Origin of the typhoid and salmonellosis meetings

Split after first meeting into two, one became ASM Salmonella meetings
Typhoid fever by region

- High incidence (>100 per 100,000 per year)
- Medium incidence (10–100 per 100,000 per year)
- Low incidence (<10 per 100,000 per year)

26.9 million cases
Mortality 1% or ~250,000 per annum

Non-typhoidal salmonella

This map shows homogeneity whereas typhoid is a patchwork

Salmonella typhi, the bacteria

- A monophyletic serovar of S. enterica that causes typhoid
  - Only emerged once several thousand years ago!
- Produces Vi capsule and novel toxin
- Human restricted,
  - Non-zoonotic!
- Carrier state

Paratyphi A a distinct monophyletic serovar
First controlled challenge model for typhoid for ~50 years

Initially funded by The Wellcome Trust

Quailes strain of S. Typhi recovered from original studies and made at GMP

Investigating the pathogenesis, immunology, vaccinology of Typhi and Paratyphi A
A human challenge model for typhoid/paratyphoid

- **1-5x10^3** Attack rate
  55%

- **1-5x10^4** Attack rate
  65%

Still looking for volunteers!
The emergence of typhoid symptoms in an individual challenged with Salmonella Typhi

Early asymptomatic signature
- Cytokines
- Transcript?

Differential response
- Transcriptional signature
- T cells (Regs)
- Cytokines
- Antibody (B cell)

Typhoid

Temperature (°C)

C-reactive protein (mg/L)

Christoph Blohmke
More persistent shedding of S. Typhi without symptoms or obvious blood carriage

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- How common is this in the field, is this the real typhoid?
- Typhoid is a stealth infection not always driving disease
Shedding of S. Typhi Ty2 ssaV (SPI-2) aroC and S. Typhimurium TML ssaV aroC in the stools of volunteers

S. Typhi Ty2 ssaV aroC

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S. Typhimurium TML ssaV aroC

- No Shedding + Shedding

Days after oral challenge

S. Typhi Ty2 ssaV aroC

S. Typhimurium TML ssaV aroC

ACUTE PHASE PROTEINS UP ONLY IN TYPHIMURIUM VOLUNTEERS
Theoretical differences in the pathogenicity of zoonotic non-typhoidal salmonellosis and typhoidal disease

Non-typhoidal Salmonella

- Luminal replication and shedding
- Inflammation
- Neutrophil infiltrate
- Limited dissemination

Salmonella Typhi

- Shedding from gallbladder

Theoretical differences in the pathogenicity of zoonotic non-typhoidal salmonellosis and typhoidal disease

Theoretical differences in the pathogenicity of zoonotic non-typhoidal salmonellosis and typhoidal disease
Proposal at the last invasive Salmonellosis meeting in Dhaka, Bangladesh, 2013

• We form an international consortium to map and genotype S. Typhi/Paratyphi A across the world
• We create a central web site based on free software to coordinate this
• We design simple SNP-based assays for field testing
• We use this to advocate typhoid control
Organization of a global collection of S. Typhi for genome sequencing

2,000+ isolates
63+ countries
6 continents
Phylogeographic analysis of the dominant multidrug resistant H58 clade of *Salmonella* Typhi identifies unappreciated inter- and intra-continental transmission events


*Nature Genetics in press this week*
S. Typhi Haplotype H58 has emerged over the past 20 years to dominate globally.
H58 is associated with drug-resistant genotypes
H58 is a hot spot for quinolone related mutations

- Inner circle: Regions within continents
  - South Asia
  - South-east Asia
  - East Asia
  - Western Asia
  - North Africa
  - Central Africa
  - East Africa
  - West Africa
  - Southern Africa
  - South Africa
  - Africa
  - Oceania
  - Australia
  - Western Europe
  - Eastern Europe
  - Southern Europe
  - North America
  - South America
  - Unknown

- Outer circle: gyr and par mutations
  - One gyrA
  - One gyrB
  - Two gyrB
  - One gyrA & parC
  - One gyrA & parE
  - Two gyrA & one parC
  - Two gyrA & one parE
  - One gyrA, gyrB and parE

- H58
- non-H58

% of isolates

Amino acid substitution

H58

16
Like all Typhi, H58 is still undergoing genome streamlining, through transposition.

Genomic signature of multidrug-resistant Salmonella enterica serovar typhi isolates related to a massive outbreak in Zambia between 2010 and 2012.

Holt 2011, PLoS Negl Trop Dis
The dissemination of *S. Typhi* H58

Emerged ~30 years ago
Global dissemination of S. Typhi H58 as a timeline
Phylogenetic relationship of African isolates within the H58 tree provides evidence of a recent expansion/epidemic

Kenya (2004-9)

Tanzania (2008-9)

Malawi (2011-13)

Tanzania (2008-9)

South Africa (2010-12)

Need to fill in the gaps
Genotypes in Malawi

Salmonella BSI at QECH, November 2010-August 2014

H58
Why is the H58 lineage so successful?

- Is it just antimicrobial resistance? (what about other AMR lineages which are less successful)
- H58 has a unique SNP repertoire with some interesting mutations e.g. effectors
- How do you assess fitness in a host restricted pathogen?
- Human challenge?
- More in depth molecular clinical analysis
S. Typhi in the Pacific region are generally island-specific

Is this an opportunity for an eradication programme?

H58 not dominant yet
How did typhoid evolve?

• Single point of origin followed by global dissemination

• Human restriction

• Gene acquisition (e.g. Vi and typhoid toxin)

• Genome degradation (~300 pseudogenes)

• Change of niche from gut to systemic system & carriers
Invasive non-typhoidal Salmonellosis in Sub-Saharan Africa – does this involve human to human transmission?

Non-typhoidal Salmonella (NTS) common in blood stream infections in sub-Saharan Africa

Dominant serotypes
- S. Typhimurium 50-80%
- S. Enteritidis 10-40%

Sam Kariuki
Rob Kingsley
Chinyere Okoro
S. Typhimurium iNTS isolates are from two related clades ST313

- >90% of iNTS isolates in two clusters not found outside of Africa
- One cluster is chloramphenicol resistant
Time-dependent phylogeographic analysis using BEAST

BEAST tree

Bayesian evolutionary analysis by sampling trees

BEAST – integrates temporal, geographic and phylogenetic information

HIV Prevalence

Some *S. Typhimurium* ST313 have altered enteropathogenicity

Aspect of this may be true for *S. Enteritidis* in Sub-Saharan Africa (Nick Feasy)

**Bovine models - Calf ileal loop experiments**

**Streptomycin-pretreatment in murine models**

**Impaired inflammasome induction**
S. Typhimurium ST313 summary

- Two clades emerged to spread across Sub-Saharan Africa associated with the HIV epidemic
- Is the ST313 wave over?
- ST313 have signatures of host adaptation
- ST313 was in Africa before HIV (in primates or children locally?)
- Is there human to human transmission of some sort?

Sam Kariuki was right, journal editors and referees were wrong!
Does remarkable pathogen evolution in an IL12/23 β1 receptor deficient individual throw light on how typhoid evolved?

IL12/23 β1 receptor deficient and chronically infected with recurrent S. Enteritidis infection

- Age 12 presents with clinically severe bacteremia with *Salmonella* Enteritidis
- Treated with antibiotics and interferon γ

Next decade

- >50 episodes of bacteremia becoming less clinically severe over time
- No stool carriage just systemic site
- Eventually no signs of chronic infection
  CRP, albumin, IgG

Bacteria originally typed as *Salmonella* enteritidis but became increasingly difficult
Patient isolates show extensive mutation accumulation and genome degradation

Maximum likelihood tree

Hypermutable phenotype caused by mutS mutation
Hallmarks of host-adaptation: genome degradation

Complete pseudogene analysis of four patient isolates sequenced by PacBio

Molecular clock rate

$r^2=0.92$

Gastrointestinal serovars

Patient isolates

Extra-intestinal serovars

level comparable to host-adapted/restricted serovars
Convergent evolution with S. Typhi and S. Paratyphi A

Intestinal metabolome disrupted

Adhesins and intestinal shedding genes gone

SPI-1 dead

SPI-2 streamlined

O antigen ligase gone

Pseudogenes by pathway/locus

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What does this study tell us, if anything?

- Microbes can evolve (mutate) at dramatically different rates in different settings
- Compromised individuals or cohorts may be sources of adapted microbes. Can we spot adaptation to humans early?
- Factors such as antimicrobial treatment are exerting unprecedented selective pressures (we see this in most pathogens)
We have typhoid vaccines that work.....but....

Vi capsule, Paratyphi A O side chain

- Length of polysaccharide?
- Typhi/Paratyphi carrier proteins?
- What is a correlate of protection (antibody, bactericidal?)

<table>
<thead>
<tr>
<th>Clinical Project</th>
<th>Clinical Trial Phase</th>
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<tr>
<td>Ty21a</td>
<td>Licensed</td>
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<tr>
<td>M01ZH09</td>
<td>Phase 2, adults and children</td>
</tr>
<tr>
<td>Ty800</td>
<td>Phase 2, adults (2008)</td>
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<tr>
<td>CVD909</td>
<td>Phase I, adults (2010)</td>
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</table>
What are the immediate challenges?
Can we......

...get conjugate vaccines used effectively?
...get any typhoid vaccine used broadly?
...get diagnosis working at the bed-side?
...track and define carriers more effectively
...eradicate typhoid!

Advocacy and driving vaccines to WHO prequalification and licensing
The urgent need for new typhoid diagnostics

Salmonella Typhi and Salmonella Paratyphi A elaborate distinct systemic metabolite signatures during enteric fever

Elin Näsström¹, Nga Tran Vu Thieu², Sabina Dongol³, Abhilasha Karkey³, Phat Voong Vinh², Tuyen Ha Thanh², Anders Johansson⁴, Amit Arjyal², Guy Thwaites², Christiane Dolecek², Buddha Basnyat³, Stephen Baker², Stephen Baker² & Philip L. Felgner¹

Metabolomics

Immune profiling with a Salmonella Typhi antigen microarray identifies new diagnostic biomarkers of human typhoid

Li Liang¹, Silvia Juarez¹, Tran Vu Thieu Nga², Sarah Dunstan², Rie Nakajima-Sasaki¹, D. Huw Davies¹, Stephen McSorley³, Stephen Baker² & Philip L. Felgner¹

PCR

Serology, new antigens
What is a typhoid carrier in 2015 and where are they!

Gall bladder (2010)
Acute typhoid (2004-2008)
High incidence (>100 per 100,000 per year)

Medium incidence (10 - 100 per 100,000 per year)

Low incidence (<10 per 100,000 per year)

Wellcome Trust Strategic Award on Typhoid
Acknowledgements

Collaborators

**WTSI, Cambridge** Gordon Dougan, Vanessa Wong, Julian Parkhill, Nick Thomson, Derek Pickard, Robert Kingsley, Andrew Page, Chinyere Okaro, Jacqueline Keane, David Harris, Simon Harris, Amy Cain, Alison Mather, Elizabeth Klemm, James Hadfield, Dafni Glinos, Rob Kingsley

**Bio21, University of Melbourne** Kathryn Holt, David Edwards, Jane Hawkey

**OUCRU, Ho Chi Minh City** Stephen Baker, Duy Pham Thanh, Nga Tran Vu Thieu, Corinne Thompson, James Campbell, Guy Thwaites, Jeremy Farrar

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**WHO, Pacific Islands Division** Eric Nilles

**WHO, Fiji** Shalini Singh

**MOH, Fiji** Mike Kama

**Fiji Health Sector Support Program, Fiji** Kylie Jenkins

**IVI, Korea** Florian Marks

**Pasteur Institute, Paris** Francois-Xavier Weill

**University of Otago** John Crump

**LSTM** Nick Feasey

**MLWT-CR Programme, University of Malawi** Rob Heyderman, Chisomo Msefula

**Institute of Infection & Global Health, University of Liverpool** Melita Gordon

**MDU, University of Melbourne** Geoff Hogg, Mary Valcanis, Joan Powling, Karolina Dimovski

**LSHTM** Christopher Parry, Kim Mulholland, W. John Edmunds, Conall Watson

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