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Case report

Queensland typhoid cluster linked to twelve-year carriage of *Salmonella* Typhi

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Abstract

In September 2021, a household cluster of three typhoid cases was investigated by Queensland public health authorities. Through case interviews and molecular typing, the investigation revealed chronic carriage of *Salmonella* Typhi persisting at least 12 years in the index case. This case report summarises the investigation and highlights the complexity of chronic pathogen carriage in the control and management of typhoid disease. Our findings raise considerations for prevention and treatment guidelines in Australia and demonstrate the beneficial role of molecular typing for complex case investigations.

Keywords: typhoid; *Salmonella*; chronic carriage; *S.* Typhi

Background

Typhoid, a disease of the gastrointestinal tract, is caused by the bacterium *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella* Typhi).[1] This bacterium is spread via the faecal-oral route, predominately transmitted through the ingestion of contaminated food or water.[2] Clinically, typhoid can present as asymptomatic infection or mild disease, through to a severe multisystem disease that can be life-threatening.[1] Most people with typhoid will recover with appropriate treatment. Some fail to clear the infection and progress to be carriers, intermittently shedding *S.* Typhi in their faeces.[3] There are three categories of typhoid carriage, classified by the duration of shedding: convalescent (between three weeks and three months); temporary (three to twelve months); and chronic (greater than twelve months).[3] Approximately 2–5% of people diagnosed with typhoid progress to chronic carriage.[4] For chronic persistence of *S.* Typhi, the organism must evade innate immune-mediated killing responses; must breach the intestinal epithelial barrier; and must localise to a permissive niche, such as the gallbladder, or less commonly, the urinary tract.[3,4]

Typhoid is a notifiable condition in all Australian jurisdictions.[2] In Queensland, typhoid is notified by laboratories upon isolation or detection of *S.* Typhi from any clinical specimen.[5] There are, on average (2015–2019), 25 sporadic cases of *S.* Typhi notified per year in Queensland.[6] These arise directly or indirectly from international importation from a variety of locations. Genetic distances between the isolates of approximately 500–800 single nucleotide polymorphisms (SNPs) are typically observed.[i] All confirmed cases are followed up by the local public health unit (PHU). Typhoid is rare in Australia and is generally identified in travellers entering or returning to Australia from endemic areas.[2]

Case report

Case investigation

On 21 September 2021, a typhoid notification was reported to Queensland Health for a hospitalised 11-year-old male. The notification was based on the laboratory confirmed evidence of positive bacterial culture and serological typing

i A/Prof Amy V Jennison, personal communication, March 2022.

of *S.* Typhi from faecal and blood specimens. The case had presented with fever, malaise, diarrhoea, vomiting, and headache. Screening activities were undertaken for household contacts; *S.* Typhi was isolated by culture in the faecal specimens of a symptomatic seven-year-old female (sister) and a 39-year-old female (mother) who was asymptomatic. The cases had no recent history of overseas travel, no contact with a recent confirmed typhoid case, and no other risk factors of note.

Further investigation revealed the mother had previously been diagnosed with an acute episode of typhoid in 2009 in Queensland. During the 2009 investigation, recent overseas travel to Northern Africa—with exposure to untreated water while travelling—was identified as the likely source of acquisition. At the time of diagnosis in 2009, the mother was in her third trimester of pregnancy and treated with amoxycillin for two weeks. Two follow-up stool specimens, taken two months apart, were culture negative for *S.* Typhi. Further overseas travel to Northern Africa was noted in 2017 for the mother.

Ethics approval was not sought for this investigation as all activities were conducted as part of the standard response under the Queensland *Public Health Act 2005*.[7]

Laboratory investigation

The Queensland Public Health Microbiology Laboratory performed whole genome phylogenetic analysis to assess genetic relatedness of the three 2021 and the 2009 isolates.[ii] This was undertaken in the context of previously-sequenced *S.* Typhi isolates and publicly available sequences of the same multilocus sequence type (MLST), ST3677. These isolates originated from a range of countries, mostly in Europe. Sequences were generated using the Illumina NextSeq genome sequencing platform. The 2021 isolates demonstrated a high degree of similarity to each other with 0–1 SNPs difference (Figure 1). The 2009 isolate was less genetically similar, demonstrating 5–6 SNPs difference from the 2021 isolates. In contrast, the publicly available unrelated ST3677 sequences were 24–64 SNPs different. In line with published literature on the adaptation of *S.* Typhi to its host environment during carriage,[3] the level of genetic similarity between the 2009 and 2021 isolates was deemed suggestive of a chronic carriage event with relapse, rather than acquisition of a new infection with subsequent transmission in 2021.

Public health response

Public health guidelines[2] were followed by the local PHU. No evidence of typhoid fever vaccination was recorded for any of the cases.

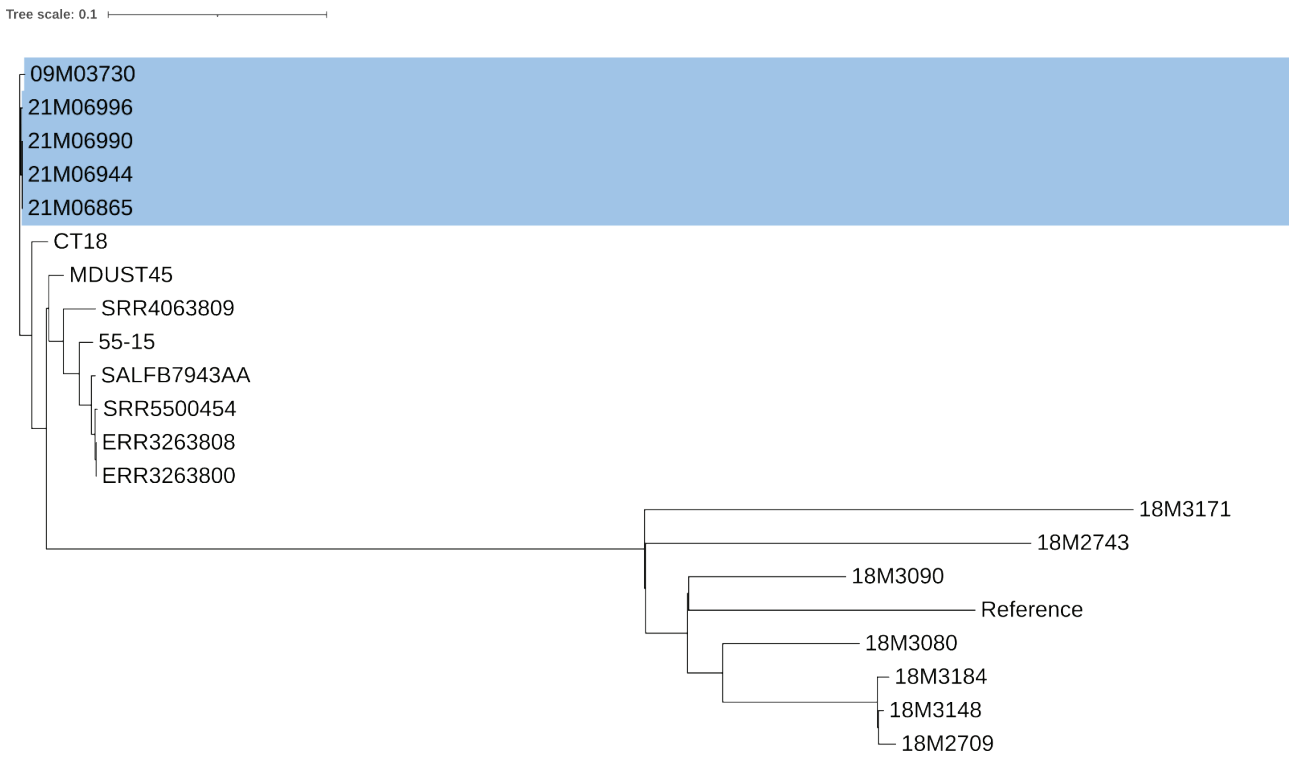
Confirmed cases received antibiotic treatment and were excluded from work or school settings until 48 hours after resolution of symptoms. Hygiene education was provided for all cases and for household and household-like contacts. Stool samples were requested for all household and household-like contacts. Other than the three cases discussed above, all specimens were polymerase chain reaction (PCR) negative for *S.* Typhi. The mother, once identified as a chronic carrier, was referred to an infectious diseases physician (IDP) for management. The mother provided two clearance samples, at least 48 hours after cessation of antibiotic therapy and at least 48 hours apart, which were PCR and culture negative for *S.* Typhi. The mother was cleared by the IDP without recommendation for cholecystectomy.

Discussion

This case study highlights the complexity of *S.* Typhi chronic carriage in the management and control of typhoid. The index case in the 2021 typhoid cluster returned two culture negative faecal specimens, more than two months apart, following an acute episode of typhoid in 2009. This met the clearance criteria according to Queensland public health guidelines at the time.[8] Culture sensitivity to assess for *S.* Typhi is 30% in faecal specimens, < 1% in urine

ii Bioproject accession: PRJNA785009.

Figure 1: Phylogenetic analysis of S. Typhi isolates received by the Queensland Public Health Microbiology Laboratory[a,b]



a Maximum likelihood tree built using SNP differences. The cluster including the recent isolates is highlighted in blue (isolates commencing with 21M are those collected in 2021, 09M03730 was collected in 2009). There are four 2021 isolates as two specimens were processed from one case (21M6865, 21M6944).

b The length of branches represents distance between groups as indicated by the scale bar.

specimens, and relies on testing during a period of bacterial shedding.[9] Sensitivity is reported to be higher in more invasive specimens: up to 80% in blood cultures of untreated patients and 40% in those treated, and > 80% in bone marrow aspirate culture.[9] Nucleic acid amplification tests of blood specimens have reported sensitivities consistent with blood culture, with some studies reporting clinically suspected typhoid cases that are PCR positive and blood culture negative.[9] In the absence of highly sensitive clearance tests, clinicians should consider chronic carriage in the differential diagnosis process for any typhoid case. Currently, the evolution of *S.* Typhi within the gallbladder is poorly understood, as is duration of carriage.[3,4] Some chronic carriers have been found to periodically excrete bacteria in their stools and urine for decades.[10] The disease progression of this cluster, in the context of the sensitivity of faecal culture and duration of chronic carriage, raises the question of the rigour required for establishing clearance.

Typhoid vaccination recommendations relevant to this cluster include vaccination for children ≥ 2 years and adults travelling to typhoid-endemic regions,[11] and for household contacts of chronic carriers.[2] The former requires individuals to seek and self-fund travel-specific vaccinations; the latter requires detection of chronic carriage and likely self-funding of vaccination. This cluster highlights the difficulty of the latter in that, in the presence of compliant clearance specimens, disease transmission is required to identify a chronic carrier.

Current public health guidelines recommend referral to an infectious diseases physician for treatment in cases of chronic carriage.[2] This is because current recommended antimicrobial

therapy is not always effective against the persistence of typhoidal *Salmonella*.[10] Treatment for chronic carriage can include combination or extended antibiotic therapy, depending on susceptibility of the organism, or cholecystectomy if there are indications for surgical intervention.[9]

An important element highlighted by this case study was the role of molecular typing in distinguishing possible sources of infection. Prior to the whole genome phylogenetic analysis of the 2009 and 2021 isolates, more recent acquisition of infection and household spread was considered, particularly given overseas travel in 2017 and negative clearance stool samples in 2009. Whole genome sequencing continues to advance our ability to understand and define enteric pathogen epidemiology. In the last twenty years, whole genomic sequencing of *S*. Typhi strains has contributed to increased understanding of disease pathogenicity, host adaption, and antimicrobial resistance.[12] Increased collection of strain provenance information, including the identification of acute or chronic carrier status, is important to better define the differences between healthy individuals and asymptomatic carriers.[12]

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