099/00221287-129-8-2659.

ETEC in post-weaned piglets

- ETEC K88/K99
- 18 piglets, 28 d
- 3 groups, 6 piglets
- Fed 7 days then euthanised

- *E. coli* shedding ▼
- Improved faecal score
- Sig. (≤0.03) K88 only



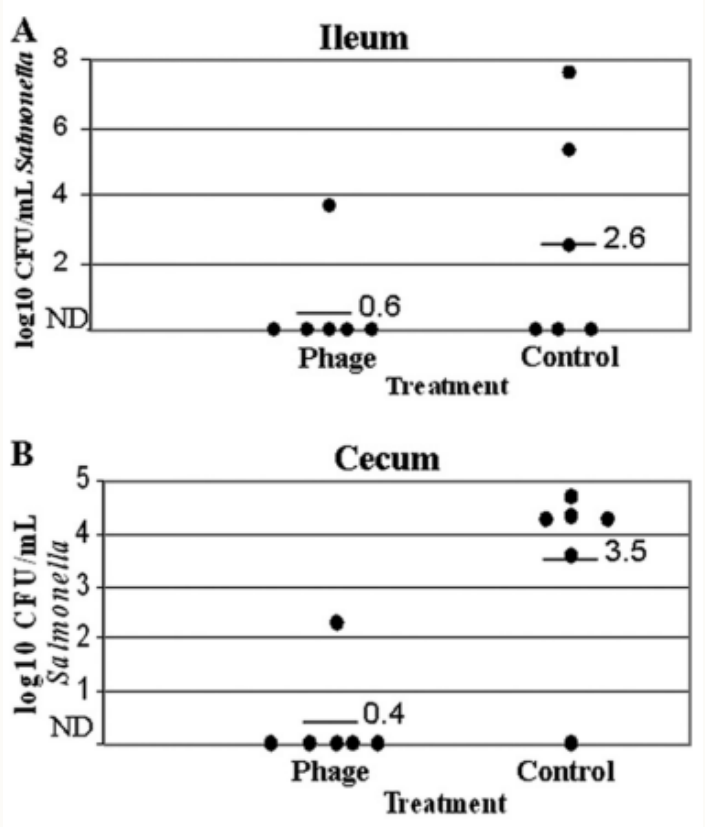
Control	Challenge	Phage-treated
PBS	10^8 ETEC	10^8 ETEC
Feed	Feed	Feed + 10^9 Phage

Segment	Challenge	Phage-treated
Duodenum	1.6	0.7
Jejunum	3.0	1.4
Ileum	7.2	5.6
Caecum	6.3	3.9
Colon	3.3	1.8
Mesenteric lymph nodes	3.8	2.1

Han, S. J. et al., 2016.
J Swine Health Prod. 24(5):259–263.

Salmonella in post-weaned piglets

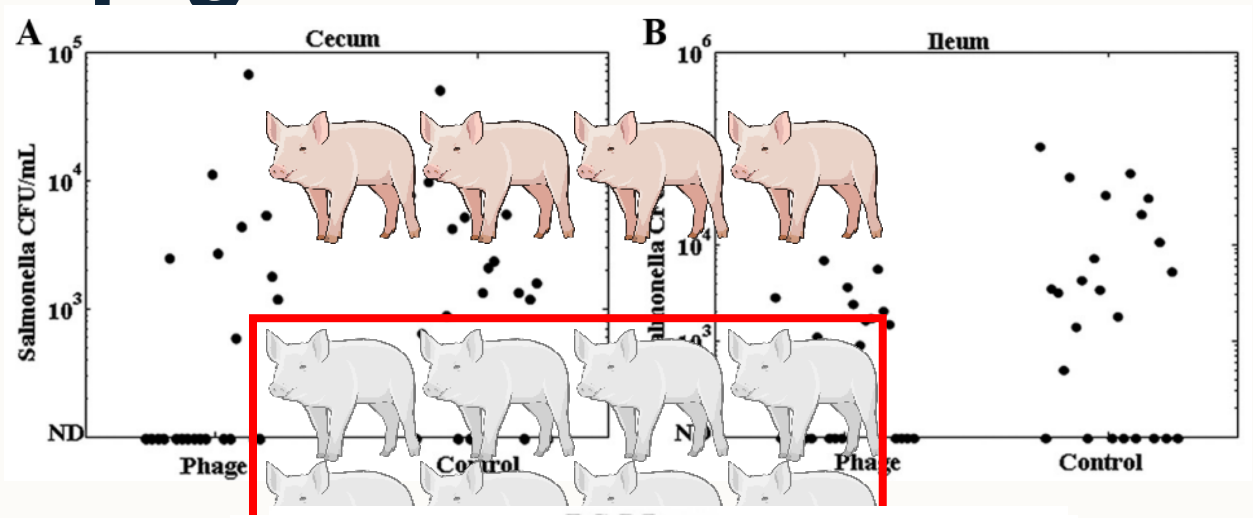
- *S.* Typhimurium
- Cocktail of 15 phage
- Alginate-encapsulated (10^{10} PFU)
- 3-4 week old piglets
- 10^{8} CFU S. Typhimurium
- 5 mL phage cocktail
- Repeated every 2h for 6h

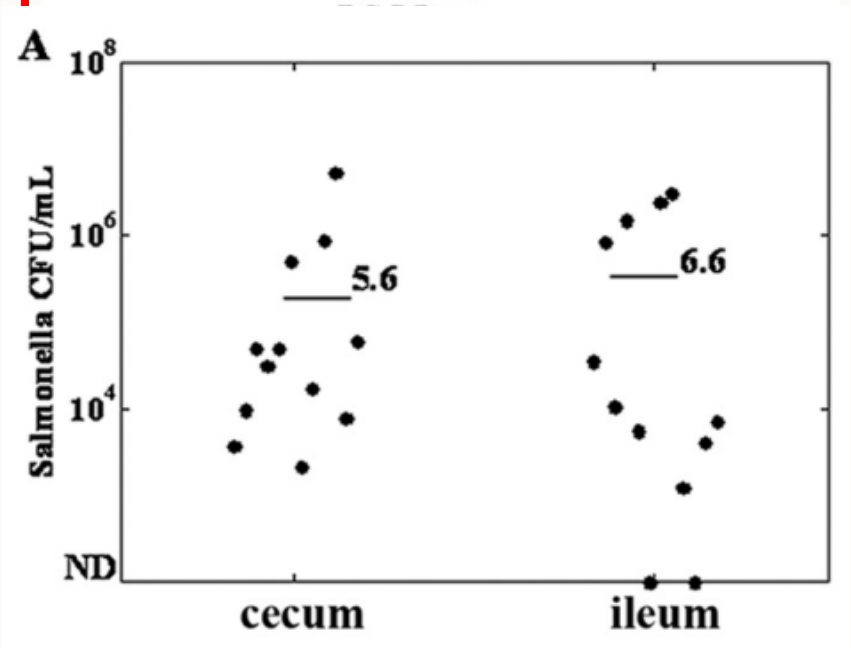


Wall, S. K., et al. 2010.
Appl. Environ. Microbiol. 76:48–53.

Salmonella in adult pigs

- Market-weight pigs
- *S.* Typhimurium seeder pigs
- Pre-treat naïve pigs
  - Encapsulated phage
  - Mock
- Repeated every 2h for 6h
- Euthanised





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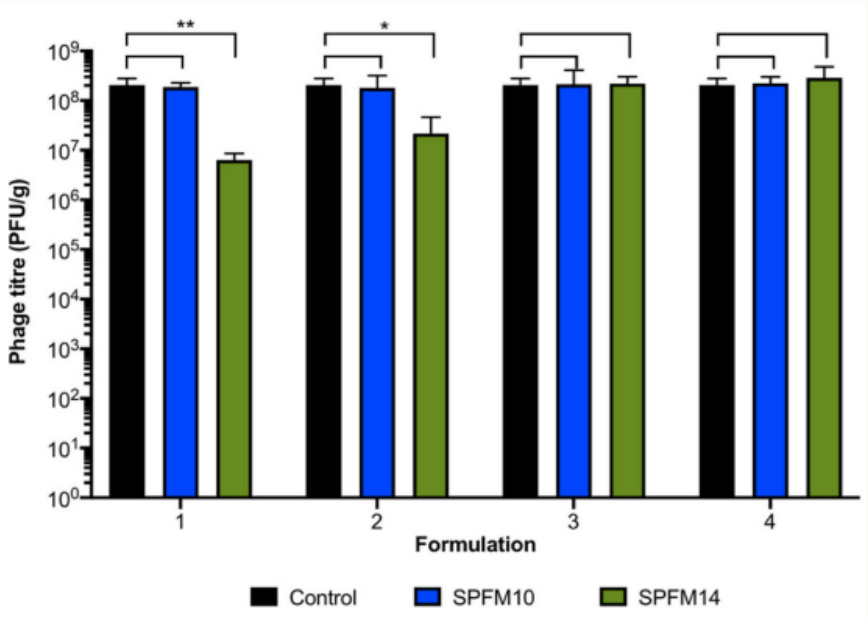
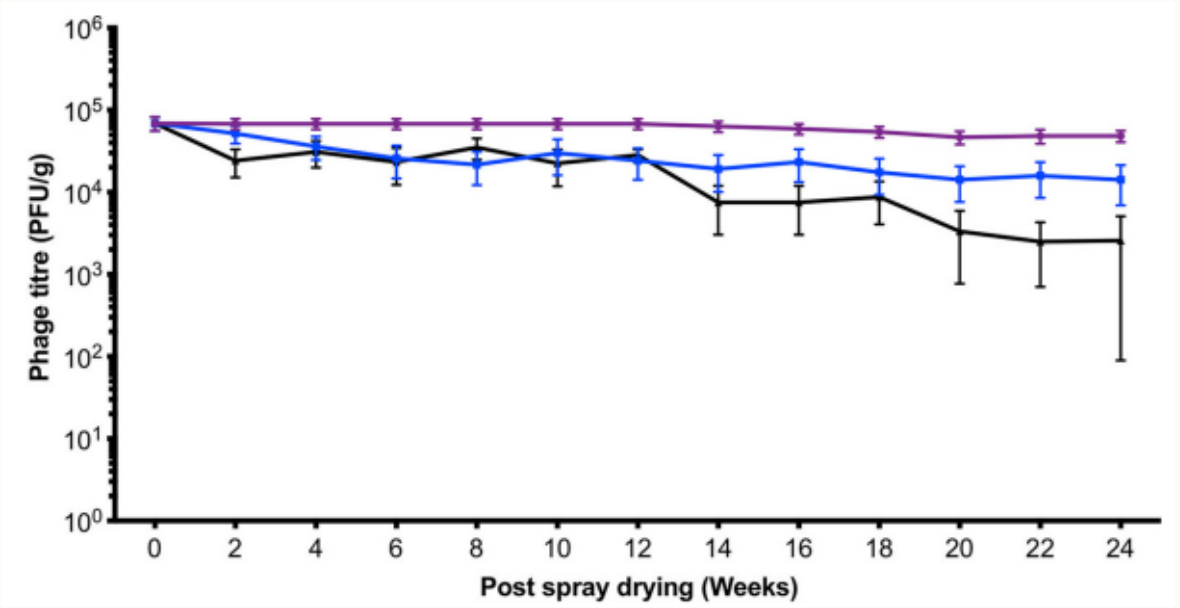
Spray-dried phage in feed

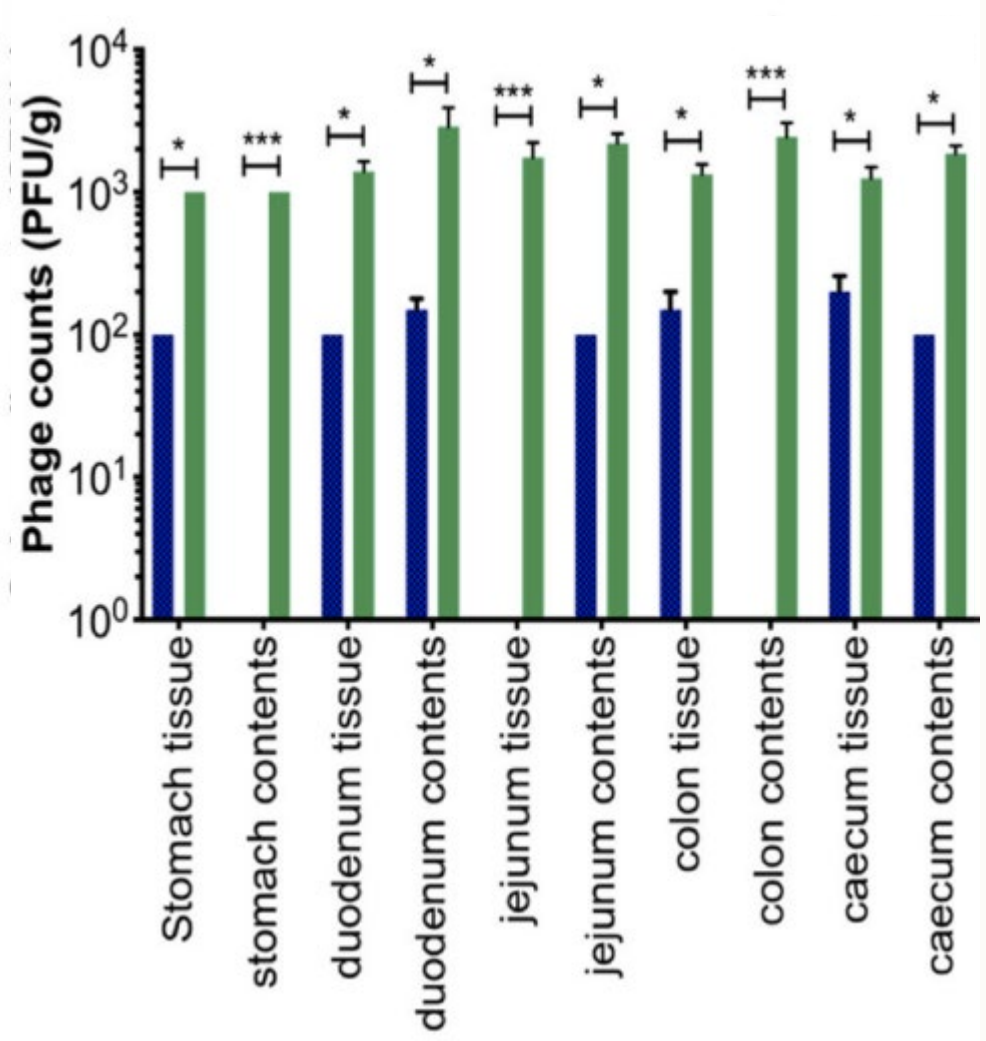




Thanki AM, et al. 2022
Microbiol Spectr. 10(3):e0042222.

Spray-dried phage in feed

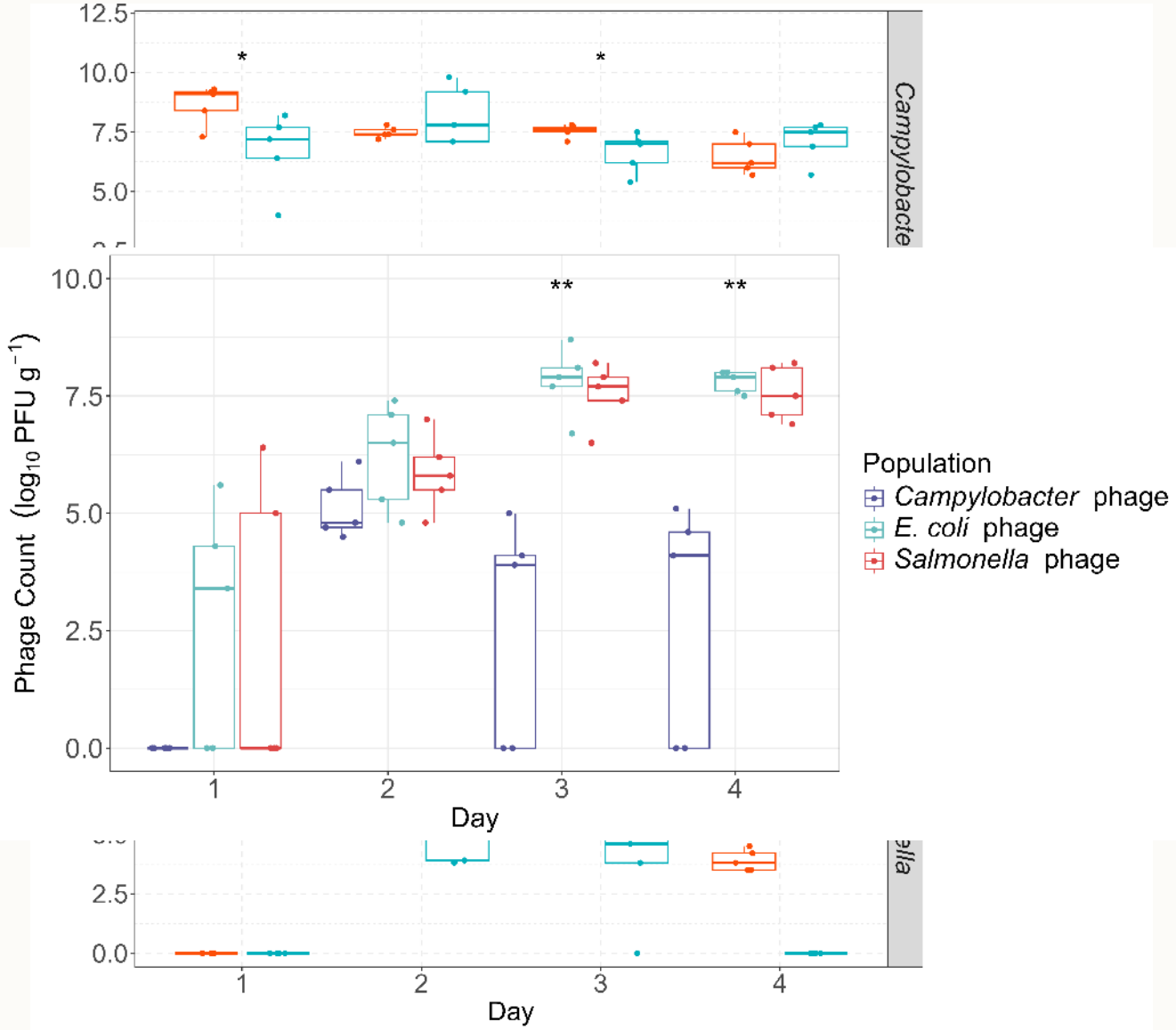
- Weaned piglets (n = 18)
  - Untreated control
  - Phage only
  - Challenge only
  - Challenge + Phage
- Phage treatment 3d pre-challenge
- *S.* Typhimurium (10^8 CFU).
- Euthanised 5 days post challenge



Thanki AM, et al. 2022
Microbiol Spectr. 10(3):e0042222.

Polybacterial infections

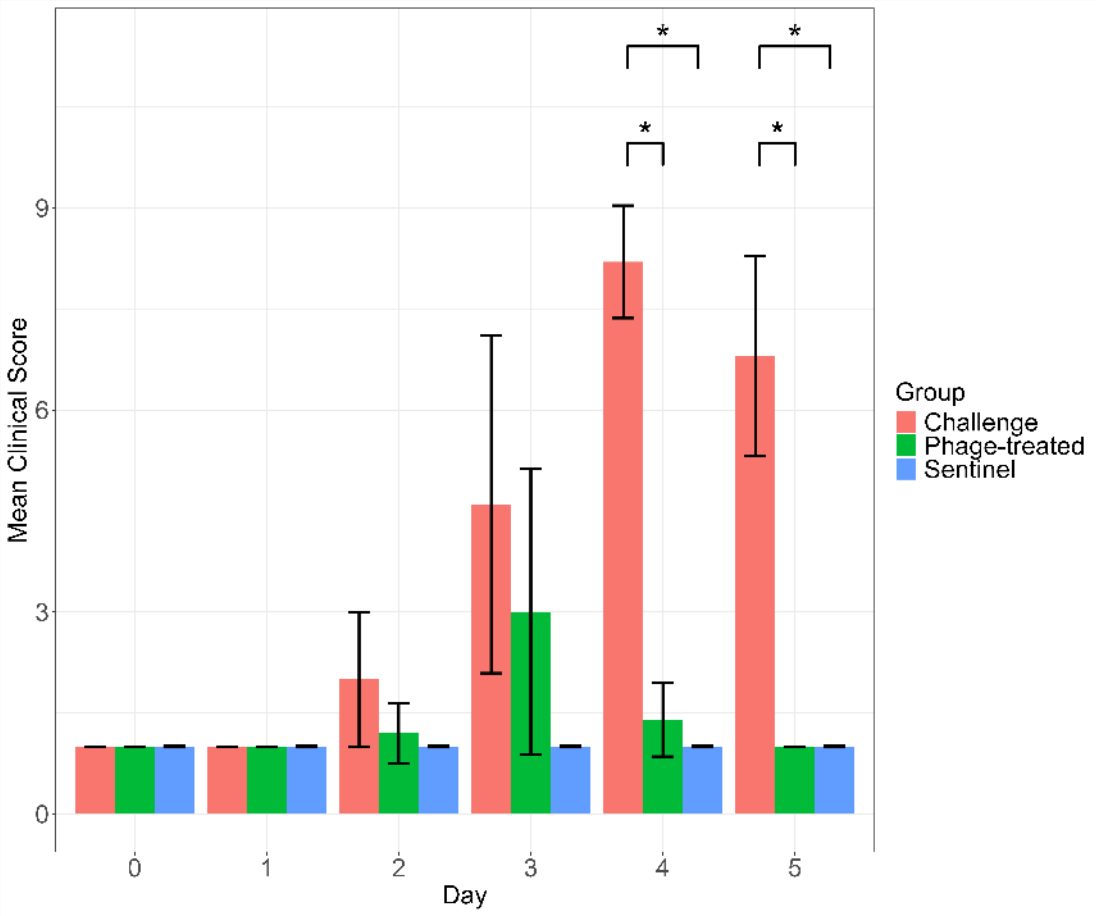
- Weaned piglets (23 d)
  - Sentinel (n=3)
  - Challenge (n = 5)
  - Challenge + Phage (n = 5)
- Challenged (10^9 CFU each):
  - ETEC
  - *S.* Typhimurium
  - *C. coli*
- Phage given 4h post-challenge
- Repeated daily for 5 days



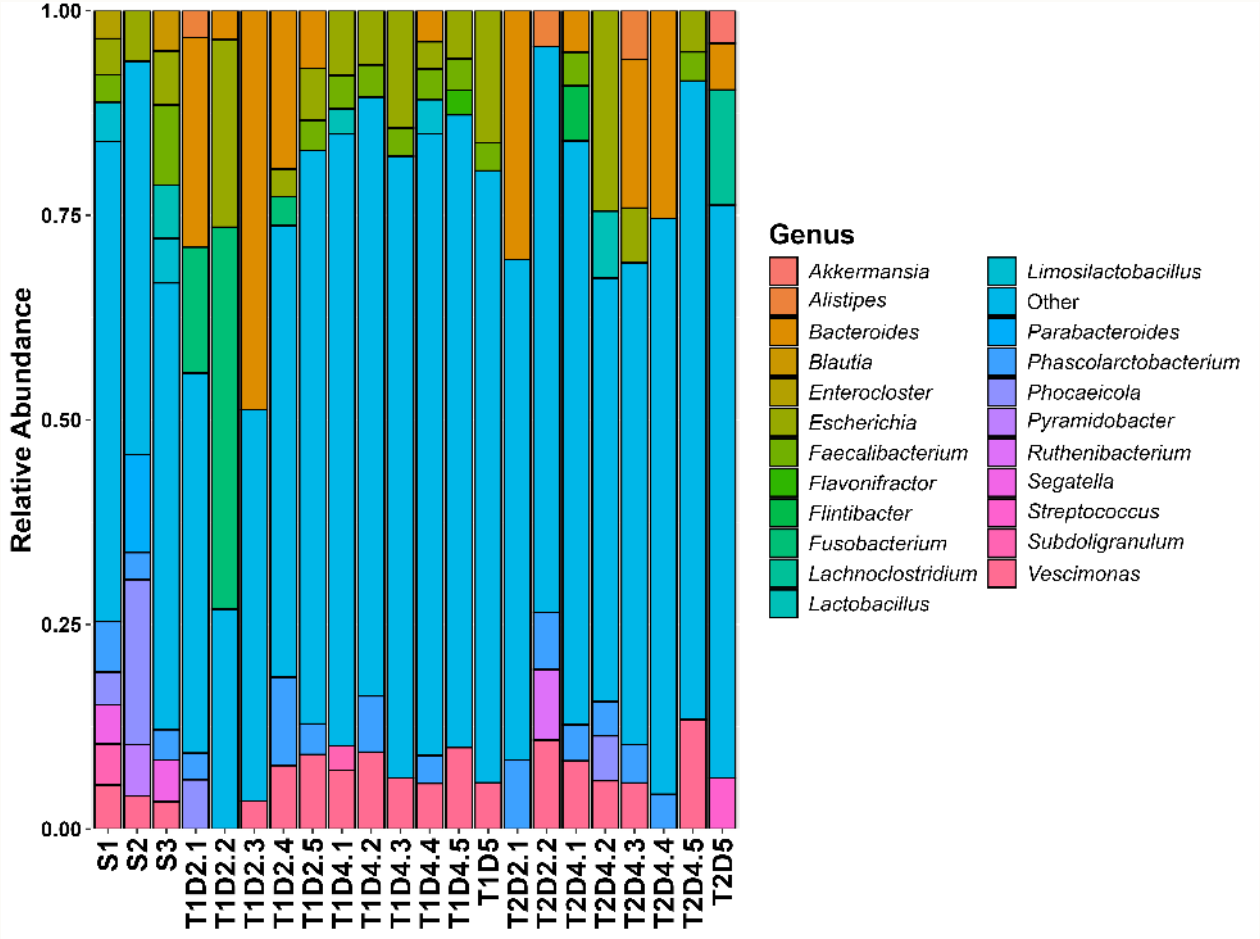
Polybacterial infections

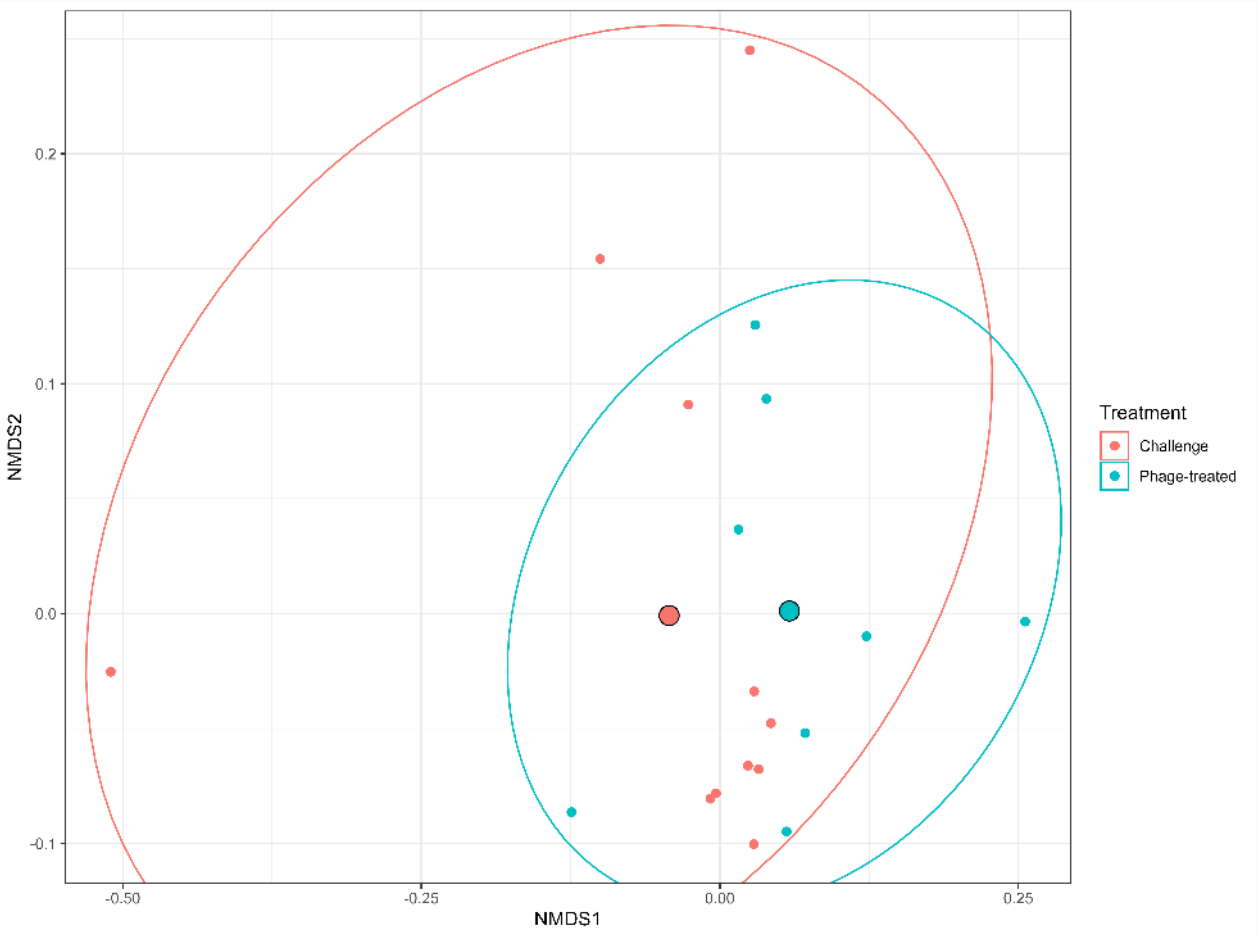
Segment	ETEC		*S.* Typhm		*C. coli*	
	Chal	Trt	Chal	Trt	Chal	Trt
Duodenum	0.0†	0	0	0	0.0†	0.0†
Jejunum	0.0†	0.0†	0	0	0.0†	0
Ileum	0.0†	0.0†	0	0	0.0†	0.0†
Colon	3.7	0.0*	3.8	0.0**	6.8	5.5
Caecum	4.1	0.0**	4.8	0.0**	5.7	5.5

Segment	*E. coli* phage		*Salmonella* phage		*Campylobacter* phage	
	Chal	Trt	Chal	Trt	Chal	Trt
Duodenum	0	2.9	0	0	0	0
Jejunum	0	3.1	0	0	0	0
Ileum	0	3.7	0	3.6	0	0.0†
Colon	0	7.3	0	7.4	0	0.0†
Caecum	0	6.9	0	7.7	0	0.0†



Polybacterial infections

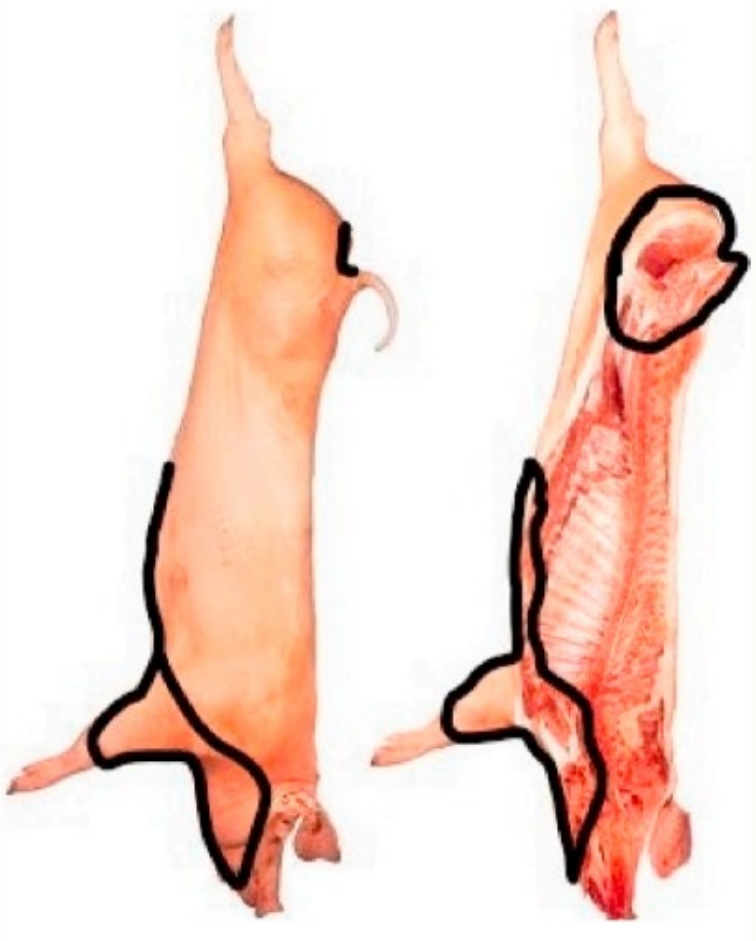




Decontamination of skin/carcases

- Multiple laboratory studies
- Ground pork (Hong et al, 2016)
- Pig skin (Hooton et al, 2011; Spricigo et al, 2013)
- Pork (Wang et al, 2017).
- Reductions of 1 – 4 $\log_{10}$ CFU

- Industrial trial
- 134 carcases (14 contam)
- 78.6% ▼ *Salmonella* positive



Volpi M, et al. 2023.
Food Microbiol. 112:104240.

Summary

- Need for alternatives to ZnO
- Relatively few trials (particularly adult)
- Prophylactic and therapeutic efficacy
  - Neonates
  - Post-wean
  - Adults
- Variability in outcomes
- Industry-scale trials lacking
- Regulatory barriers
- Consumer acceptance

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