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Outbreak of ceftriaxone-resistant *Salmonella enterica* serotype Typhi-Tiruchirappalli, Tamil Nadu, India, June 2018

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ABSTRACT

Objectives: In May 2018, a laboratory network for antimicrobial resistance (AMR) surveillance in Tamil Nadu, India, detected a cluster of *Salmonella enterica* serotype Typhi (*S.* Typhi) isolates resistant to ceftriaxone. We investigated to describe the epidemiology and identify risk factors for the outbreak.

Methods: We conducted unmatched case-control studies. We defined a case as illness (fever with abdominal pain, diarrhea or vomiting) in a person with blood culture-confirmed ceftriaxone-resistant *S.* Typhi isolated between January 1 and July 4, 2018 in Tiruchirappalli, Tamil Nadu. We interviewed cases using a semi-structured questionnaire to identify common exposures to food, water and places visited.

Results: We identified 7 cases (5 men) during March 25–June 8, 2018, median age 23 years (range: 12–42); all were hospitalized, none died. Eating at Restaurant A (odds ratio [OR]=22) and chicken gravy (OR=16) was associated with illness. Of the 10 workers at Restaurant A, stool culture from 8 did not detect *S.* Typhi; 2 did not consent to provide samples. Five water samples around the restaurant showed low or no residual chlorine content.

Conclusions: The investigation highlights the value of AMR surveillance in detecting emerging pathogens and the need for timely investigations, along with strengthening food safety.

Introduction

Globally in 2017, there were an estimated 14 million cases and 136 000 deaths from typhoid and paratyphoid fever. South Asia had the highest burden, accounting for 72% of global cases and 70% of deaths (Stanaway et al., 2019). Typhoid fever is endemic in India, with an estimated incidence of 380 (180–800) per 100 000 person-years (John et al., 2016). Outbreaks of multidrug-resistant (MDR) isolates of *Salmonella enterica* serotype Typhi, defined as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, have been reported from India and elsewhere (Olarte et al., 1973, Zaki et al., 2011, Oh et al., 1994, Sabherwal et al., 1992, Sudarsana et al., 1992, Akinyemi et al., 2015). A third-generation cephalosporin, ceftriaxone, is the drug of choice for *S.* Typhi in India. Extensively drug-resistant (XDR) isolates of *S.* Typhi, defined as MDR plus resistance to ciprofloxacin and ceftriaxone, have been reported from Pakistan (Klemm et al., 2018, Qamar et al., 2018). Although XDR strains of *S.* Typhi have not been reported in India, sporadic cases of ceftriaxone-resistant strains have been reported (Patel et al., 2017). Published reports on associated exposures and risk factors for ceftriaxone-resistant *S.* Typhi in India are limited.

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Antimicrobial resistance (AMR) is a significant threat to global health. It is estimated that 10 million lives could be lost annually due to drug-resistant infections by 2050 (Jim, 2016). In response to the threat, the Government of India established the National Programme on AMR Containment coordinated by the National Centre for Disease Control (NCDC), New Delhi. The program includes a national AMR surveillance laboratory network of 25 state medical college laboratories in 23 states. This network conducts surveillance for 7 priority bacterial pathogens (i.e., Enterococcus species, Staphylococcus aureus, Escherichia coli, Klebsiella species, Pseudomonas species, Acinetobacter species, and Salmonella enterica serotypes Typhi and Paratyphi (NCDC, 2019)). The surveillance network reports emerging AMR alerts within 1 week of detection and sends the strains for confirmation to the AMR National Reference Laboratory (NRL) at NCDC.

In May 2018, KAP Vishwanatham Government Medical College (GMC), Tiruchirappalli, Tamil Nadu, a member of the national AMR surveillance network, reported 4 unique isolates of ceftriaxone-resistant *S.* Typhi in an emerging AMR alert. The isolates were from 4 patients' blood samples obtained within 24 hours of admission. The AMR NRL, NCDC, confirmed the resistance pattern of the 4 isolates and initiated an investigation to confirm the outbreak, describe the epidemiology, and provide evidence-based recommendations for control and prevention.

Methods

Case definitions

We defined a confirmed case as illness (fever with abdominal pain, diarrhea or vomiting) in a person with blood culture-confirmed ceftriaxone-resistant *S.* Typhi isolated between January 1 and July 4, 2018, in Tiruchirappalli, Tamil Nadu.

Case search and data collection

We searched for all typhoid cases in the registers of 23 laboratories (government=2 and private=21) empaneled with the Tiruchirappalli district surveillance unit and recorded antibiotic susceptibility profiles. We conducted in-depth, open-ended interviews with laboratory-confirmed ceftriaxone-resistant *S.* Typhi cases to generate hypotheses on common exposures to food, water or place (i.e., travel, mass gathering or social activity) visited a month before illness onset.

Case-control studies

Restaurant case-control study

We conducted an initial case-control study to test the hypothesis generated from interviewing the cases that eating in Restaurant A (a small roadside eatery) was associated with illness. We included all the cases identified and enrolled all the eligible controls identified from the reporting laboratory records in Tiruchirappalli. Controls were persons with culture-confirmed *S.* Typhi sensitive to ceftriaxone who lived or worked in Tiruchirappalli between January 1 and June 1, 2018, and were within the same age range (12–42 years) as the cases. All cases and controls provided informed verbal consent to take part in the investigation.

We interviewed cases and controls using a semi-structured questionnaire for information on demographics, clinical presentation, similar illness in household members in the last 6 months, and potential exposures, including eating venues, food and beverages consumed outside the home, drinking water sources at home.

Food vehicle case-control study

We conducted a second case-control study to find the exposure in the restaurant associated with illness. We included cases having reported exposure to Restaurant A between March 1 and May 31, 2018. Controls were the meal companions of the cases who ate at Restaurant A during the same time and had no history of fever, abdominal pain, diarrhea, or vomiting any time after. We enrolled all the eligible controls in the ratio 1:2 and interviewed both the selected cases and controls for information on restaurant food and beverage exposures.

Data analysis

We calculated odds ratio (OR) with 95% CIs for both case-control studies using Epi Info software version 7.2.

Laboratory investigations

We collected serum and stool samples using Cary Blair media from all consenting workers for Widal testing and stool culture to determine their status of being a potential carrier for *S.* Typhi.

The 2 laboratories, GMC and Kauvery Medical Centre, identified *S.* Typhi from blood specimens of cases. Both laboratories performed blood culture using conventional methods and performed antibiotic susceptibility testing using the Kirby Bauer disk diffusion method (Hudzicki, 2009). The AMR NRL, NCDC, confirmed pathogen and antibiotic susceptibility testing. We analyzed the resistance pattern of the isolated *S.* Typhi strain resistant to ceftriaxone.

Environmental investigations

We interviewed the manager of Restaurant A using a semi-structured questionnaire about the procurement of raw materials, food preparation, food storage, food waste disposal, drinking water sources, and operation of Restaurant A (e.g., license, serving capacity, employees during January–June 2018). We used a separate questionnaire to interview employees of Restaurant A for information on any illnesses in the past 6 months, medical examination history, typhoid vaccination in the past 2 years, assigned tasks at Restaurant A, and hand hygiene practices.

We used a modified version of the Food Safety and Standards Authority of India (FSSAI) checklist for catering to inspect Restaurant A and its kitchen for the availability of running tap water, food storage, cooking process, waste disposal, washing facilities, and toilets (FSSAI, 2017). We also tested water samples around the locality of the restaurant for residual chlorine content.

Results

Descriptive epidemiology

We identified 7 confirmed ceftriaxone-resistant *S.* Typhi cases. The median age of the cases was 23 years (range: 12–42 years), and 5 (71%) were male. All 7 cases reported fever and fatigue, 3 reported having abdominal pain and vomiting, and 1 reported diarrhea. Illness onset spread over a period from March 25–June 8, 2018 (Figure 1). Despite the continued laboratory surveillance to raise alerts, no new cases of this resistant strain were reported until December 2019. All the cases were hospitalized with a median duration of 9 days (range: 4–23 days), and none died. Five (71%) of the 7 cases lived in and around the government medical college; 2 lived away but worked in and around that area. Five of the 7 cases (71%) reported a common exposure, eating at Restaurant A situated 100 meters from the GMC.

Case-control studies

Restaurant case-control study

Among the 7 cases and 10 eligible controls, eating at Restaurant A (OR=22) was the only exposure significantly associated with illness (Table 1).

Food vehicle case-control study

Among the 5 cases who ate in Restaurant A and 10 meal-companion controls, chicken gravy (OR=16) was the only food item associated with illness (Table 2).

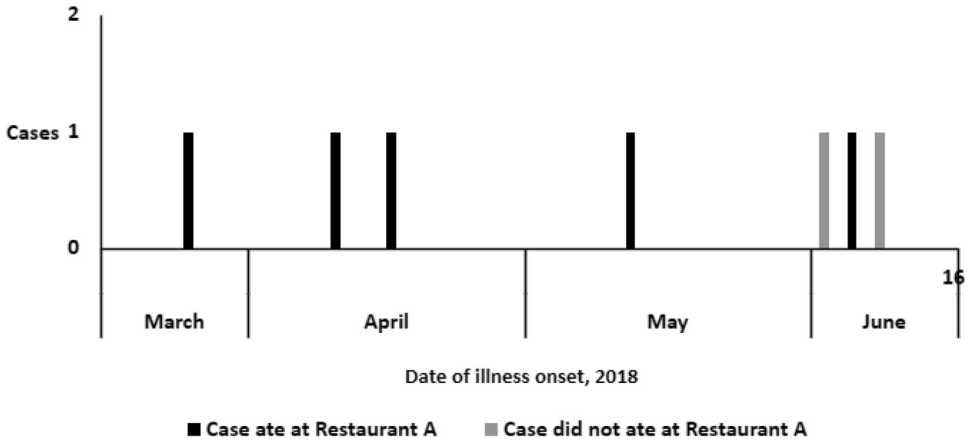

Figure 1. Distribution of Ceftriaxone-resistant *S.* Typhi Cases by Illness Onset Date, Tiruchirappalli, Tamil Nadu, India, March-June 2018 (n=7)

Description: The black vertical lines represents the cases that ate in Restaurant A and the grey vertical lines represents cases that did not ate in Restaurant

Table 1
Risk Factors for Ceftriaxone-resistant *S.* Typhi, Tiruchirappalli, Tamil Nadu, India, June 2018 (N=17)

	Case (n=7) n	Control (n=10) n	Case %	Control %	Odds ratio	(95 % CI)
Ate at Restaurant A*	5	0	83	0	**22**	**(1.8-260.7)**
Ate at a restaurant	6	6	86	60	4	(0.3-47.1)
Hand-wash without soap after defecation	4	4	57	40	2	(0.02-14.2)
Hand-wash without soap before eating	5	7	0	70	1.1	(0.1-9)
Treating drinking water at home	4	6	57	60	0.8	(0.1-6.3)

* Added one to each cell for calculation

Laboratory investigation results

All 7 isolates of *S.* Typhi were susceptible to azithromycin, chloramphenicol and trimethoprim-sulfamethoxazole but resistant to ceftriaxone, ampicillin, ciprofloxacin, and cefotaxime (Table 3). All *S.* Typhi isolates were sub-cultured, reconfirmed for resistance to ampicillin, ciprofloxacin and ceftriaxone using disk diffusion and micro broth dilution method at AMR NRL, NCDC, New Delhi.

Among 10 Restaurant A workers, 9 consented to provide serum and 8 to provide stool samples. All serum samples were negative by Widal testing, and all stool samples showed no growth of *S.* Typhi on culture. Two female workers did not consent to give stool samples, and 1 of them refused to give a blood sample.

Environmental investigation

Restaurant A has a serving capacity of 16. The restaurant purchased fresh raw ingredients such as meat (e.g., chicken and mutton), vegetables and eggs from the nearby local market daily. Ten workers played multiple roles; 7 were cooks, 5 handled meat, 4 did cleaning, and 6 served food. None reported fever with a headache or abdominal pain or diarrhea in the past 6 months. None had a medical examination or received typhoid vaccination in the past 2 years.

Tiruchirappalli Municipal Corporation water supply was in use at Restaurant A for drinking, cleaning and cooking. The restaurant used a reverse osmosis method for filtering tap water for drinking and cooking. However, water was not chlorinated thereafter. Two persons cooked the food at a time: 1 person cooked curries and rice while the other prepared dosa (rice pancake). The chicken gravy was prepared one time for the whole serving duration. It was reheated and brought to a boil before serving. We saw cooks and waiters handling the waste; no one wore gloves while preparing food or disposing of waste. A hand washing basin was available with running tap water, but there was no soap or sanitizer. There was no toilet in Restaurant A; a municipal toilet was available 150 meters away with running tap water but no soap. We tested 5 water samples collected from 5 sites around the locality of the restaurant (2 at the main distribution site, 1 at the air valve pit leakage site and 2 from household tap water) for residual chlorine content. Two samples from the main distribution site gave a reading of 0.2 ppm, while the other 3 samples had nil residual chlorine.

Discussion

This was the first reported outbreak of laboratory-confirmed ceftriaxone-resistant *S.* Typhi identified in Tiruchirappalli, Tamil Nadu, through India's National AMR laboratory surveillance network. Eating at Restaurant A during a two-and-a-half-month period was associated with illness. Environmental investigation showed that both food and water served at the restaurant could have been contaminated by a potentially infected food handler. Our investigation highlights India's National AMR laboratory surveillance network capacity to successfully detect outbreaks and trigger in-depth epidemiological investigations.

Our investigation identified eating at Restaurant A as the probable risk factor for illness but was unable to conclusively determine the exact risk factor within the restaurant. In a separate case-control study among cases with restaurant exposure and their healthy meal compan-

Table 2
Risk Factors for Ceftriaxone-resistant *S.* Typhi, Tiruchirappalli, Tamil Nadu, India, June 2018 (N=25)

Characteristics	Case (n=5) %	Control (n=20) %	Odds ratio	(95 % CI)
Median age (range) in years	23 (13-27)	24 (15-54)	1.1	(0.9-1.3)
Male	80	90	1	(0.1-12.4)
Food/beverages consumed at Restaurant A during March 1-May 30, 2018				
Chicken gravy	**80**	**20**	**16**	**(1.1-234)**
≥ ate 6 times in week/month	60	20	6	(0.5-63.9)
Vegetables	100	80	3	(0.1-24)
Water and uncooked food	100	70	3	(0.2-34)
Meat/poultry	100	70	3	(0.3-34)
Dinner	60	80	0.4	(0.03-3.9)
Rice/dough products	100	100	-	-

Table 3
Resistance Pattern of the Isolates of Ceftriaxone-resistant *S.* Typhi Cases, Tiruchirappalli, Tamil Nadu, India, June 2018 (n=7)

Antibiotic	Isolates tested	Isolates resistant	Sensitive	Non-susceptible*
Ampicillin	7	7	0	0
Cefotaxime	7	7	0	0
Ceftriaxone	7	7	0	0
Ciprofloxacin	7	0	0	7
Azithromycin	7	0	7	0
Chloramphenicol	7	0	7	0
Cotrimoxazole	7	0	7	0
Imipenem	5	0	5	0

* Non-susceptible=resistant + intermediate sensitive

ions as controls, consuming chicken gravy was associated with illness. However, given the daily procurement of ingredients and the scattering of illnesses over two and half months, the probable source could also be linked to an infected food handler. However, we were unable to confirm shedding of the infective organism in a food handler. Two female restaurant workers did not consent to provide a stool sample. One of the nonconsenting female workers might have been the source, or 1 of the consenting 8 could have been the source but was not shedding at the time of testing. As seen from other studies, typhoid carriers are more common among females (Levine et al., 1982, Ames et al., 1943).

The restaurant used a reverse osmosis method for filtering tap water for drinking and cooking. However, water was not chlorinated thereafter. The water supply used to make food (gravy) over an extended period could also be a source of infection. As shown in a typhoid fever investigation in Saudi Arabia, water-borne bacteria (e.g., coliforms) could degrade reverse osmosis membranes leading to the passage of microorganisms through the membrane and cause infection (al-Quarawi et al., 1995).

Our investigation highlights the importance of adhering to food safety norms by restaurants, including roadside eateries. Restaurant A neither had soap for handwashing nor proper waste disposal area, reflecting a common finding in roadside eateries in India and highlighting the food safety risk in the country. Food safety is a concern in India, with food-borne illnesses expected to rise from 100 million (8.3%) in 2011 to 150–177 million (10%–12%) in 2030 (Kristkova et al., 2017). In India, the FSSAI provides science-based standards to ensure the availability of safe and wholesome food for human consumption (FSSAI, 2019). For both consumers and food sellers, simple measures including personal and safe food practices play an important role in the prevention and control of food-borne illnesses. These illnesses eventually result in the increased usage of antibiotics and increased risk of pathogens developing resistance.

There is a growing concern of infections by AMR pathogens globally, with an estimated 700 000 deaths occurring annually (Jim, 2016). India has a high burden of infectious diseases and was the leading consumer of antibiotics among low-income countries in 2015 (Klein et al., 2018). The National AMR surveillance data reveals a rise of AMR and has detected

the emergence of resistance to last-resort antibiotics, such as linezolid-resistant *S.* aureus and *Enterococcus* spp. and colistin-resistant strains of gram-negative bacteria (NCDC, 2020). A robust AMR laboratory surveillance system is necessary to detect resistant strains, follow trends and generate alerts for early response.

Our investigation was not without limitations. First, we could not describe the extent of the outbreak as blood culture was not done routinely for the diagnosis of typhoid in the district. Second, the food item case-control study was prone to recall bias as the reference period included 3 months before the investigation. We tried to minimize this bias by developing an event calendar for the entire duration of interest and having a list of the most common food items served by the restaurant. Third, we could not obtain blood and stool samples from all the Restaurant A workers for testing. Only a single sample of stool was feasible for collection from each of the consenting workers, but multiple samples might have had a higher probability for detection of *S*. Typhi in a chronic carrier (Ismail, 2000).

The AMR surveillance system set up by the Government of India at NCDC has demonstrated the capacity for detecting outbreaks. A strong laboratory capacity coupled with epidemiological investigations is the way forward for early detection and response to an outbreak of AMR pathogens. This study highlights the need to enable timely and thorough outbreak investigations to gather credible evidence, along with strengthening food safety and knowledge of food-borne illnesses.

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Conflicting interest

None declared

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Ethical approval statement

Not required as this work was carried out as part of a public health response with prior approval of the National Centre for Disease Control, Delhi, India.

Disclaimer

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Centers for Disease Control and Prevention or the institutions with which the authors are affiliated.

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