International collaboration tracks typhoid fever cases over two continents from South Africa to Australia

Salmonella enterica serovar Typhi (S. Typhi) is the causative agent of typhoid fever. The disease is primarily waterborne or foodborne, but person-to-person spread by direct contact is well recognized. The bacterium is of great clinical importance as humans are the only recognized reservoir of S. Typhi and typhoid fever is a major cause of morbidity and mortality in humans, particularly in developing countries. For the year 2000, it was estimated that, worldwide, typhoid fever caused 21,650,974 illnesses and 216,510 deaths (Crump et al., 2004). In South Africa (SA), some rural areas remain endemic for typhoid fever and these areas are associated with the lack of potable water. The disease has become uncommon in most urbanized areas of the country where safe water supplies are mostly guaranteed. In recent years, the number of typhoid fever cases notified in SA has decreased. However, outbreaks of typhoid fever do occasionally still occur in the country: a recent outbreak of typhoid fever occurred in 2005 in the town of Delmas (Keddy et al., 2011). In the present study, we report on the epidemiological investigation of a cluster of typhoid fever cases in Pretoria, SA, in 2010 and further report on how this outbreak strain was tracked from SA to Australia.

In May 2010, an increase in S. Typhi cases in the Pretoria district was noted. In recent years, this district has been associated with very few cases of S. Typhi, with only three cases reported to the Enteric Diseases Reference Unit (EDRU) of the National Institute for Communicable Diseases (NICD) during the 2008–2009 period. Further investigation revealed a cluster of eight cases with links to the Pretoria district, with dates of disease onset ranging from 22 April to 27 May 2010. Most of the cases were in students or friends of students living in a particular area of the Pretoria district. Isolates were available for five of these cases and these were forwarded to the EDRU for further laboratory analysis. The identity of isolates was confirmed using standard microbiological identification and serotyping techniques. Susceptibility testing to antimicrobial agents was determined by the Etest (bioMérieux). Genotypic relatedness of isolates was investigated by PFGE analysis of XbaI-digested genomic DNA on a CHEF-DR III electrophoresis system (Bio-Rad Laboratories) using a PulseNet protocol (Ribot et al., 2006). PFGE patterns were analysed using BioNumerics (version 6.01) software (Applied Maths) with dendrograms of the patterns created using the unweighted pair group method with arithmetic averages, with analysis of banding patterns incorporating the Dice coefficient at an optimization setting of 1.5% and a position tolerance setting of 1.5%. Patients were interviewed and case investigation forms were completed to determine information including date of onset of disease, symptoms, places of eating and drinking, type of water supply and sanitation at home, travel history, etc. A single restaurant (Restaurant X) was linked to the outbreak; an audit of the restaurant was conducted and this included a collection of specimens (staff rectal swabs and environmental surface swabs) for testing for S. Typhi. Restaurant staff were also interviewed regarding recent illnesses.

Analysis of the five available S. Typhi isolates showed an identical antimicrobial susceptibility profile for all isolates. They were susceptible to all of the following antimicrobials: ampicillin, augmentin, trimethoprim, sulframethoxazole, chloramphenicol, nalidixic acid, ciprofloxacin, tetracycline, kanamycin, streptomycin, imipenem, ceftriaxone and cefazidime. PFGE analysis of the isolates revealed an indistinguishable DNA fingerprint pattern (Fig. 1). These data suggested that all isolates were an identical strain. Interviews with patients revealed a common place of eating and drinking, namely Restaurant X; all patients had frequented this restaurant over the weekend of 16–18 April 2010. During the audit of the restaurant, it was found that hand hygiene was substandard: there were no hand-washing facilities within the restaurant and staff had to make use of such facilities located outside the restaurant within a communal shopping centre bathroom. Rectal swabs from restaurant staff and environmental surface swabs from the restaurant all tested negative for S. Typhi. Interviews with restaurant staff then identified a further case (case number 9) of typhoid fever in a barman who worked at the restaurant (disease onset: 16 April 2010). Of the cases identified in this outbreak, the barman was the first to become ill. He also had recent travel history (February 2010) to Lesotho, a neighbouring country land-locked within SA. He was a Canadian national on a working holiday in SA. He subsequently resigned from employment at the restaurant, departed SA and journeyed to Perth, Australia. He fell ill while travelling to Australia and on arrival in that country was admitted to a hospital where he was diagnosed with typhoid fever. The PFGE pattern of this S. Typhi isolate was obtained from a participating Australian laboratory linked to PulseNet International (http://www.pulsenetinternational.org/Pages/default.aspx); the PFGE pattern was found to match our outbreak pattern. Our continual routine PFGE analysis of S. Typhi isolates from all cases across SA then identified another isolate with a PFGE pattern matching our outbreak pattern (case number 10). The patient worked in Lesotho, fell ill and then sought medical treatment in SA in Bloemfontein, a city situated ~500 km south of Pretoria. Unfortunately, limited epidemiological information was available regarding this case: the patient’s specimens were collected for analysis on 28 May 2010 and the patient had no travel history to Pretoria.

PFGE analysis of these S. Typhi isolates has demonstrated the value of this technique.
in linking our typhoid fever cases and showing a relationship between the isolates. This investigation involved the PulseNet International Laboratory Network (an international molecular subtyping network for foodborne pathogens) and showed just how effective such a laboratory network is in tracking a pathogen around the world. Most diseases, including foodborne and waterborne diseases, do not respect any borders. The impact of these diseases is amplified through increasing international travel and population mobility. As a result, a local disease outbreak investigation can rapidly shift into a worldwide investigation of the outbreak. This is where international networks such as PulseNet particularly prove their worth through rapid communication, alerts, response and investigation within a global laboratory.

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**Fig. 1.** Section of a dendrogram of PFGE fingerprint patterns (XbaI digestion) for *Salmonella* Typhi, highlighting a cluster of isolates showing the Pretoria outbreak pattern.
network. As many public health issues increasingly become global concerns, so many more international networks are likely to be established in the future, with PulseNet offering a good model of an effective network that works and delivers.

Interestingly, the currently described PFGE outbreak pattern is unique and has not previously been seen in the SA Database, nor has it been seen in the Global PulseNet S. Typhi Database. The outbreak strain was susceptible to all antimicrobials tested, a phenotype commonplace within susceptible to all antimicrobials tested. Therefore, in theory, this outbreak strain may have been of local origin and mutated sufficiently to evolve into a new strain with a unique PFGE pattern. However, we speculate that this outbreak strain had its origin in Lesotho and this is supported by the following data. Isolates from cases numbers 9 and 10 showed an indistinguishable PFGE pattern; the patient in case number 9 had travel history to Lesotho, while the patient in case number 10 worked in Lesotho and had no travel history to Pretoria. Unfortunately, this cannot be supported by data or analysis of isolates from Lesotho as no further information could be acquired regarding typhoid fever in Lesotho. We further speculate that case number 9 (the barman working at Restaurant X) may well have been the source of the typhoid fever outbreak in Pretoria. Restaurant-associated outbreaks of S. Typhi appear to be an uncommon occurrence as suggested by very few published reports of such outbreaks (Yoon et al., 2004; Olsen et al., 2001); a PubMed literature search of published data (English language) found that the most recently reported restaurant-associated outbreak of S. Typhi occurred in 2000 in Queens, New York, USA (Yoon et al., 2004).

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