The future of *Salmonella* vaccines in a geographically diverse and changing epidemiological environment, with emphasis on poultry

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Bangkok, ATA conference, december 2019

A brief introduction on the global *Salmonella* problem

- Host-specific serotypes

  - Systemic spread to bloodstream
  - Cause septicemia, severe disease
  - Specific serotypes affect specific hosts

Examples: *Salmonella* Cholerasuis, Gallinarum, Dublin, …

SYSTEMIC DISEASE !

A brief introduction on the global *Salmonella* problem

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Examples: *Salmonella* Cholerasuis, Gallinarum, Dublin, …

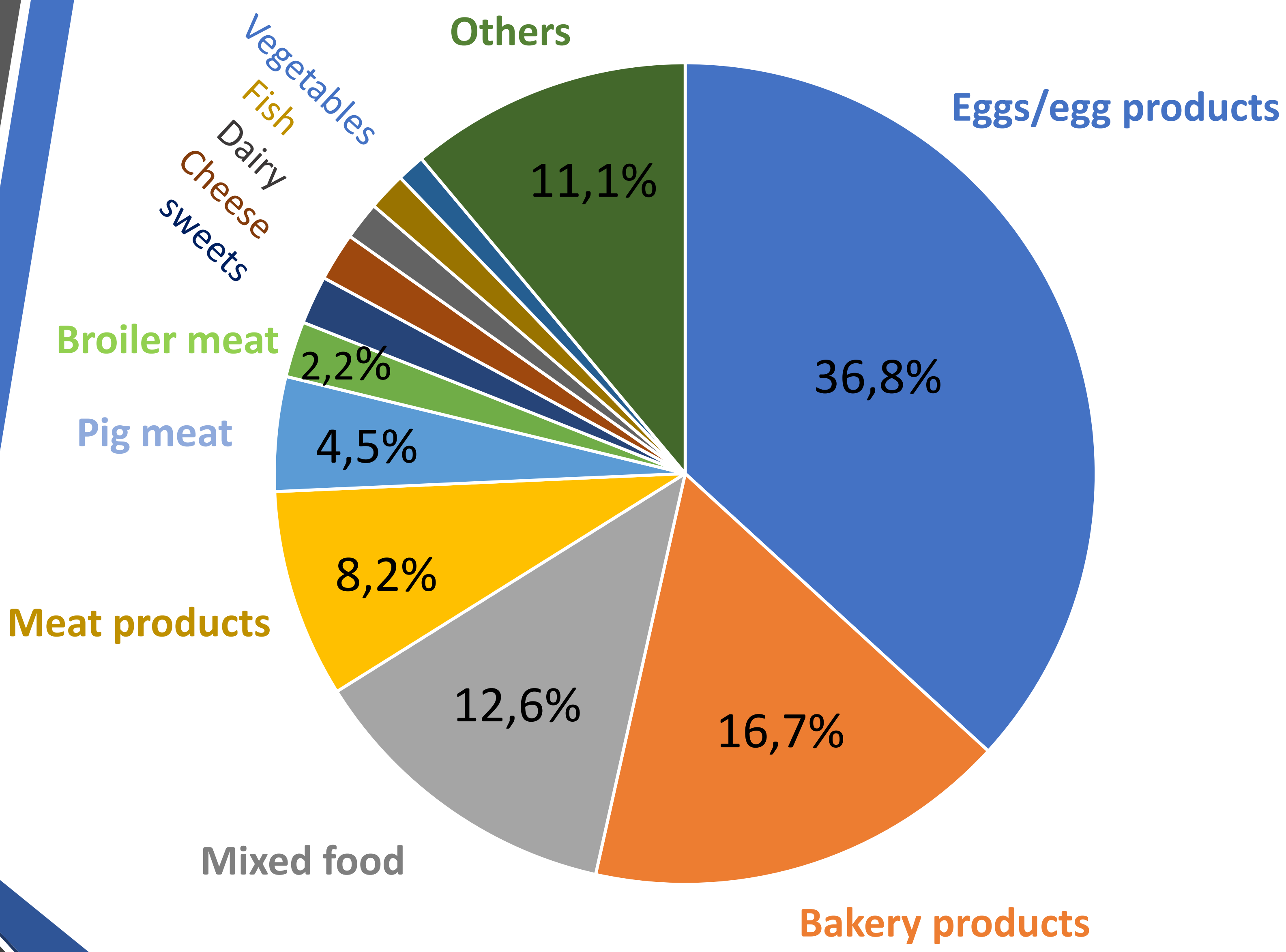
SYSTEMIC DISEASE !

- Broad host-range serotypes
  - Intestinal colonization is most important
  - Either asymptomatic or causing diarrhea
  - Spread between different animal species, and humans

Examples: *Salmonella* Enteritidis, Typhimurium, many others …

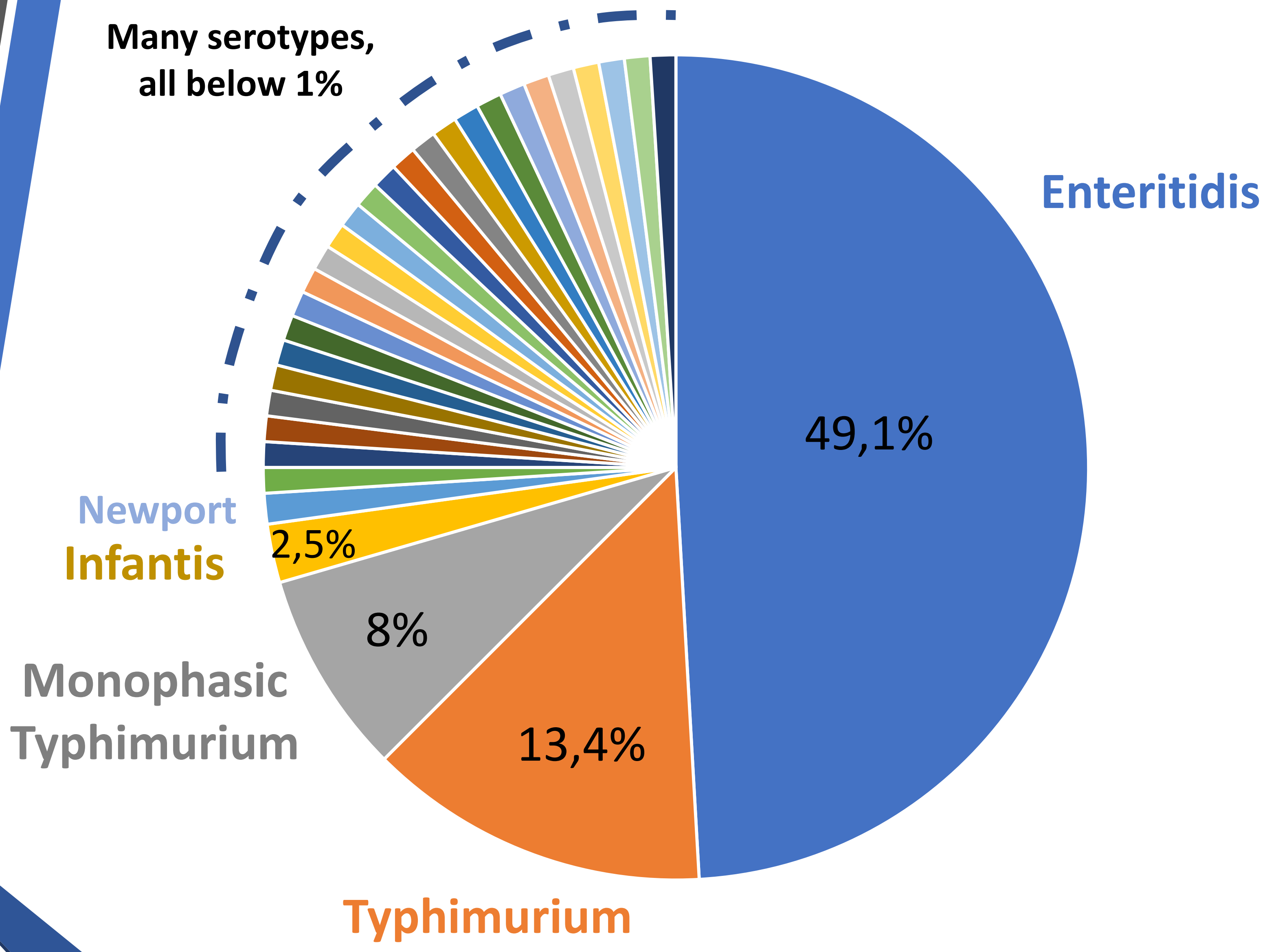
FOOD POISONING !

Food sources of human outbreaks of *Salmonella* (EU 2017)



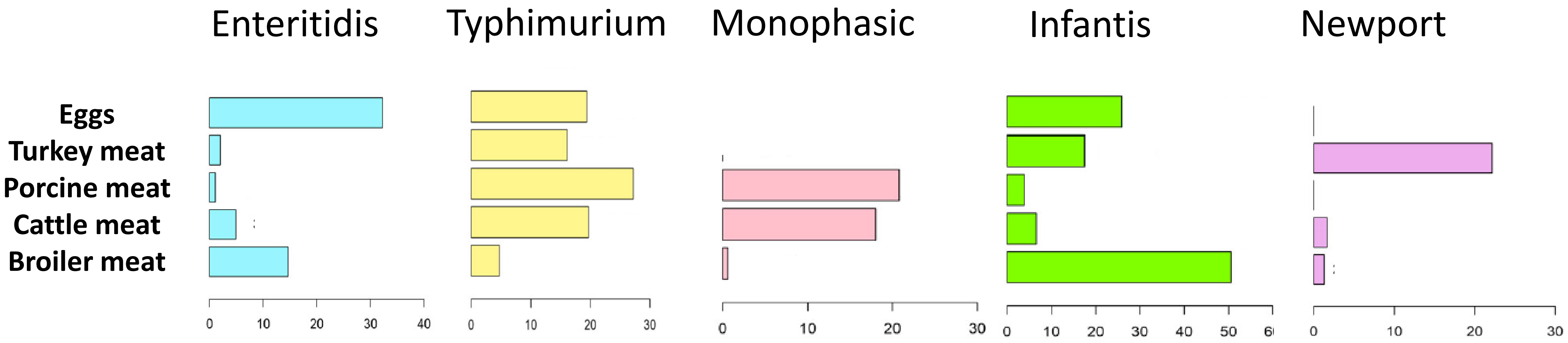
The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017

Serotypes involved in human *Salmonella* cases (EU 2017)



The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017

Link between serotypes and animals/food sources



% of isolates from that specific serotype derived from a feed source

Distribution of serotypes in animal species and products is key for control plans

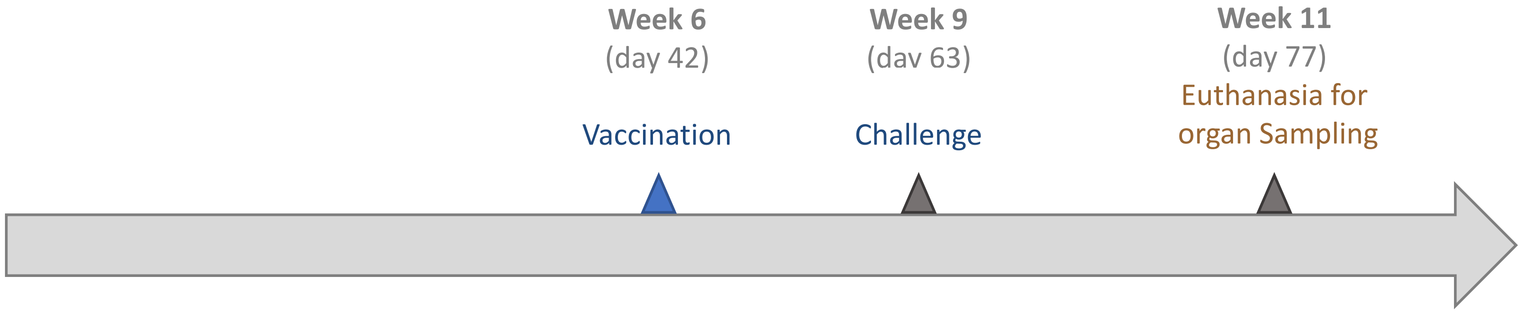
The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017

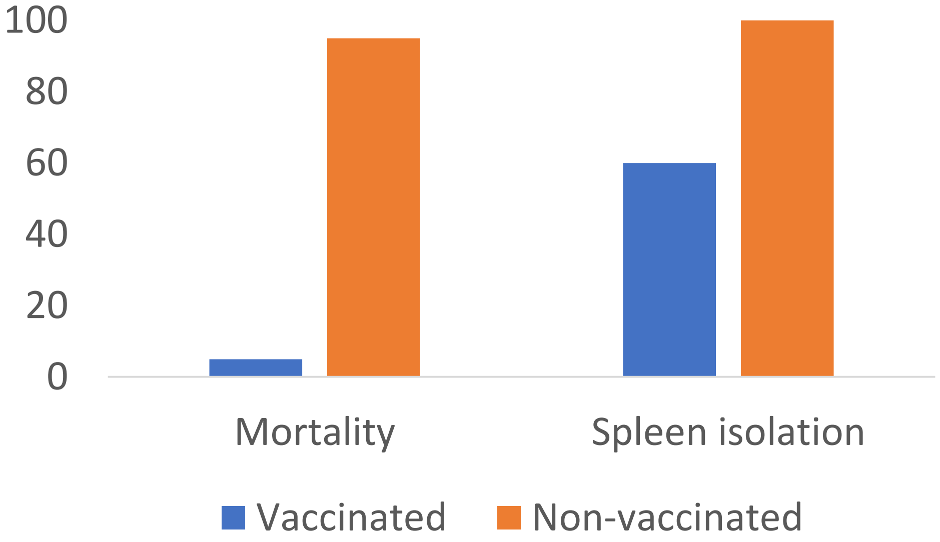
Current vaccines and their protection

	Live vaccines	Inactivated vaccines
Immune mechanism	Cell-mediated immunity, mucosal immunity, IgA, antibodies	Antibodies
Administration method	Drinking water, spray	Injection
Type	Chemical mutagenesis, metabolic drift mutants, undefined mutants	Bacterins
Safety issues	Potential persistance, spread, reversion to virulence	No isolation possible
Animal species	layers, broilers, pigs	breeder poultry, cattle
Other aspects: adjuvant requirement, cost, duration of immunity, markers (DIVA), multivalent use, etc …		

Current vaccines and their protection

Host-specific serotypes (example *Salmonella* Gallinarum in poultry)



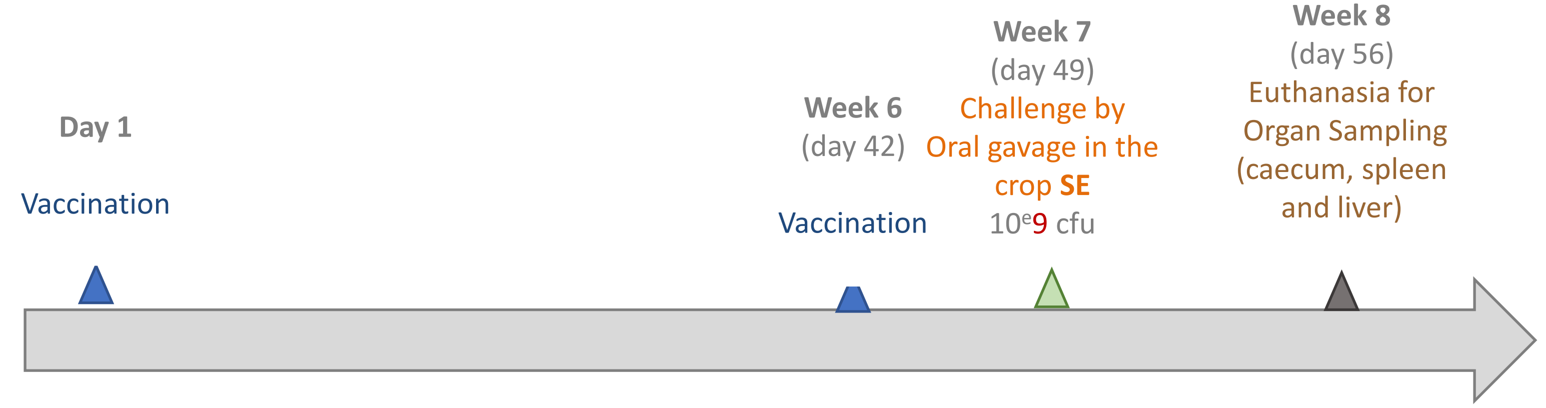


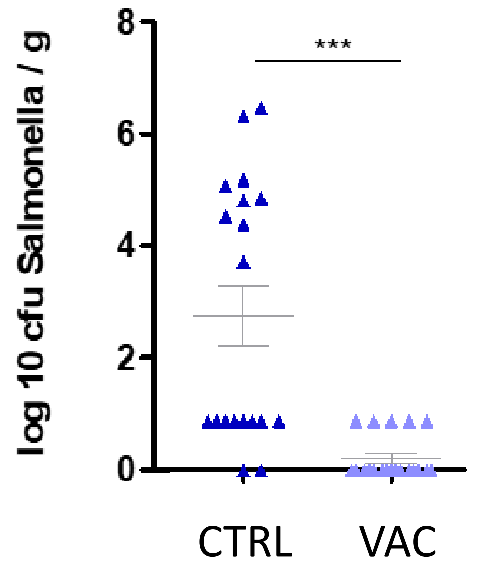
Decreased mortality
Less diseased animals
Lower organ colonization levels
No complete elimination

Lee, Mo and Kang, 2005

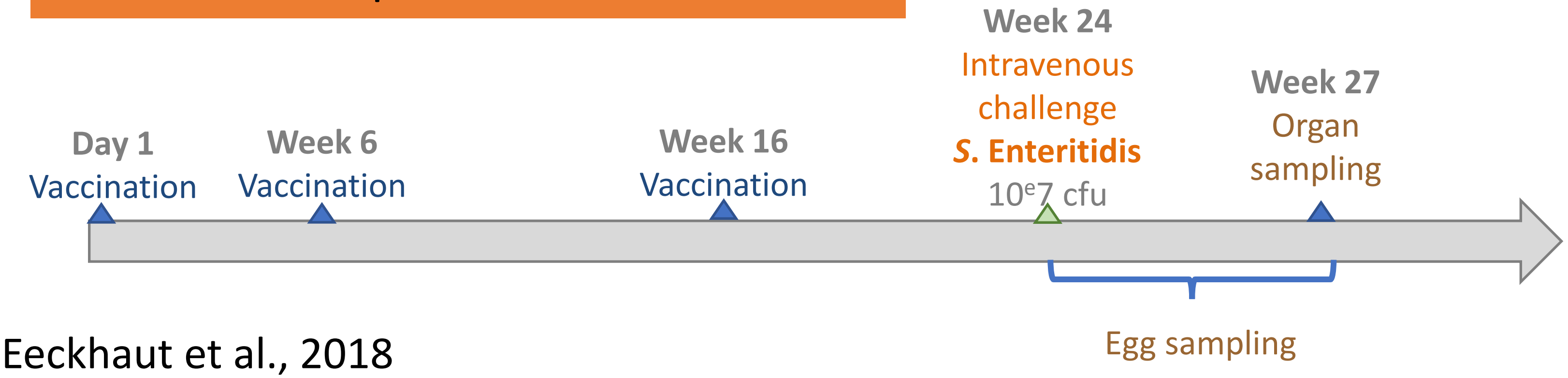
Current vaccines and their protection

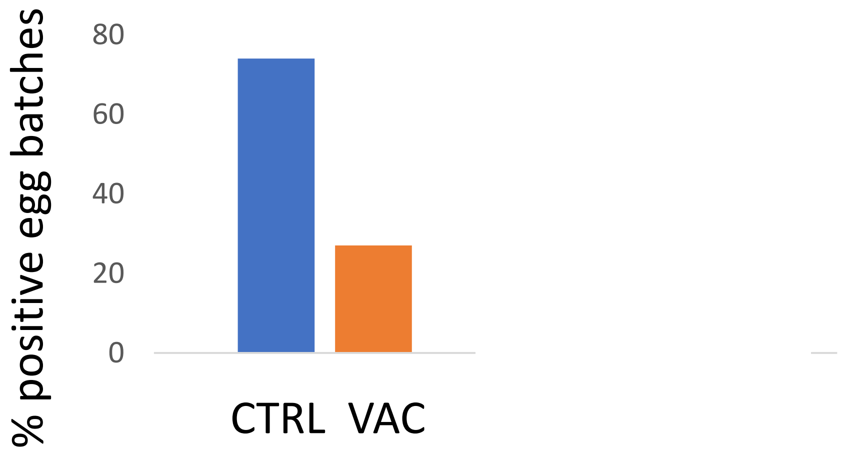
Food poisoning serotypes (example *Salmonella* Enteritidis in poultry)





Lower gut colonization levels, shedding
Lower organ colonization levels
Less egg contamination
No complete elimination





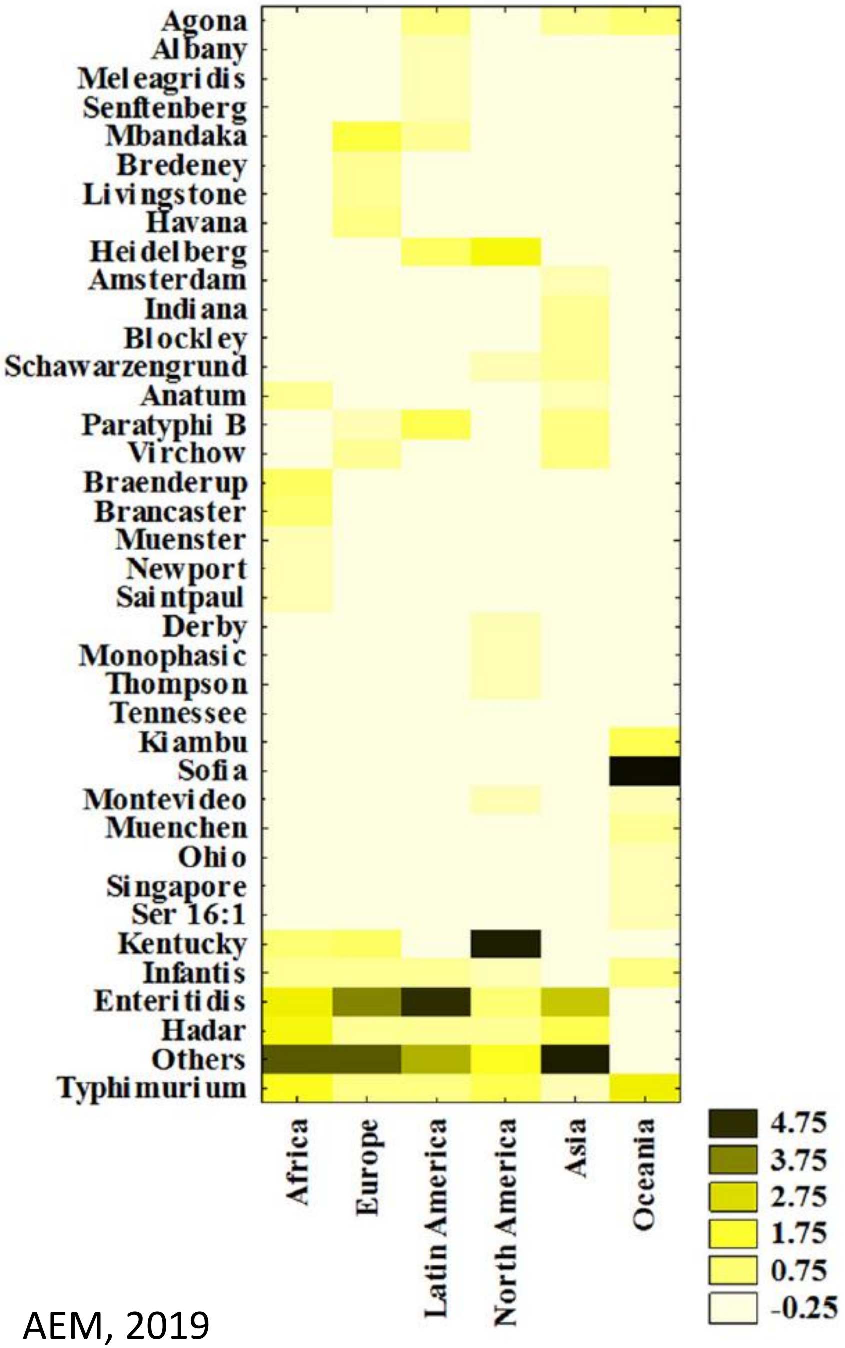
Eeckhaut et al., 2018

Challenges in *Salmonella* control, vaccine design and use

Challenge 1. Geographical differences in serotype distribution (example of poultry)

Regional

Global



Worldwide Epidemiology of *Salmonella* Serovars in Animal-Based Foods: a Meta-analysis

Rafaela G. Ferrari,[a,d] Denes K. A. Rosario,[a,d] Adelino Cunha-Neto,[a,c] Sérgio B. Mano,[a] Eduardo E. S. Figueiredo,[b,c] Carlos A. Conte-Junior[a,d,e]

AEM, 2019

Challenge 2. New emerging *Salmonella* serotypes

Contents lists available at SciVerse ScienceDirect
International Journal of Food Microbiology
journal homepage: www.elsevier.com/locate/ijfoodmicro
ELSEVIER

Short communication

Multidrug resistant clones of *Salmonella* Infantis of broiler origin in Europe

N. Nógrády [a], M. Király [a], R. Davies [b], B. Nagy [c,*]
aw, Surrey, KT153NB, UK
1143, Budapest, Hungária krt. 21, Hungary

Emergence of a Clonal Lineage of Multidrug-Resistant ESBL-Producing *Salmonella* Infantis Transmitted from Broilers and Broiler Meat to Humans in Italy between 2011 and 2014

Alessia Franco[1], Pimlapas Leekitcharoenphon[2], Fabiola Feltrin[1], Patricia Alba[1], Gessica Cordaro[1], Manuela Iurescia[1], Rita Tolli[1], Mario D'Incau[3], Monica Staffolani[4], Elisabetta Di Giannatale[5], Rene S. Hendriksen[2], Antonio Battisti[1]*

International Journal of Poultry Science 12 (3): 185-191, 2013
ISSN 1682-8356

Salmonella Infantis, a Potential Human Pathogen has an Association with Table Eggs

Samiullah Samiullah
School of Environmental and Rural Science, University of New England, Armidale, 2350, Australia

Abstract: Food borne Salmonellosis in human is mainly caused by the consumption of contaminated eggs and other poultry products. Trans-shell route is considered the underlying phenomena leading to the production of *Salmonella* Infantis contaminated eggs. *Salmonella* Infantis comes in the top 10 human pathogenic *Salmonella* serovars, been isolated from human and poultry from diverse group of countries in patients linked to contaminated food. Majority of the *Salmonella* cases are sporadic, outbreaks occur frequently with a direct or indirect link to contaminated food especially poultry. This review has mainly highlighted the factors affecting *Salmonella* transmission with a special emphasis on hen eggshell quality.

Key words: Hen eggshell, salmonellosis, transmission route, factors

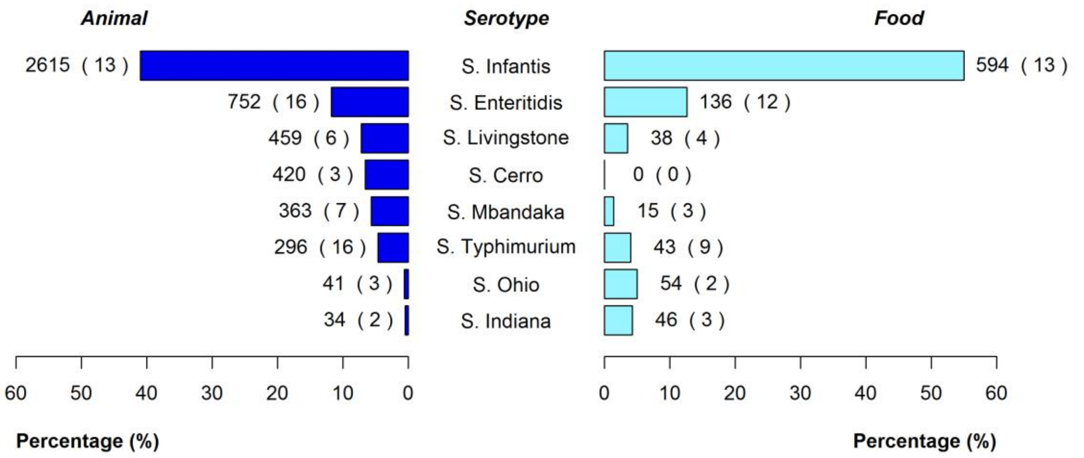
Example: *Salmonella* Infantis

environmental microbiology
Environmental Microbiology (2014) 16(4), 977–994
doi:10.1111/1462-2920.12351

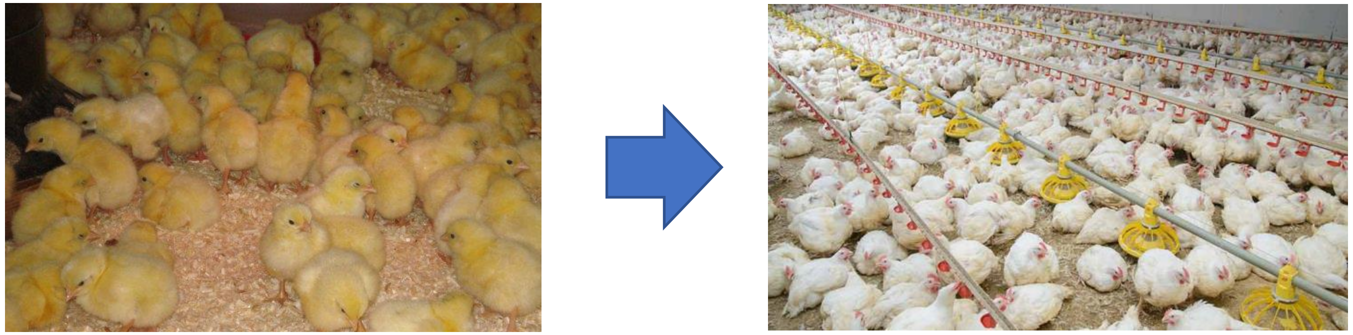
A unique megaplasmid contributes to stress tolerance and pathogenicity of an emergent *Salmonella enterica* serovar Infantis strain

Gili Aviv,[1,2] Katherine Tsyba,[1,2] Natalie Steck,[3,4] Mali Salmon-Divon,[5]† Antje Cornelius,[3,4] Galia Rahav,[1,2] Guntram A. Grassl[3,4] and Ohad Gal-Mor[1]*

higher pathogenicity and increased intestinal inflammation caused by an *S.* Infantis strain harboring pESI compared with the plasmidless parental strain. Our results indicate that the presence of pESI that



Challenge 3. Critical periods of increased sensitivity, age

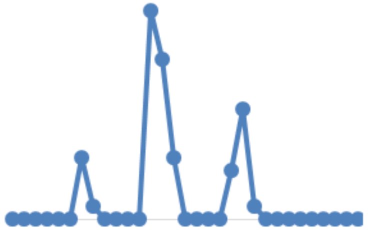


- Young animals
- Short life span (eg. broilers)
- Limits in duration of protection for laying hens

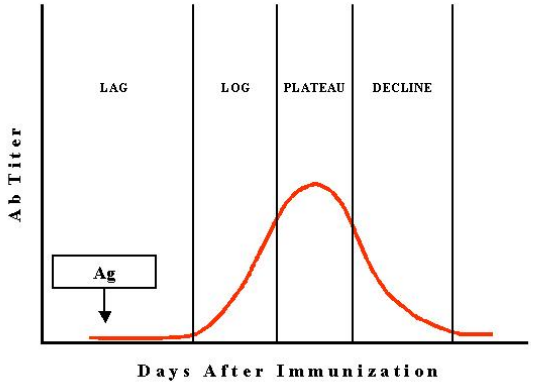
- Stress periods (lay, molting)
- Interference with feed additives and antimicrobials

Challenge 4. Interference with monitoring programs

- Bacteriological testing:
  - Limited shedding
  - Low environmental survival
  - Differentiation on culture media



- Serological testing:
  - Differentiation of vaccinated from infected animals (DIVA)



Questions for future vaccines

- Challenge 1. Geographical differences in serotype distribution
- Challenge 2. New emerging *Salmonella* serotypes

Are current vaccines cross-protective? Against which serogroups or serotypes? Broad cross-protection? Level of cross-protection? Do we need serotype-specific vaccines?

- Challenge 3. Critical periods of increased sensitivity, age

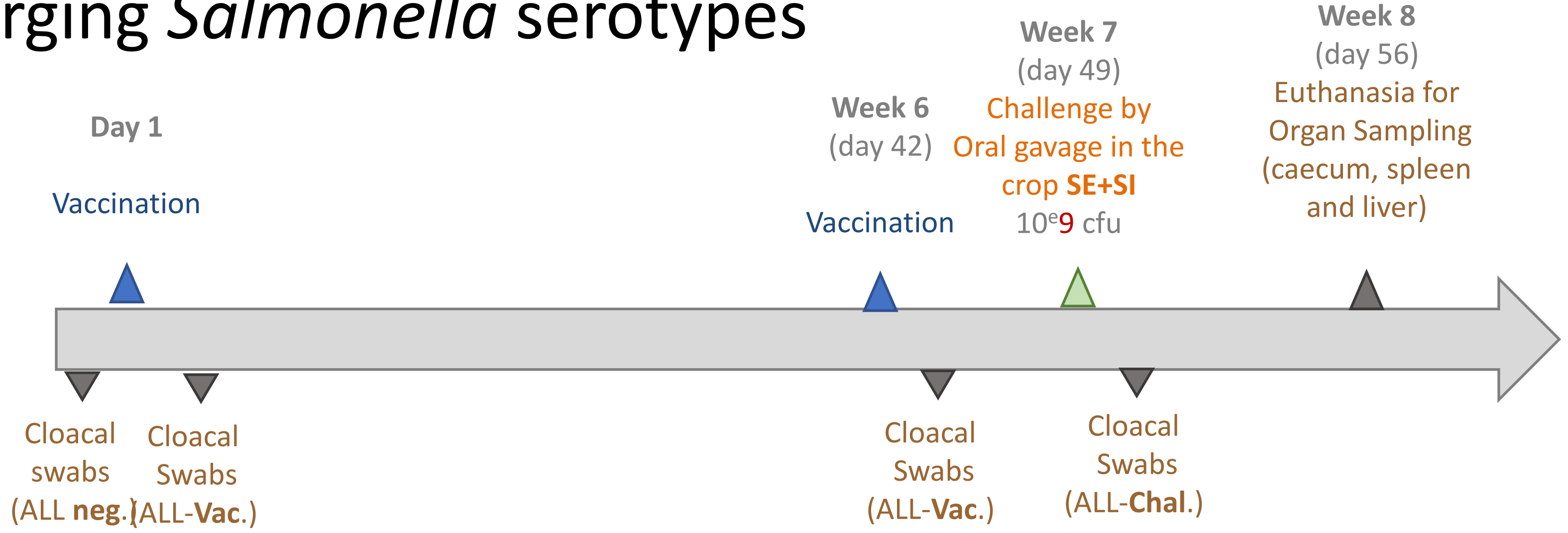
Can we have immediate protection from day 1 of life? Can we get good data on dynamics of protection in time? Can we boost protection at susceptible periods?

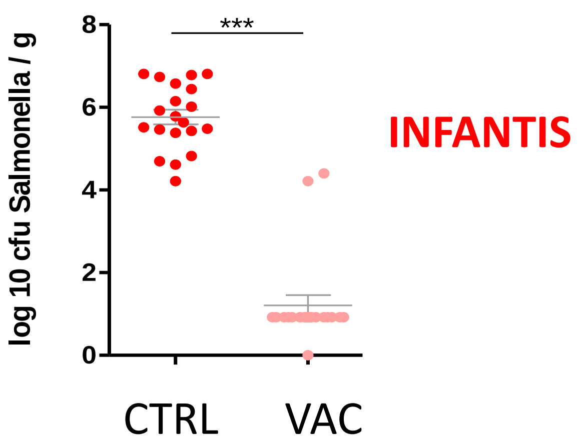
- Challenge 4. Interference with monitoring programs

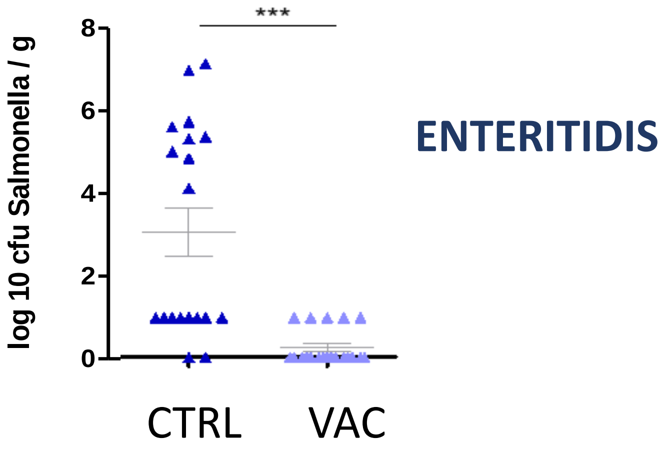
Can we introduce markers to differentiate bacteriologically and serologically?

Cross-protection between serotypes

- Challenge 1. Geographical differences in serotype distribution
- Challenge 2. New emerging *Salmonella* serotypes







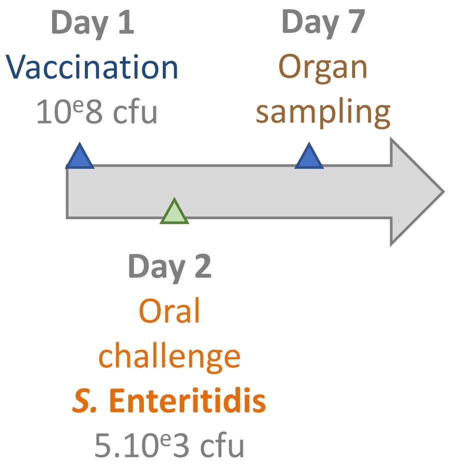
Cross-protection of a *Salmonella* Enteritidis/Typhimurium vaccine against Infantis

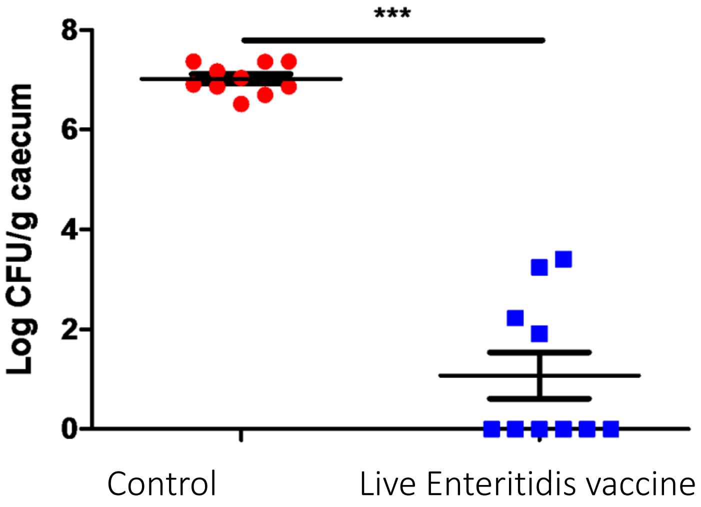
How broad is cross-protection? Unclear

Eeckhaut et al., 2018

Early protection

- Challenge 3. Critical periods of increased sensitivity, age





Colonization-inhibition
(serotype-specific effect)

1000-fold reduction in caecal colonization
at day 7 post-infection

Introduction of targeted gene deletions for future vaccines

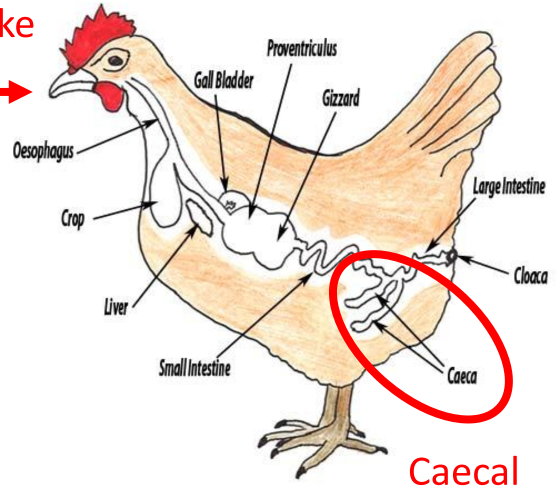
Genetically modified organisms (GMO)

- Guaranteed safety for poultry and mammals, based on pathogenesis
- Marker genes (eg. LPS, fli for serology; biochemical pathways for bacteriology)
- Risk to revert ~ zero (multiple gene deletions)
- Introduce markers that change phenotype (cfr isolation)
- Consumer acceptance? Regulatory issues?

Example: Choice of mutations based on pathogenesis

Intestinal colonization

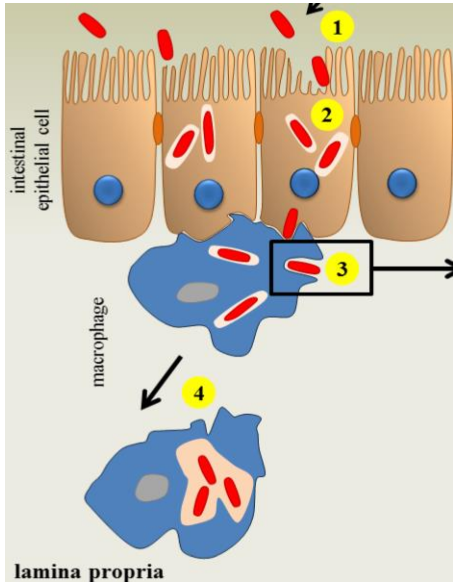
Oral uptake



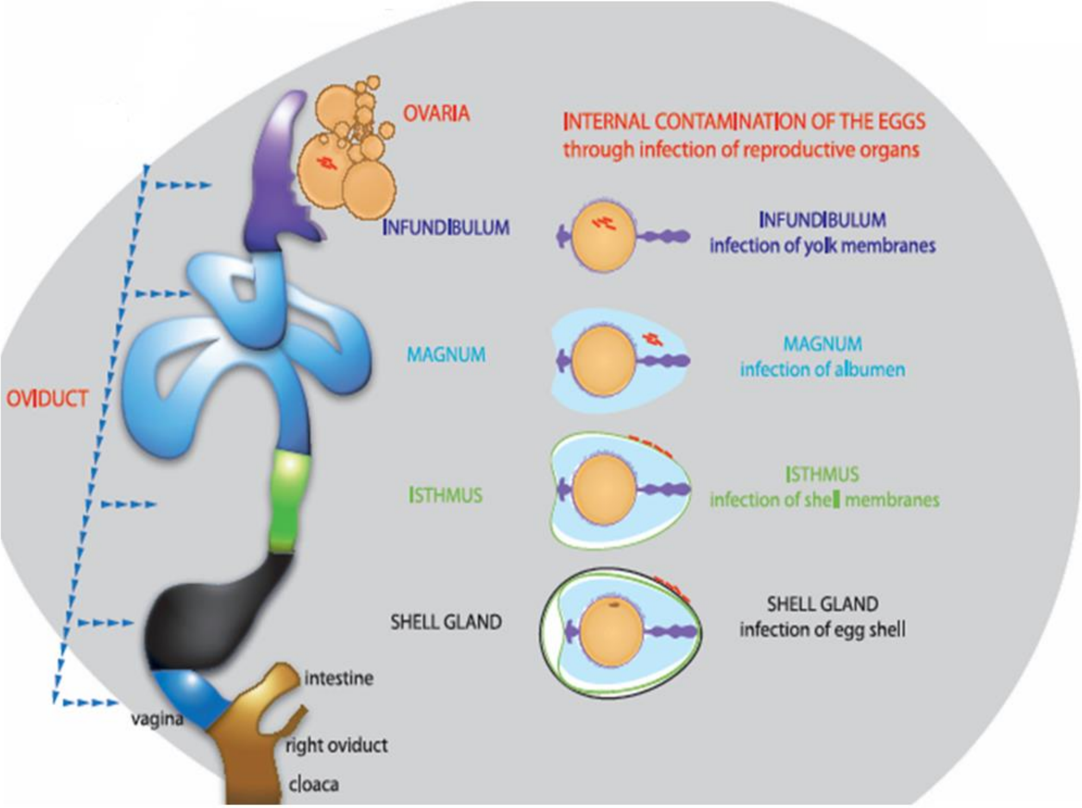
Caecal colonization

ΔhilA

Systemic spread



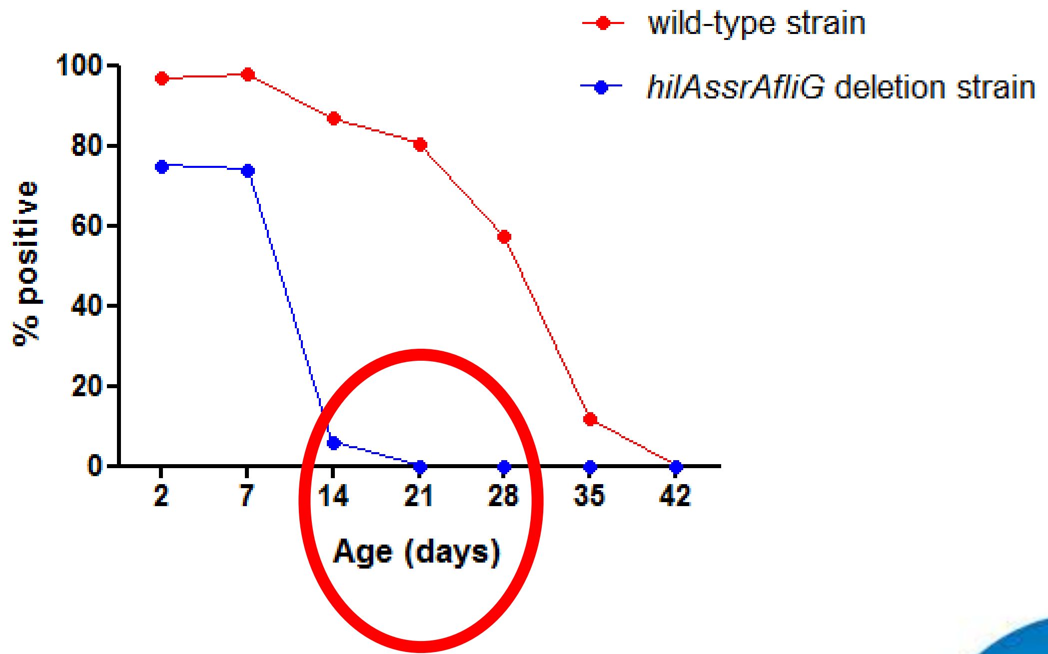
ΔssrA

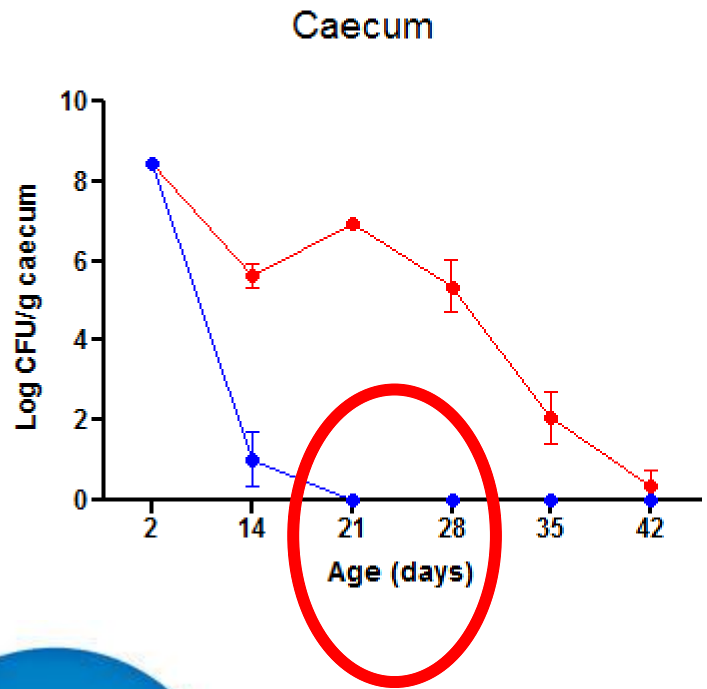


Egg contamination

ΔtolC

Example 1. A *Salmonella* Enteritidis *ΔhilA Δ ssrA ΔfliG* mutant

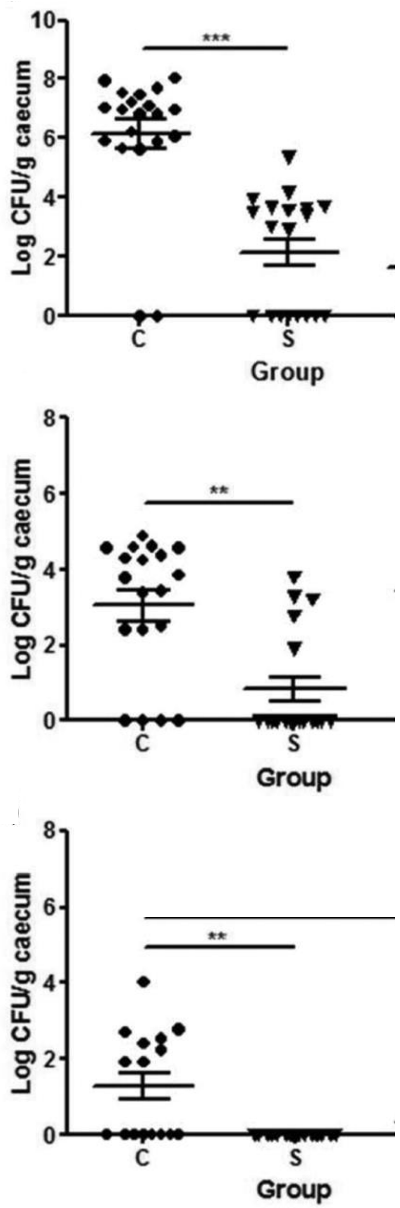


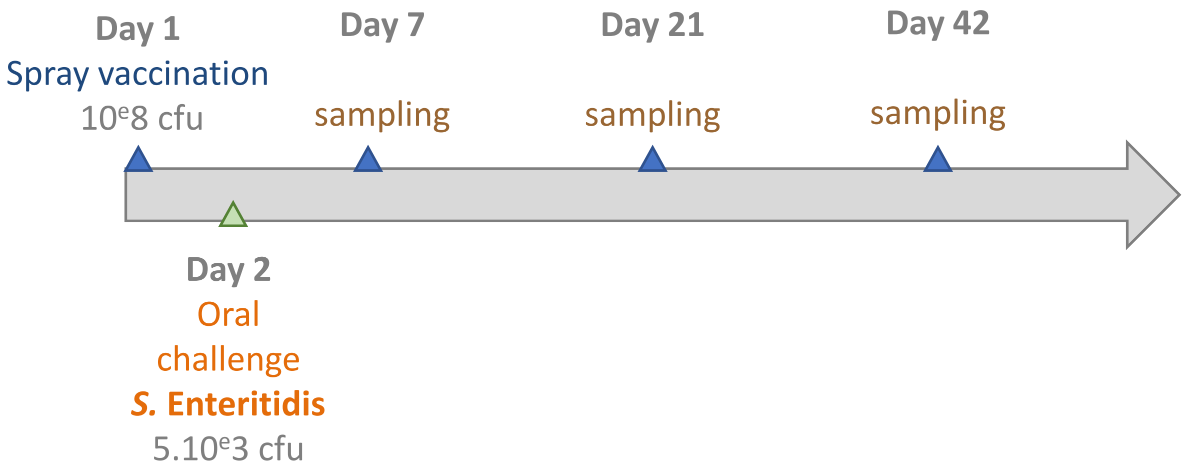


+ not pathogenic in rodent models
+ contains a serological marker
+ does not grow on MSRV

Safety confirmed

Example 1. A *Salmonella* Enteritidis *ΔhilA Δ ssrA ΔfliG* mutant





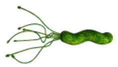
Early and persistent protection in broilers

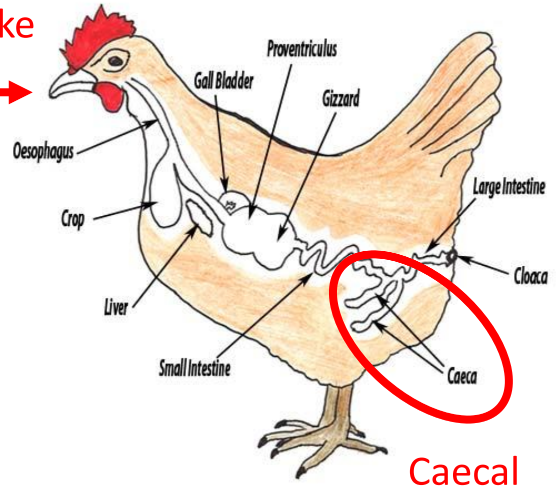
De Cort et al., 2015

Example: Choice of mutations based on pathogenesis

Intestinal colonization

Oral uptake

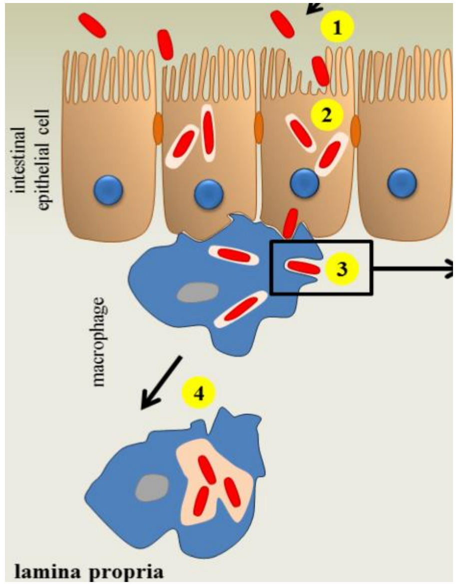




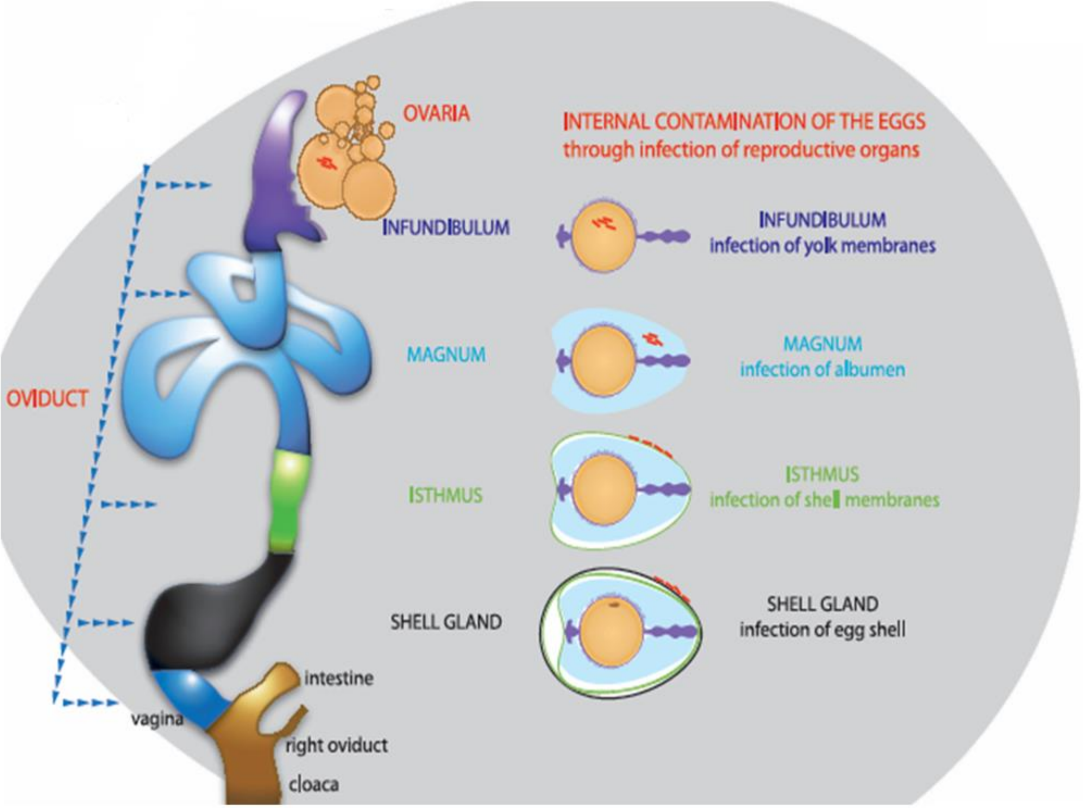
Caecal colonization

ΔhilA

Systemic spread



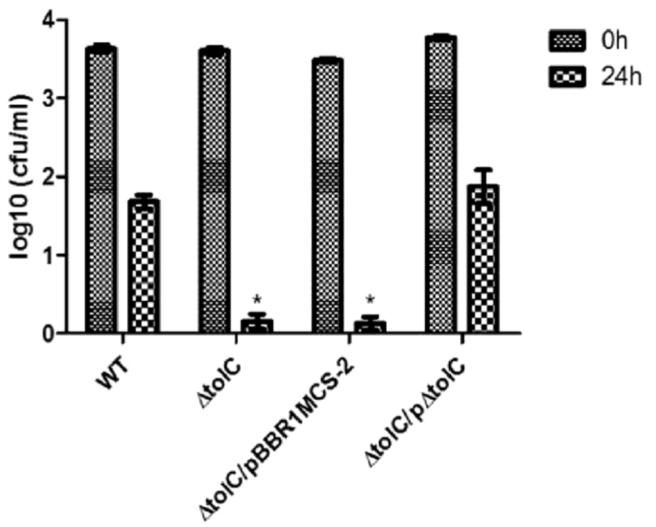
ΔssrA

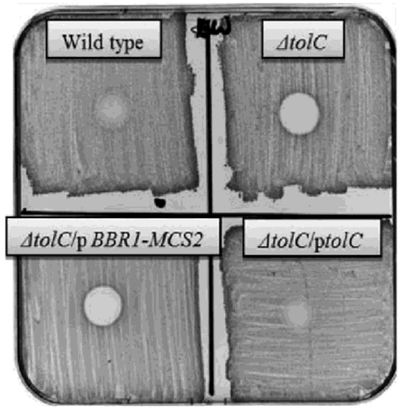


Egg contamination

ΔtolC

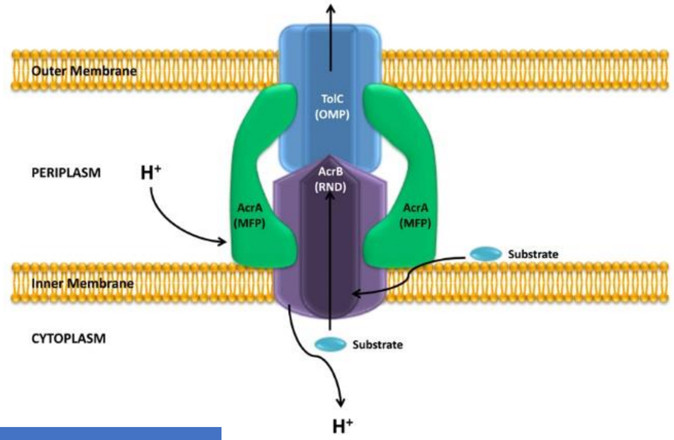
Example 2. A *Salmonella* Enteritidis *ΔtolC* mutant



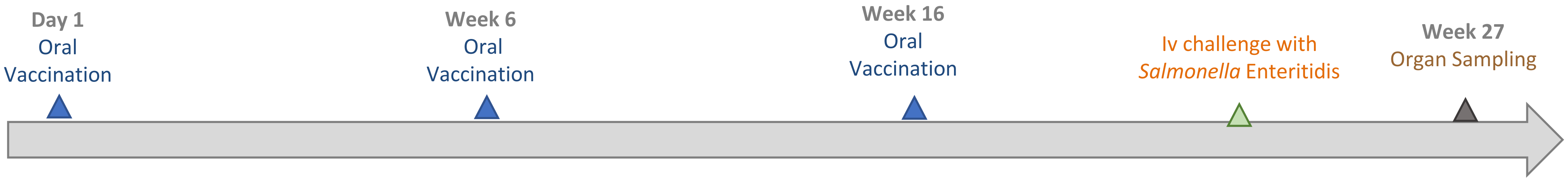


No egg white survival at body temperature, no transmission

+ defects in resistance in environment
+ defects in resistance against host responses

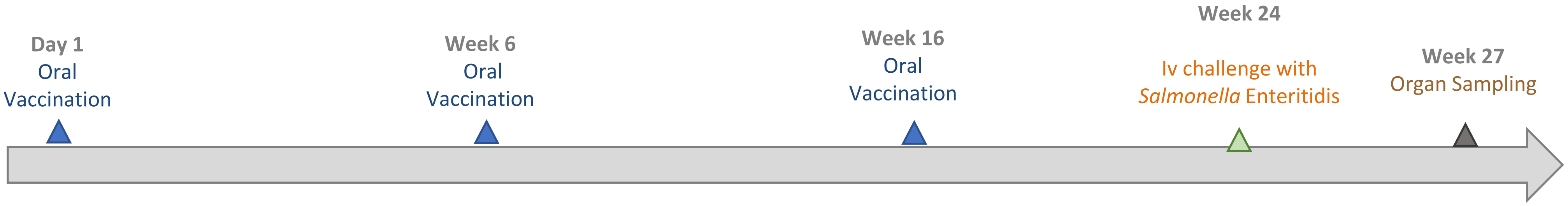


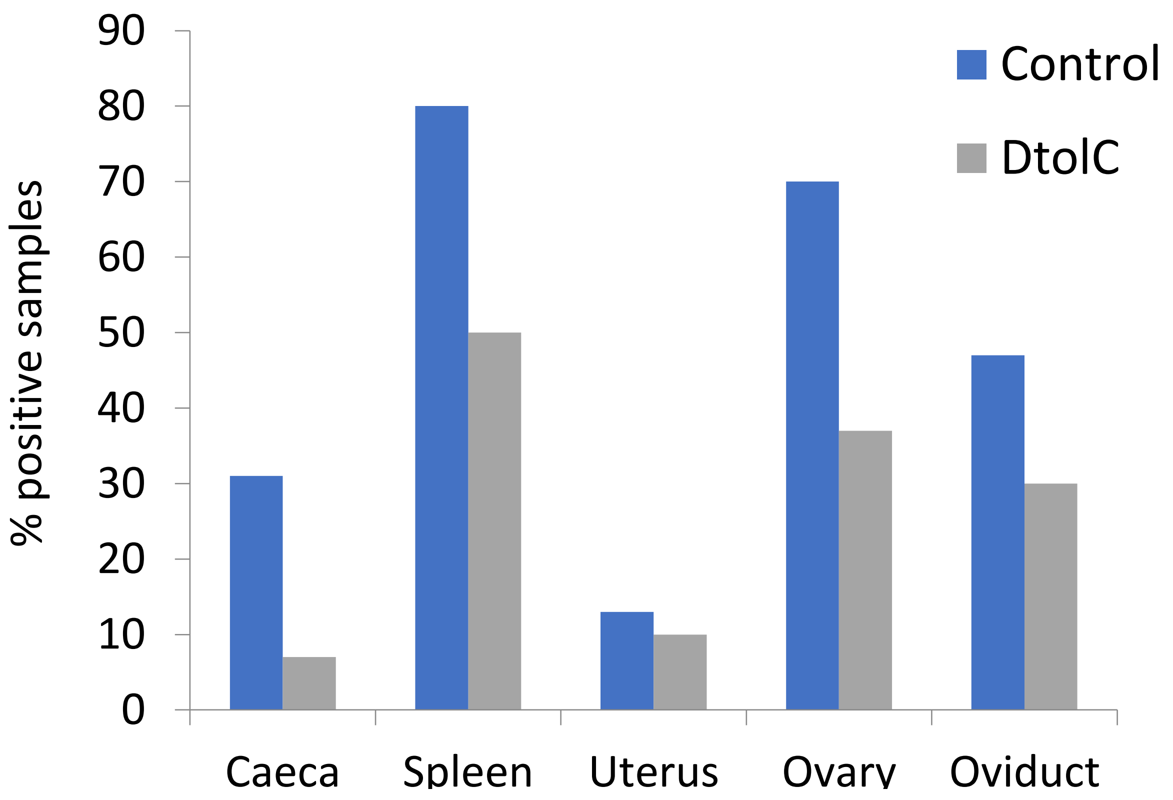
No isolation of vaccine strain

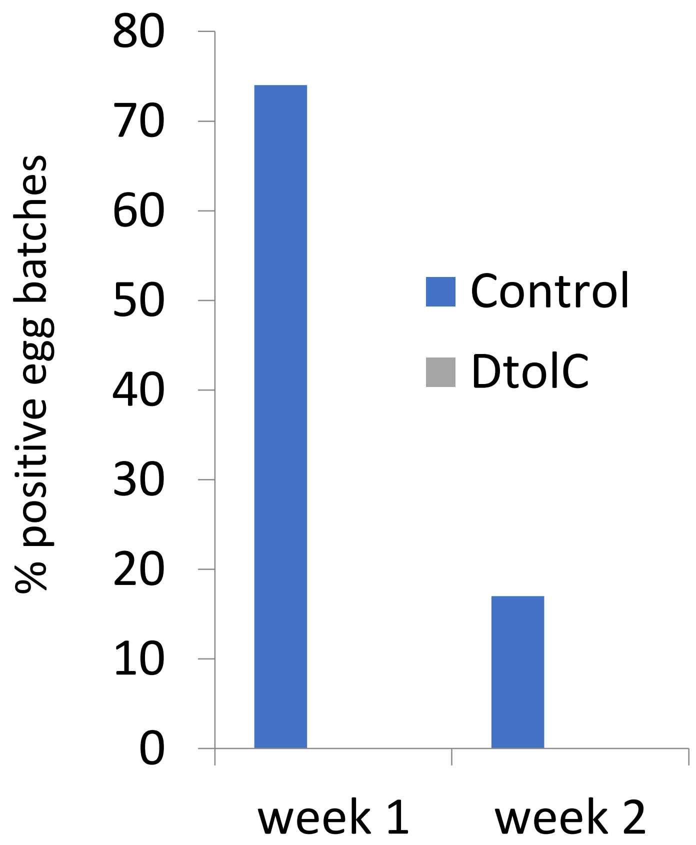


Raspoet et al., 2019

Example 2. A *Salmonella* Enteritidis *ΔtolC* mutant

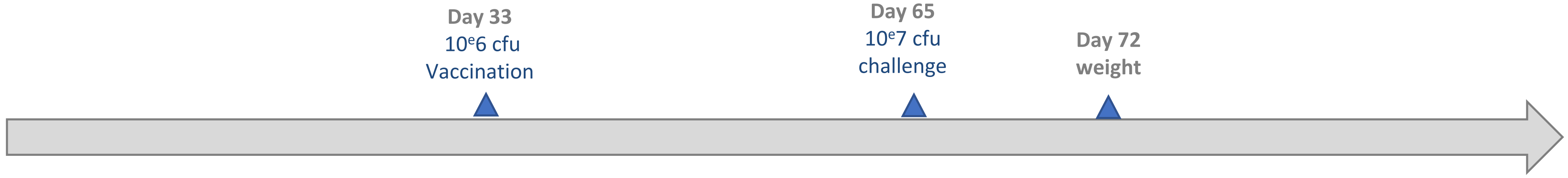


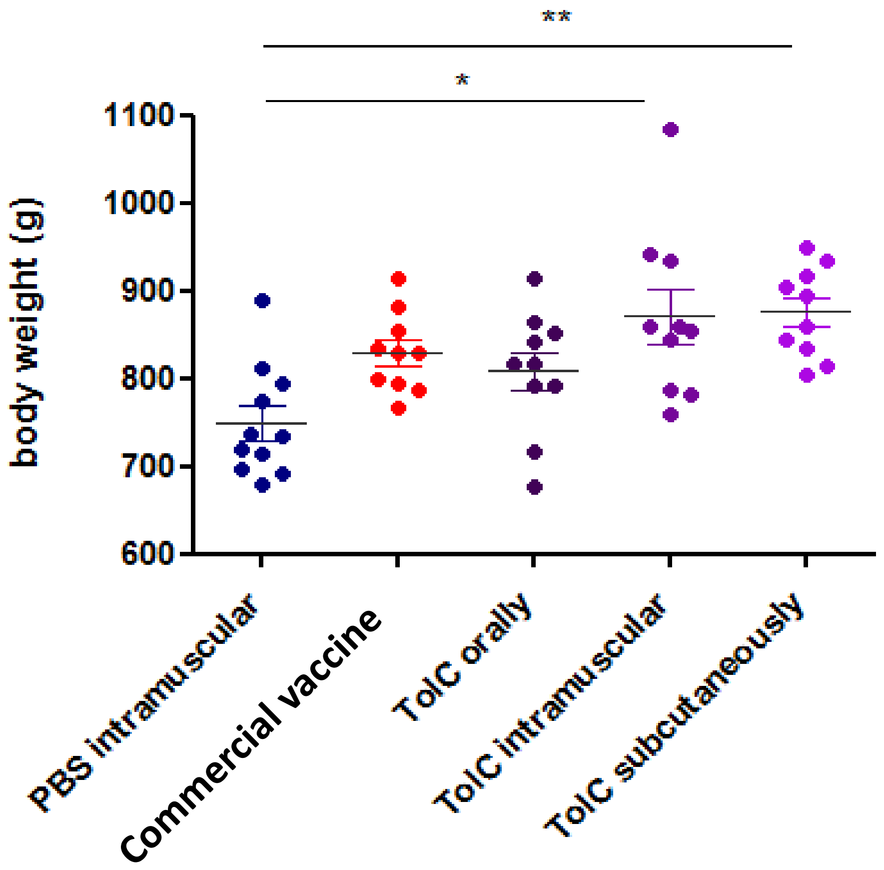




Kilroy et al., 2016

Example 2. A *Salmonella* Gallinarum *ΔtolC* mutant





Challenge 5. Regulatory aspects

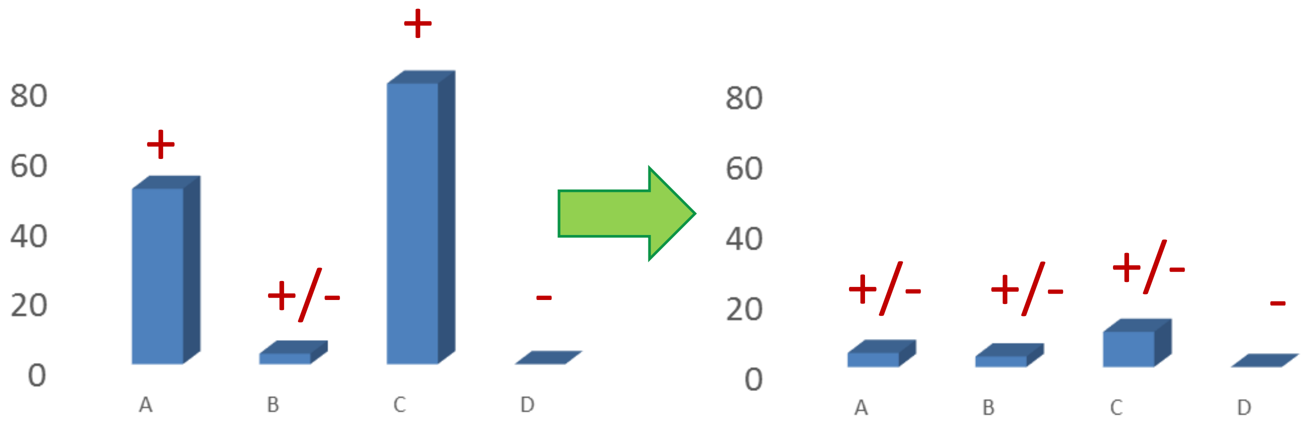
- GMOs
- Transfer mutations to other serotypes/strains for rapid vaccine production
- …

Challenge 6. Evaluating safety and efficacy under field conditions

- Expectations and misconceptions
  - Flock still positive = vaccine did not work?

    - Was biosecurity optimal?
    - What about sources of *Salmonella*? Infection pressure?

Can work because less gut colonization, shedding, organ spread …
but only combined with good biosecurity measures



What can we expect in the future?

- *Salmonella* will remain a problem because of
  - Globalization and trade
  - Intensification of poultry production
  - Antibiotic resistance?
  - The asymptomatic nature of the infection (food poisoning strains)
  - Specific virulence traits
  - New serotypes, strains

→ Monitoring and control is essential and cannot be weakened !

What can we expect in the future?

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Technologically, platforms for serotype, strain or flock-specific vaccines are easy to set up