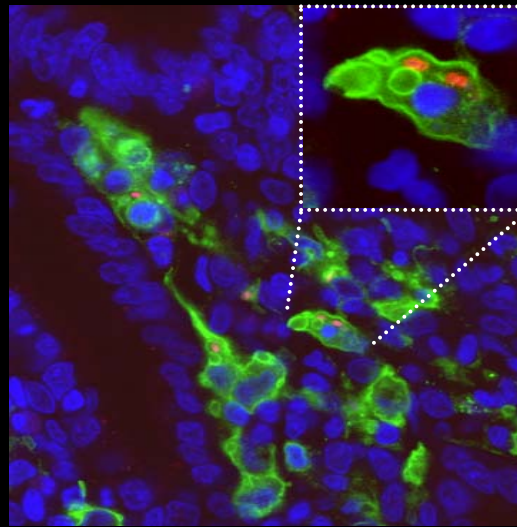
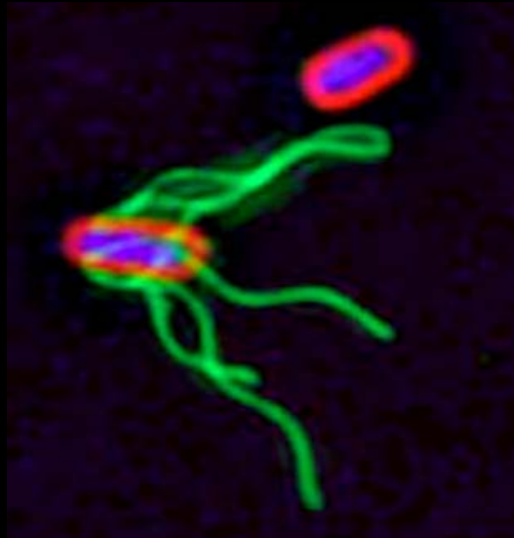


Toward control of bacterial infections of poultry using novel 3R methods

Mark Stevens



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www.iah.ac.uk/research/enteric

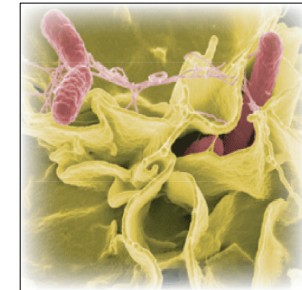
Research on bacterial pathogens of poultry at IAH

We aim to improve animal welfare and food safety by defining bacterial and host factors influencing the carriage and virulence of:

Salmonella enterica

Acute enteritis in humans. Asymptomatic-to-typhoidal disease depending on strain and host-specific factors

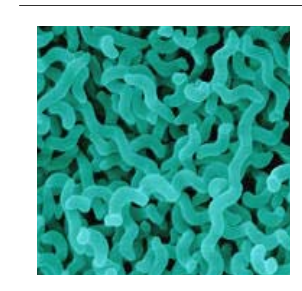
Chickens, pigs & cattle



Campylobacter jejuni

Acute enteritis in humans. Mostly asymptomatic in poultry (cf. vibriotic hepatitis)

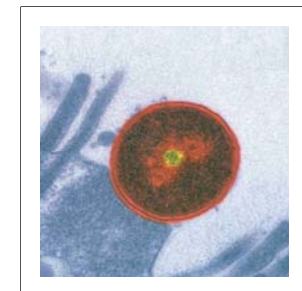
Chickens



Escherichia coli

Colibacillosis and Poult Enteritis & Mortality Syndrome

Turkeys



Why study bacterial pathogens of poultry at IAH?

- Target animal models at high containment
 - Bacterial strains of defined virulence
- An ability to manipulate pathogens...
 - Random and targeted mutagenesis
- ...and natural hosts
 - Inbred chickens of defined MHC type
 - Lines of defined resistance to *Salmonella* & *Campylobacter*
 - Conventional to germ-free status
 - In ovo* bursectomy, depletion & adoptive transfer
 - Immunological 'toolboxes'
- Research at all levels from molecules to intervention
- Nucleus of molecular, genetic, immunological & veterinary expertise

Strategic objectives

1. To define the role of *Salmonella*, *Campylobacter* and *E. coli* genes in food-producing animals
2. To define the role of host components, with emphasis on the role of innate & adaptive immunity and heritable resistance
3. To define the structure, function and interactions of key factors
4. To interpret the impact of genetic variation on pathogenesis and protection
5. To develop, test and refine methods of control

Expected outcomes

Fundamental knowledge of the role of bacterial and host components during infection of target animals and the mechanism by which they act

Applied to

- Develop, test and refine vaccines
- Develop non-immune intervention strategies
- Selective breeding & transgenesis
- Optimise diagnosis, surveillance & risk analysis

Funding from Defra and industry is vital for translation to practice

Challenges in the post-genomic era

Complete or partial genomes exist for *Salmonella* (23), *E. coli* (15), *Campylobacter* (17) and chickens **but...**

What roles do genes play in pathology, protection and transmission?

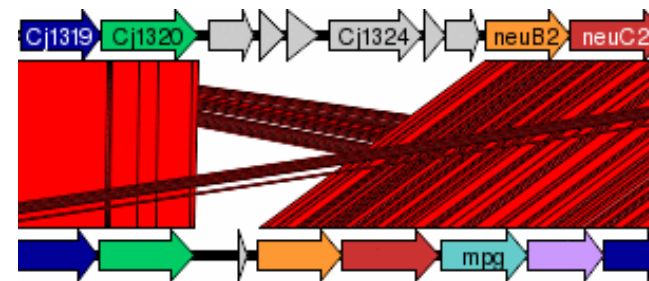
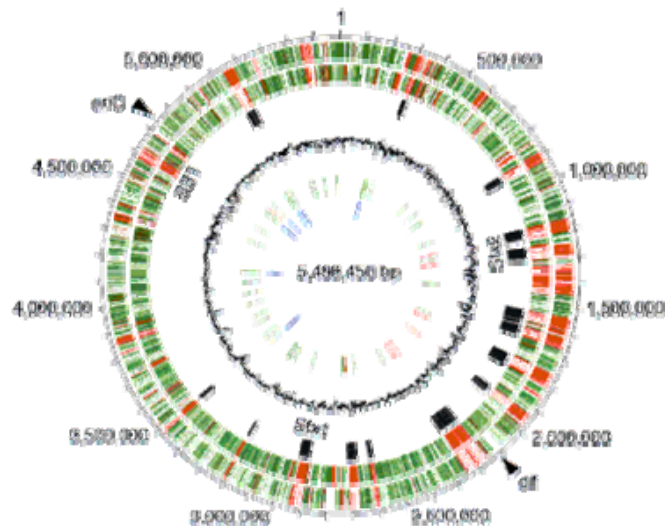
When, where and at what level are they expressed?

How conserved are they in natural populations?

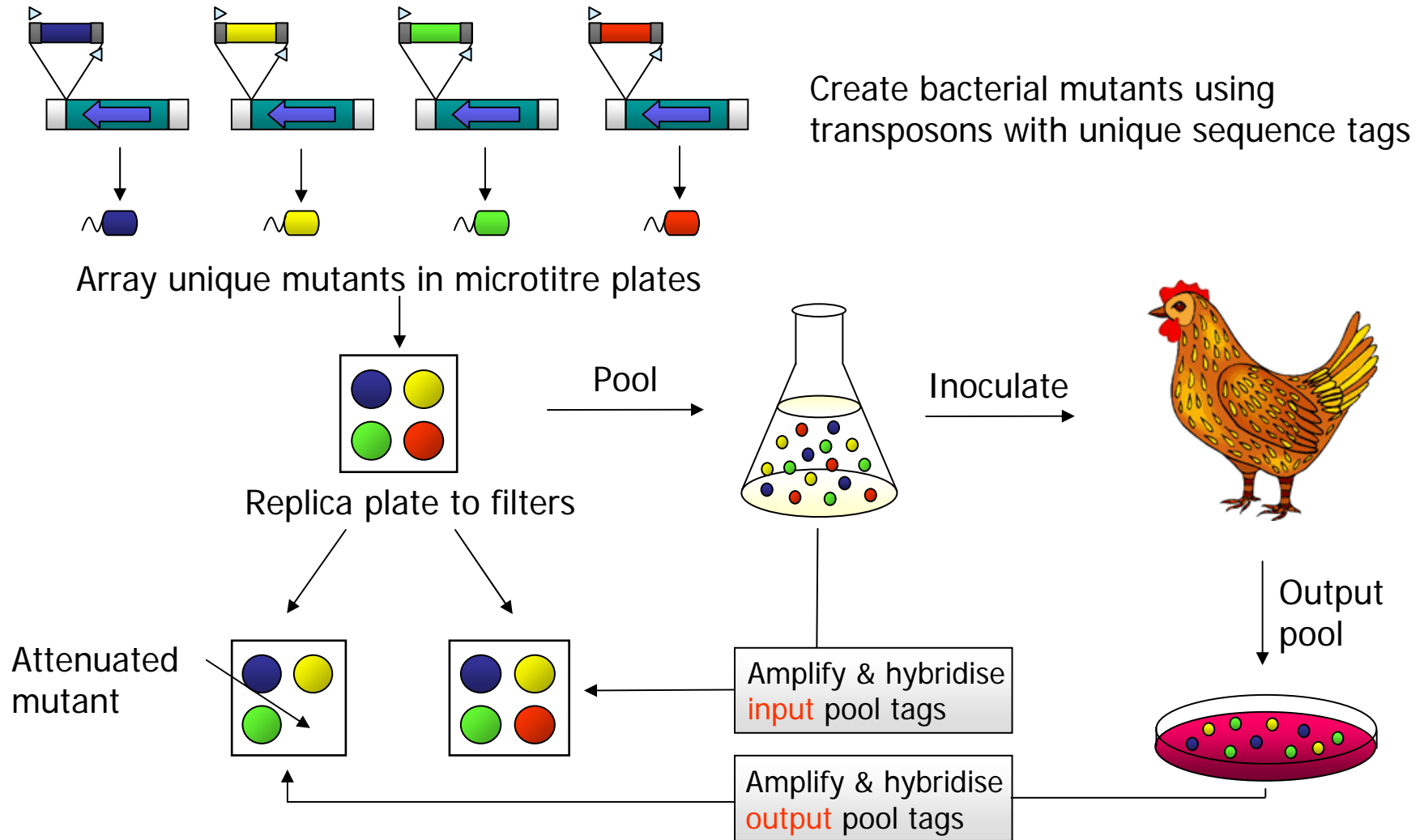
Does redundancy exist?

What is the impact of variation in repertoire or sequence?

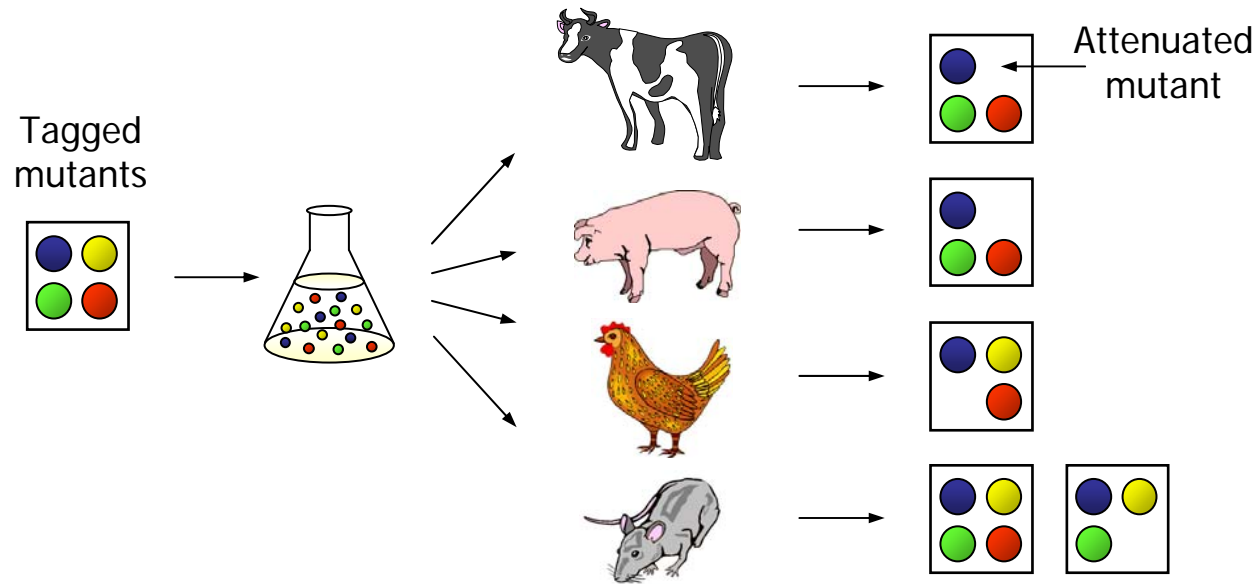
How do the encoded proteins work?



Identification of bacterial virulence factors by signature-tagged mutagenesis

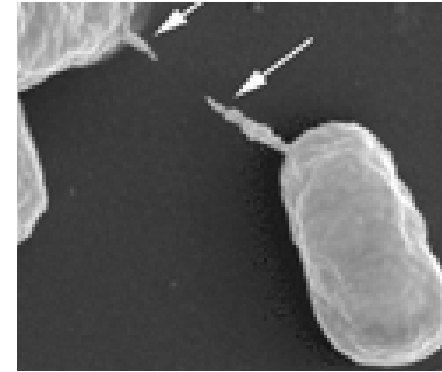
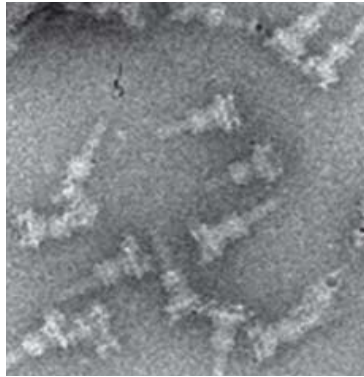
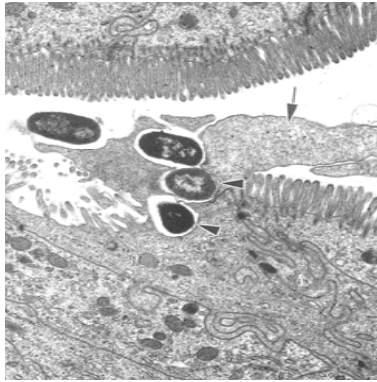


Identification of *Salmonella* virulence factors by signature-tagged mutagenesis



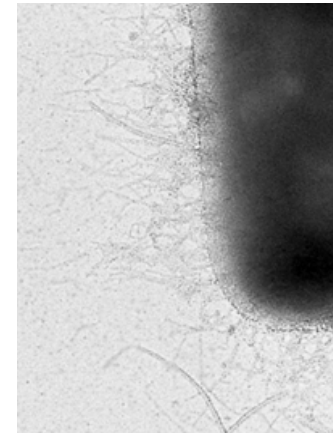
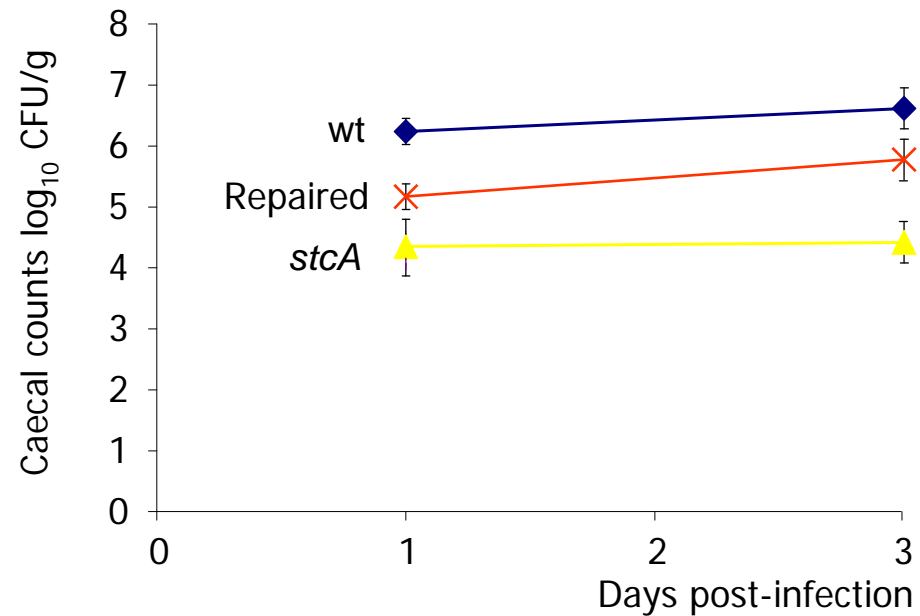
- 1045 *S. Typhimurium* mutants screened in calves, pigs, chickens & mice
- 227 attenuated mutants identified
- Factors playing a conserved role identified
- Host-specific factors identified
- Mice often failed to detect factors needed in livestock

'Molecular syringes' vital for invasion and replication in mammals play little role in colonisation of the avian gut



- Type III secretion systems mediate colonisation and enteritis in mammals
- Not essential for intestinal colonisation of chickens
- Weak role in systemic disease (fowl typhoid)
- Inhibitors and vaccines under test in livestock unlikely to be useful in poultry
- Studies in the natural host are vital

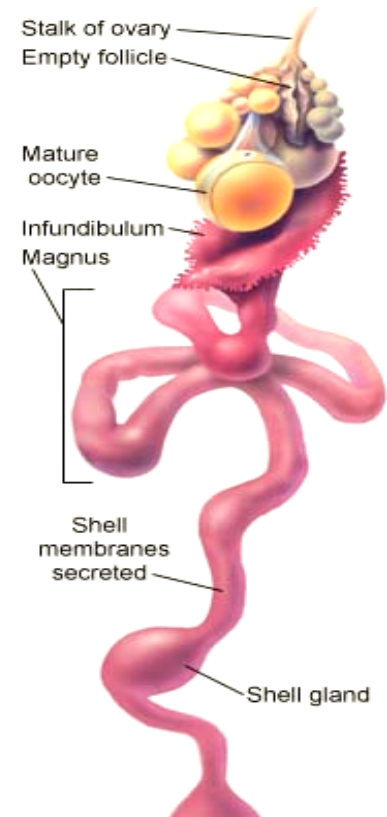
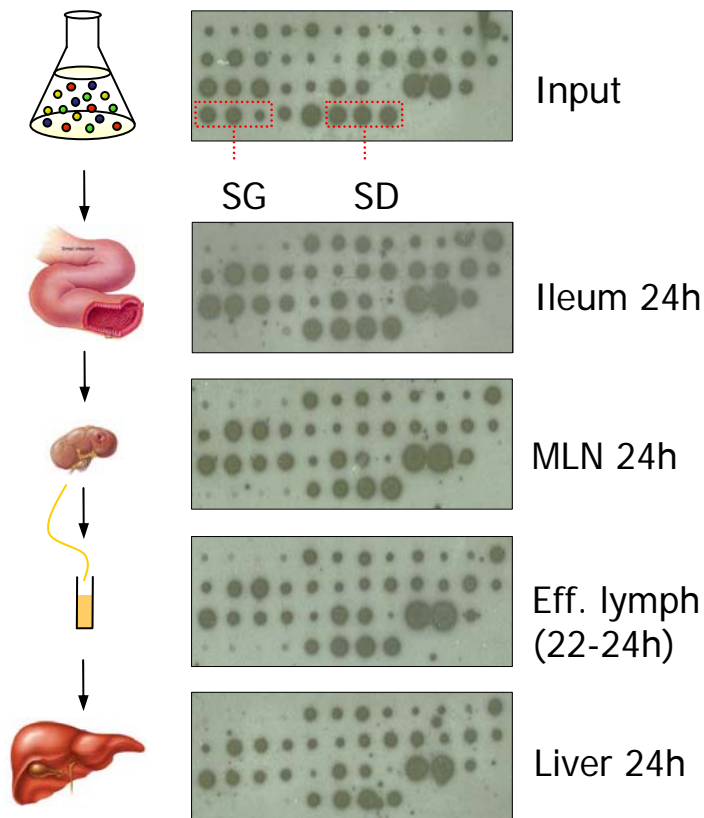
Hair-like surface structures (fimbriae) mediate persistence of *Salmonella* in chickens



- Several fimbriae play a role in colonisation of chickens (Stb, Stc, Sth, Csg)
- Attenuated mutants may be useful as live vaccines
- Purified fimbriae may elicit protective responses

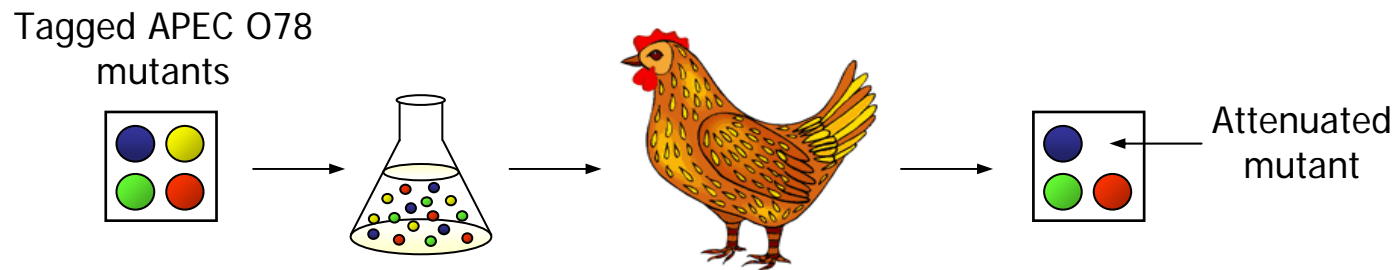
Analysis of the temporal and spatial roles of *Salmonella* genes

- The same tagging methods can be used to track the fate of *Salmonella* mutants through tissues over time
- This is to be used to understand how some types of *Salmonella* leave the gut and contaminate eggs or cause typhoid



Combating avian colibacillosis by application of proven technologies

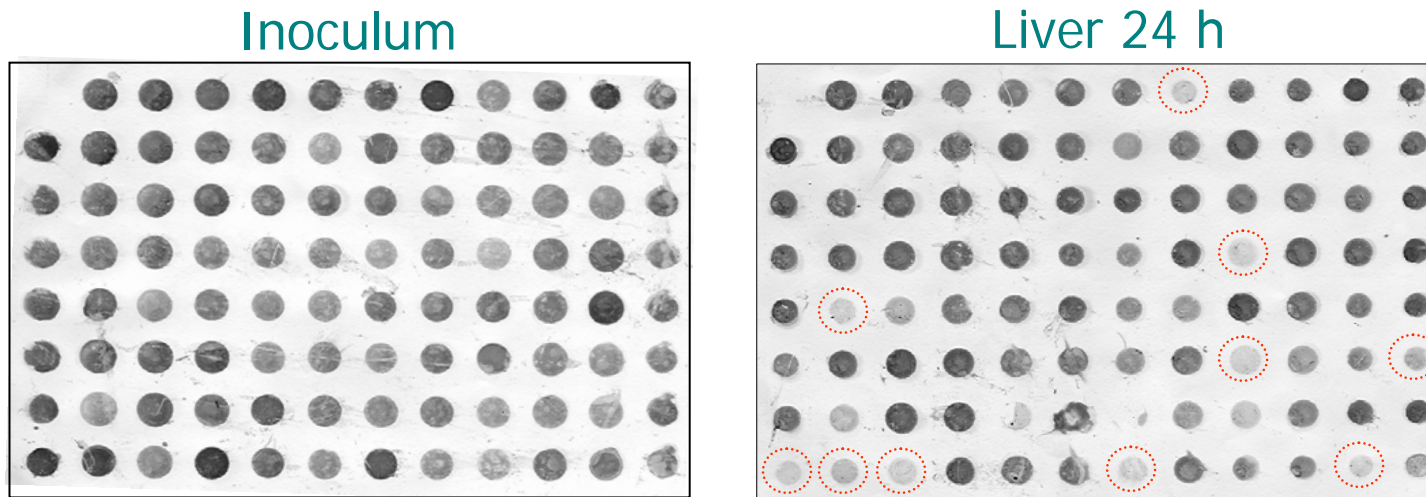
BBSRC-British Poultry Council project with support from BUT



- Screening of signature-tagged APEC O78 in turkeys
- Construction and characterisation of defined mutants
- Surveys to confirm conservation of key factors
- Pilot vaccine trials

Progress to date

- Reliable models of turkey colibacillosis developed
- Intra-air sac, intra-tracheal & intra-venous routes compared \pm TRTV
- Library of ca. 3000 random APEC O78:K80 mutants created
- Genes required for persistence in lung & systemic spread being mapped



- Attenuation can be detected prior to onset of clinical signs
- Animal use reduced by screening mutants in pools

BPC-supported research in the press

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Thursday, May 24, 2007

Dieter Lütticken Award

UK - The annual award for research into reducing, refining and replacing the use of pharmaceuticals in poultry production

The Dieter Lütticken Award, which replaces the use of pharmaceuticals in poultry production, is intended to be awarded to the best development, in Tokyo, Japan.

Dr Stevens' laboratory has developed several animal models to study the pathogenesis of enteric bacterial infections of livestock and uses novel genetic methods to dissect the molecular basis of bacterial virulence.

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NEWS

Prof Stevens gets Dieter Lütticken Award // 27 Aug 2007

The British professor Mark Stevens has been honoured with the Intervet Dieter Lütticken Award at the Sixth World Congress on Alternatives, held on August 24th in Tokyo, Japan.

Stevens, attached to the Institute for Animal Health in Compton, UK, received his award for his excellent contribution to the principle of 3Rs (Refinement, Reduction, Replacement) for the development and production of veterinary medicinal products.

Stevens' laboratory has developed several animal models to study the pathogenesis of enteric bacterial infections of livestock and uses novel genetic methods to dissect the molecular basis of bacterial virulence.

Relevant

Attila von Hanko, president of Intervet Japan, who presented the award, with a prize fund of €20,000 said: "The work of Prof Stevens and his colleagues is highly relevant in terms of the 3Rs, to better understand the pathogenesis of bacterial

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In the News

Professor Mark Stevens (right) receiving his award from Attila von Hanko, president of Intervet Japan

UK professor receives Intervet honour

At the 6th World Congress on Alternatives, Professor Mark Stevens of the Institute for Animal Health (Compton, UK) was honoured with the Intervet Dieter Lütticken Award. This recognises his contribution to the principle of the 3Rs (Refinement, Reduction, Replacement) for the development and production of veterinary medical products.

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Intervet UK Ltd is a company registered under registration no. 948942 with a registered office at Walton Manor, Walton, Milton

Previous winners of the award include:

- 2004: Professor Andrew Hemphill from the University of Bern for his outstanding research into the development and evaluation of *in-vitro* approaches for culture and investigation of helminthic and protozoan parasites, in particular *Neospora caninum* and *Echinococcus multilocularis*.

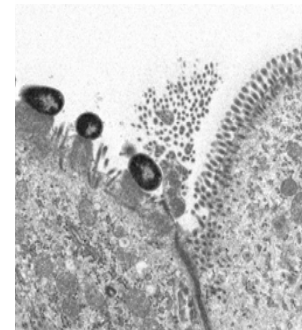
Aetiology of poult enteritis & mortality syndrome

- BPC-funded researchers defined the cause of first PEMS case in the UK
[Vet. Rec. \(2006\) 159:209-10.](#)

SHORT COMMUNICATIONS

Poult enteritis and mortality syndrome in turkeys in Great Britain

F. CULVER, F. DZIVA, D. CAVANAGH,
M. P. STEVENS



- Associated with concurrent TCoV/TAstV and EPEC infection
- Ongoing interest as EPEC are potential human pathogens and are closely related to EHEC O157
- No evidence that EPEC isolated from PEMS cases have acquired Shiga toxin genes

Research on *Campylobacter* at IAH

- We also use targeted mutagenesis to define roles for *Campylobacter* genes in poultry
Capsule, motility & amino acid metabolism are important
- The role of sugar modifications of surface structures is under study
- Factors expressed in the chick gut that elicit host immunity defined
- Protective efficacy of live-attenuated *Salmonella* expressing some of these factors under test
- Population dynamics of *C. jejuni* studied to define the number of bacteria required to initiate infection & transmit
- Role of host parameters in clearance also studied

Identification of traits associated with gut health and improved responses to enteric pathogens

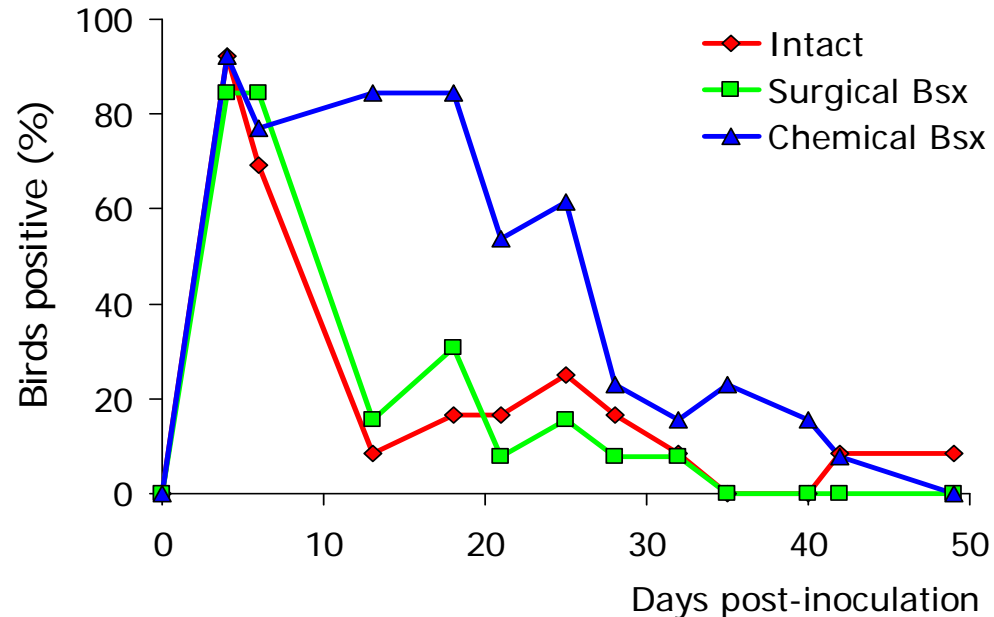
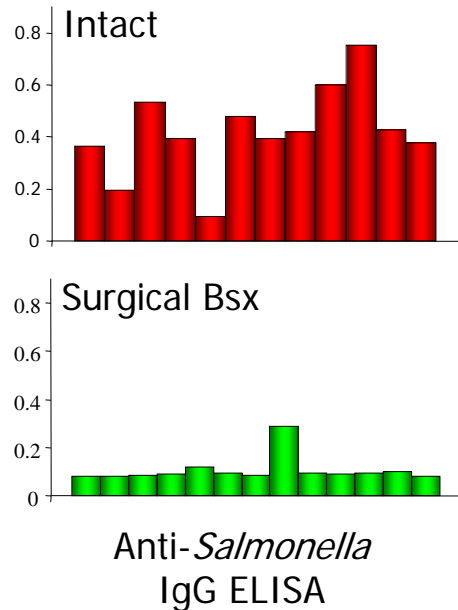
P. Kaiser et al

- Inbred and commercial chicken lines exhibiting heritable differences in resistance to *Salmonella* and *Campylobacter* exist. These differ in:
 - Production of pro-inflammatory cytokines and chemokines
 - Heterophil function
 - Defensin production
- Such differences are under genetic control
- Ongoing projects aim to identify genetic traits and properties that correlate with protection
- Expected to yield resistance markers for selective breeding



Analysis of the role of host immune compartments in clearance of enteric pathogens

A. Smith et al



- Surgical removal of the source of B cells during embryo development revealed that antibodies are not needed to clear *Salmonella*
- The role of different immune cell types is being assessed by depletion and adoptive transfer
- May identify responses needed for clearance and/or vaccine protection

Role of gut flora in the development of resistance to enteric pathogens



- How does possession of a gut flora protect?
Competitive exclusion vs. maturation of the immune system
- Chickens reared at IAH at germ-free status
- Expansion of immunological repertoire and function followed over time, with and without a gut flora
- Impact of mucosal immune development on resistance to colonisation by *Salmonella* & *Campylobacter* to be tested \pm flora
- May yield preparations that can be given in early life

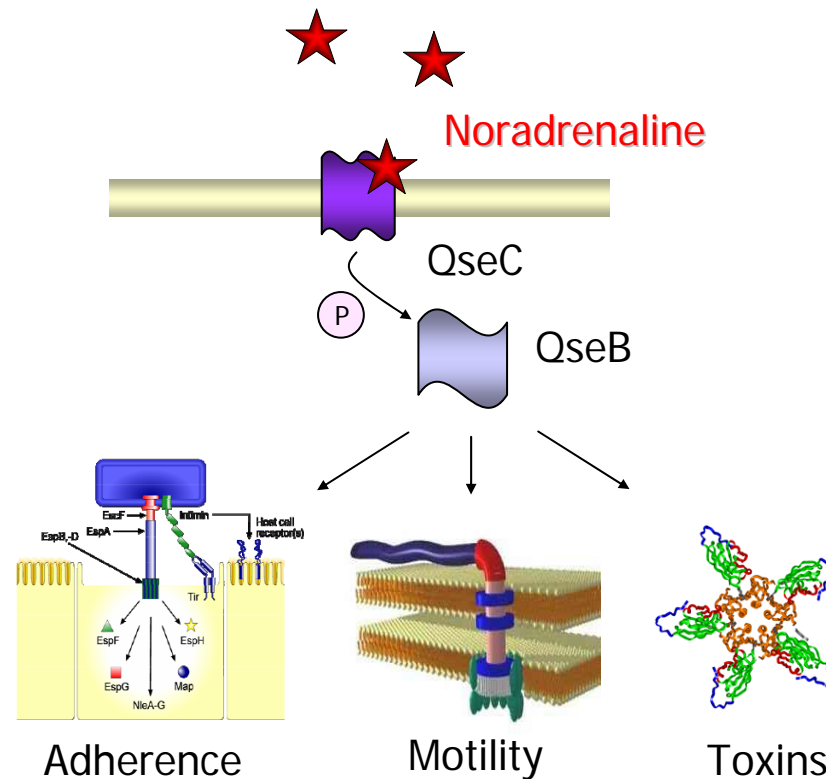
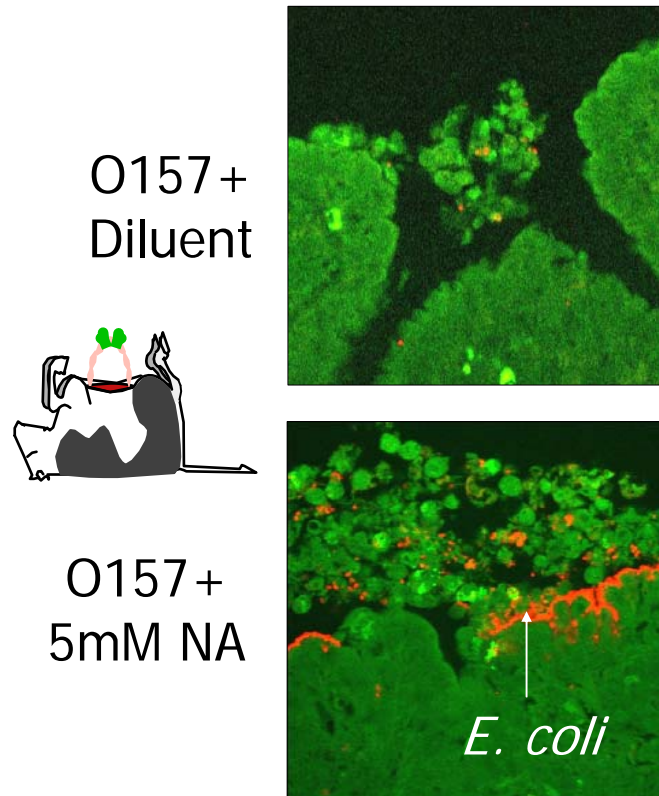
Stress and susceptibility to microbial infection



- Transportation can reactivate subacute *Salmonella* infection in pigs
- Mixing (social) stress in pigs increases faecal excretion of *Salmonella*
- Physical handling of pigs can increase excretion of *E. coli*
- Evidence emerging that chickens exhibiting signs of stress have elevated levels of *Campylobacter*

The host stress hormone noradrenaline communicates with enteric bacteria

- *Salmonella*, *Campylobacter* & *E. coli* respond to NA by growing faster and deploying virulence factors
- *Salmonella* & *E. coli* have a receptor for NA
- Antagonists of hormone signalling may have therapeutic potential



Concluding remarks

- IAH fills a vital niche by using natural hosts to understand diseases
- *Salmonella*, *Campylobacter* & *E. coli* pose an ongoing threat to food safety and may adversely affect animal health
- Portfolios of bacterial virulence factors have been defined
- Host genetic traits and immune responses associated with protection defined
- The information is being used to develop and test control strategies
- Input from Defra and industry is vital for translation to practice

Acknowledgements

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