An infectious, genetically diverse Typhi carrier: A case study

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Introduction

Salmonella Typhi is an enteric bactrial pathogen, responsible for diarrhoea and typhoid fever. Long-term carriage of S. Typhi is typically asymptomatic and is generally mediated through colonisation of the gall bladder. Even when asymptomatic, long-term carriers can still contribute to transmission of S. typhi.

Case 1 Risk factors - Vomiting and diarrhoea Clinical information provided by HIV negative - 2 week history of feeling unwell Rushana Hussain No animal contact - Fever No report of recent travel - Deranged liver function tests Reported family members unwell Case 3 - COVID-19 negative Recent return of grandmother from Pakistan - Asymptomatic household contact - Stool sample -> S. Typhi Initial treatment: I.V. piperacillin-tazobactam Follow-up of all household contacts was requested No treatment issued - Blood cultures +ve for Gram -ve bacillus at 24h Infection control information was issued - Blood cluture = S. Typhi No recent travel abroad Final treatment = I.V. ceftriaxone for 2 weeks

Day 8 Day 20 5 months Day 0 Day 18

Case 2

- Symptomatic household contact
- 1 week history of feeling unwell
- Stool sample -> Salmonella sp.

Treatment: 7 days azithromycin

- No recent travel abroad

Case 4

- Asymptomatic significant contact
- Stool sample -> S. Typhi
- Returned from extended holiday to Pakistan 6 weeks prior to case 1
- No illness during or upon return from Pakistan

Treatment: 7 days azithromycin then 4-6 weeks fosfomycin 1x per week

Stool sample -> Salmonella sp. after treatment

Case 4

Presented with diarrhoea at GP

Stool sample -> Salmonella sp.

Treatment: 7 days azithromycin

Whole genome sequence analysis

All isolates collected from all four Cases were sequenced

Multi-sampling

10 total isolates were selected from the final Case 4 stool sample, all were inculded in the WGS analysis

Results

- All study isolates genotyped: 4.3.1.1
- All within a 25 SNP threshold cluster
- Ratio of nonsynonymous to synonymous (dn/ds) SNPs (dn/ds for S. Typhi = 1.18)

Mutations in genes linked to:

- Metabolism Outer membrane
- Hypothetical - AMR

Tree scale: 11.6 SNPs ⊢ Multipick SRR12807764 SRR15334694 AMR gene SRR15334815 SRR15340843 Present SRR13833659 SRR13833654 Absent SRR15334714 SRR13163225 SRR12672341 SRR15334737 aac(6)-ly gene SRR15334775 aac(6)-ly* SRR13772107 aac(6)-ly[u]

Fig. 1. Maximum likelihood phylogenetic tree shows high relatedness of all study isolates Genetic diversity of Case 4 isolates is suggestive of Case 4 being an S. Typhi carrier. Black dot terminal node = multipick from last case 4 stool sample. Isolate accession numbers colured by source Case: pink = Case 1, blue = Case 2, green = Case 3, black = Case 4. Presence or absence of antimicrobial resistance gene

Discussion

Clinical data suggests Case 4 patient is an S. Typhi carrier, and the source of infection for Cases 1-3 Supported by relatedness of isolates:

- a. Within 25 SNP threshold; similar to previous carriage isolates (21 SNPs average) and more than for acute case isolates (13 SNPs) [1]
- b. Multipick isolates diverse = Case 4 shedding diverse isolates at a single time point
- c. Case 1-3 isolates closely related to, and dispersed amongst, Case 4 isolate, suggesting Case 4 is the source of infection

indicated to the right of tree.

Ratio of synonymous to non-synonymous SNPs shows divergent evolution within sample set, with greater positive selection than across S. Typhi collectively



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