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Typhoid fever acquired in the United States, 1999–2010: epidemiology, microbiology, and use of a space–time scan statistic for outbreak detection

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SUMMARY

Although rare, typhoid fever cases acquired in the United States continue to be reported. Detection and investigation of outbreaks in these domestically acquired cases offer opportunities to identify chronic carriers. We searched surveillance and laboratory databases for domestically acquired typhoid fever cases, used a space–time scan statistic to identify clusters, and classified clusters as outbreaks or non-outbreaks. From 1999 to 2010, domestically acquired cases accounted for 18% of 3373 reported typhoid fever cases; their isolates were less often multidrug-resistant (2% *vs.* 15%) compared to isolates from travel-associated cases. We identified 28 outbreaks and two possible outbreaks within 45 space–time clusters of ⩾2 domestically acquired cases, including three outbreaks involving ⩾2 molecular subtypes. The approach detected seven of the ten outbreaks published in the literature or reported to CDC. Although this approach did not definitively identify any previously unrecognized outbreaks, it showed the potential to detect outbreaks of typhoid fever that may escape detection by routine analysis of surveillance data. Sixteen outbreaks had been linked to a carrier. Every case of typhoid fever acquired in a non-endemic country warrants thorough investigation. Space–time scan statistics, together with shoe-leather epidemiology and molecular subtyping, may improve outbreak detection.

Key words: Epidemiology, outbreaks, surveillance system, typhoid fever (*Salmonella* Typhi).

INTRODUCTION

Typhoid fever is an acute systemic infection caused by *Salmonella enterica* serotype Typhi (*S.* Typhi). An estimated 13·5 million cases of typhoid fever occurred worldwide in 2010 [1]. Infection spreads by the faecal–oral route, primarily through ingestion of contaminated food or water and is common in populations without access to safe drinking water or sanitation and hygiene [2]. Symptoms are non-specific, and the incubation period is variable, ranging from 3 days to >60 days, with a median of 8–14 days [3]. Some patients with acute illness become chronic carriers and serve as reservoirs of *S.* Typhi [2].

In the United States, the incidence of typhoid fever has been low since the 1940s [2], but it remains an important public health issue due to its high hospitalization rate and the potential for infected individuals to

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contaminate food and water sources. Typhoid fever is nationally notifiable and about 350 acute infections are reported annually [4]. Most patients report travel within 30 days preceding their illness onset to a country where typhoid fever is endemic. However, about 50 patients each year do not report any foreign travel, suggesting they were infected in the United States.

Outbreaks of typhoid fever in the United States are uncommon, but thorough investigation to identify the source is indicated. From 1960 to 1999, 54 outbreaks with exposure in the United States were documented; an asymptomatic carrier was identified in 16/26 foodborne outbreaks [5]. Typhoid fever outbreaks caused by chronic carriers can be difficult to detect because carriers typically shed the bacterium intermittently for many years, potentially causing few infections over a long period. These small but prolonged outbreaks may escape detection by routine surveillance. Early outbreak detection offers an opportunity to treat chronic carriers and prevent illnesses.

A wide range of statistical algorithms is used for surveillance and outbreak detection [6, 7] and an increasing number of disease cluster detection tools have been developed and evaluated [8–10]. The space–time scan statistic is an analytical method that has been used to detect and evaluate clusters of infectious and non-infectious diseases [11–15]. Its ability to detect infectious disease outbreaks has been evaluated using epidemiological evidence such as previously reported outbreak and molecular data [11, 15].

We analysed clinical, epidemiological, and microbiological characteristics of typhoid fever cases acquired in the United States and compared them to those acquired abroad. We then focused on the domestically acquired typhoid fever cases, applying a space–time scan statistic to screen for outbreaks of domestically acquired typhoid fever in the United States. We evaluated how well a space–time scan statistic approach identified reported outbreaks and whether it uncovered any previously unrecognized outbreaks.

METHODS

Case definition and identification

For every laboratory-confirmed typhoid fever case in the United States, state and local health officials are requested to report the case to the National Notifiable Diseases Surveillance Systems (NNDSS); complete and submit an enhanced case investigation form to the National Typhoid and Paratyphoid Fever Surveillance (NTPFS) system at the Centers for Disease Control and Prevention (CDC); subtype the isolate using pulsed-field gel electrophoresis (PFGE) and upload the PFGE pattern to PulseNet, the national molecular subtyping network for foodborne disease surveillance; and send the isolate to the National Antimicrobial Resistance Monitoring System (NARMS) at CDC. The NTPFS case report form (CDC Form 52·5) collects basic information about patient demographics, travel and vaccine history, hospitalization and outcome, and whether the case was known to be part of an outbreak or linked to a carrier. NARMS tests all *S.* Typhi isolates for susceptibility to 15 antimicrobial agents using broth microdilution (Senititre; Trek Diagnosis, USA) and interprets the results according to Clinical and Laboratory Standards Institute (CLSI) criteria, when available [16, 17].

We linked the NTPFS and NARMS databases for typhoid fever cases occurring during 1999–2010. We defined domestically acquired typhoid fever as a compatible illness in a person with culture-confirmed *S.* Typhi infection who denied foreign travel during the 30 days before illness onset, and a travel-associated case as a compatible illness in a person with culture-confirmed *S.* Typhi infection who reported foreign travel during the 30 days before illness onset. For each domestically acquired typhoid case in the NTPFS, but not for travel-associated cases, we identified matching isolates in the PulseNet database. When PFGE data were missing in PulseNet, but the isolate was available from the NARMS collection, we performed PFGE characterization using standard methods and analysed patterns using BioNumerics v. 5·1 software (Applied Maths, Belgium) [18].

Identification of previously reported outbreaks

Outbreaks of foodborne illness have been voluntarily reported to the Foodborne Disease Outbreak Surveillance System (FDOSS) at CDC by state and local health departments since 1973. Similarly, since 1971, outbreaks of waterborne diseases have been reported to the Waterborne Disease and Outbreak Surveillance System (WBDOSS) also at CDC. All waterborne and enteric disease outbreaks involving foodborne, person-to-person contact, animal contact, environmental contamination, and indeterminate means have been reported to the National Outbreak

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Reporting System (NORS) since 2009. We searched these systems for outbreaks of typhoid fever that occurred in the United States from 1999 to 2010. In addition, we searched the published literature for reports of domestically acquired typhoid fever outbreaks in the United States during the same period.

Characteristics of typhoid cases

We calculated frequencies of epidemiological, clinical, and microbiological characteristics. We defined multidrug resistance as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole [4], and nalidixic acid resistance as minimum inhibitory concentration (MIC) >32 μg/ml [4, 16]. We used the χ^2 test and Fisher's exact test (when expected cell frequencies were <5) to compare characteristics of domestically acquired and travel-associated cases. We calculated crude rates for domestically acquired and travel-associated typhoid fever cases for ten states that reported the largest number of domestically acquired cases.

Detection of domestically acquired typhoid clusters

We identified clusters of $\geqslant 2$ domestically acquired typhoid cases using a space–time scan statistic. This approach identifies excess cases in space and time, using a cylindrical scanning window [11, 13, 19]. Briefly, at each space–time location, the window increases in size in both space and time and a Poisson likelihood ratio test comparing the observed disease rate inside and outside the cylinder is provided by the space–time scan statistic [13, 19]. The input data for the space–time scan analysis comprised domestically acquired typhoid case counts reported to NTPFS per month per county, census population estimates per year per county, and the centroid coordinates for each county. We used a cylindrical scan statistic with a circular base and set the maximum temporal scanning window to be 50% of the study period (i.e. 6 years) and the maximum spatial scanning window to be the area covering 50% of the study population to detect clusters that do not spatially overlap. We used 999 Monte Carlo iterations to estimate the significance levels of the clusters. We computed scan statistics separately for detecting clusters within states with $\geqslant 2$ domestically acquired typhoid cases, selected regions, and the continental United States. We selected regions that consistently reported a large number of domestically acquired typhoid cases by identifying states ranked in the top five in domestically acquired typhoid reporting rates for $\geqslant 3$ years during 1999–2010 and included their adjacent states. We considered all clusters detected with P values < 1 to increase sensitivity for outbreak detection. Demographic variables were not used to generate sub-population cluster profiles. When overlapping clusters were detected using more than one scan (e.g. state and region scans), the larger cluster was selected for further analysis, except when the larger cluster was determined to include multiple unrelated clusters based on epidemiological information. We compared the number of detected outbreaks and the positive predictive values when all clusters were considered regardless of statistical significance and when only statistically significant clusters (alpha = 0·05) were considered. All scan statistic procedures were performed using SaTScan™ v. 9·1·1 [20]. The geographical information system ArcMap 10 (ESRI, USA) was used for visualizing the scan statistic outputs.

Classification of domestically acquired typhoid clusters

We classified space–time clusters as outbreaks, non-outbreaks, or possible outbreaks, using domestically acquired typhoid outbreaks previously reported in the literature and CDC outbreak reporting systems, epidemiological data from the NTPFS case report forms, PFGE patterns, and additional information obtained from state health departments during follow-up. We defined a space–time cluster as an outbreak if it involved $\geqslant 2$ cases with a common exposure, such as a food item, a chronic carrier, or a household contact. We defined a space–time cluster as a non-outbreak if it involved $\geqslant 2$ cases in which common exposure was unlikely either because cases had different exposures that could explain typhoid fever or had different PFGE patterns and no epidemiological link. Clusters with insufficient data to determine outbreak status were classified as possible outbreaks.

Characteristic of domestically acquired typhoid outbreaks

We characterized the source of infection and PFGE patterns of cases in detected outbreaks and compared with previously reported outbreaks.

RESULTS

Case identification

A total of 3499 typhoid fever cases were reported to NTPFS during 1999–2010; travel status was known

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for 3373 (96%) cases and domestically acquired typhoid cases accounted for 610 (18%) of them. Antimicrobial susceptibility data were linked with 356 (58%) domestically acquired typhoid cases and 1669 (60%) travel-associated cases. PFGE data were linked with 416 (68%) domestically acquired typhoid cases.

Characteristics of typhoid cases

While the number of travel-associated cases increased gradually over the study period, the number of domestically acquired cases remained stable at around 50 cases per year (Fig. 1). The median age of domestically acquired typhoid patients was 24 years [interquartile range (IQR) 7–39, range 0–89], and 46% were female (Table 1). Compared to travel-associated typhoid patients, domestically acquired typhoid patients were more often aged $\leqslant 5$ years (21% *vs.* 15%, $P < 0{\cdot}001$) or >60 years (9% *vs.* 3%, $P < 0{\cdot}001$). Seventy-one per cent of domestically acquired typhoid patients were hospitalized, and one patient died. Patients with domestically acquired illness were less likely to report typhoid vaccination within 5 years before illness onset compared to patients with travel-associated illness (1% *vs.* 6%, $P < 0{\cdot}001$). Compared to isolates from travel-associated cases, those from domestically acquired cases were less frequently multidrugresistant (2% *vs.* 15%, $P < 0{\cdot}001$) or nalidixic acid resistant (13% *vs.* 60%, $P < 0{\cdot}001$). Of 416 cases with PFGE pattern information, there were 249 unique *Xba*I patterns (median number of isolates per *Xba*I PFGE pattern = 1; IQR 1–2, range 1–14). California reported 24% of all travel-associated cases, followed by New York (17%), and New Jersey (8%). California also reported the largest proportion of domestically acquired typhoid cases (30%), followed by New York (13%) and Florida (6%) (Table 2). Twenty-three states each reported between 1 and 9 domestically acquired typhoid cases during these 12 years. New Jersey and New York had relatively high crude rates of travel-associated typhoid fever cases (2·05 per million and 1·99 per million, respectively) while Minnesota and California had relatively high crude rates of domestically acquired typhoid fever cases (0·43 per million and 0·42 per million, respectively).

Detection of domestically acquired typhoid clusters

In state-level analysis, 44 space–time clusters were detected in 24 states (Supplementary Table S1). Eighteen (41%) clusters had P values <0·05. The number of clusters per state ranged from 0 to 3. The median number of cases per cluster was 3 (IQR 2–6, range 2–16), the median duration for each cluster was 3 months (IQR 1–9·5, range 1–62), and the median number of counties per cluster was 3 (IQR 1–6·5, range 1–27). As an example, the locations and the number of cases per county in the three space–time clusters detected in California are shown in Figure 2*a*.

For region-level analysis, we identified three regions that consistently reported a large number of domestically acquired typhoid cases: a region in the western United States (Arizona, California, Idaho, Oregon, Nevada, Washington), a region in the eastern United States (Connecticut, Delaware, Kentucky, Massachusetts, Maryland, North Carolina, New Jersey, New York, Pennsylvania, Rhode Island, Tennessee, Virginia, Vermont, West Virginia), and a region around Minnesota (Iowa, Minnesota, North Dakota, South Dakota, Wisconsin). Eleven space–time clusters were detected in region-level scans: five in the first region (Fig. 2*b*), five in the second, and one in the third region. Four (36%) clusters had P values <0·05. Three clusters crossed state lines. The median number of cases per cluster was 5 (IQR 2–13, range 2–57), and the median duration was 2 months (IQR 1–7, range 1–62).

In the continental United States-level analysis, nine space–time clusters were detected (Fig. 2*c*). Seven (78%) clusters had P values <0·05. The number of cases ranged from 2–85 (median 6, IQR 4–15), and the duration ranged from 1–62 months (median 2, IQR 1–2). Seven clusters were in single states and had been detected by state-level analysis, one cluster that crossed a state line had been detected by a regional analysis. Multiple small clusters detected in state- and region-level scans appeared as one single cluster, in and around California, in the continental United States-level scan.

Considering all clusters detected by state, region, and the continental United State scans and eliminating smaller overlapping clusters detected in more than one scan, we identified 45 distinct space–time clusters of $\geqslant 2$ domestically acquired typhoid cases. Eighteen (40%) clusters had P values <0·05 (Table 3).

Classification of domestically acquired typhoid clusters

Within the 45 identified space–time clusters, we identified a total of 28 outbreaks in 26 clusters

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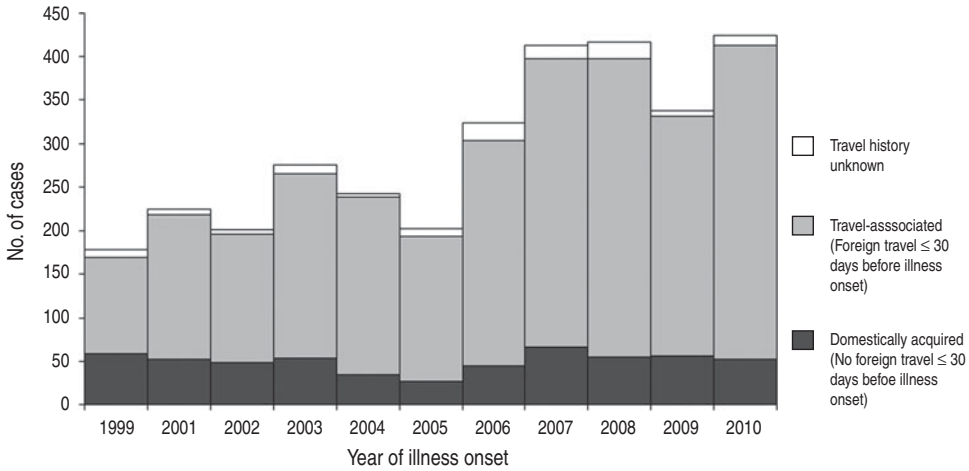

Fig. 1. Reported typhoid fever cases by travel status, National Typhoid and Paratyphoid Fever Surveillance, United States, 1999–2010.

Table 1. *Characteristics of patients and isolates from domestically acquired and travel-associated typhoid fever cases, United States, 1999–2010*

	Domestically acquired typhoid fever cases			Travel-associated typhoid fever cases			
Characteristic	*n*	*N*	(%)	*n*	*N*	(%)	*P* value‡
Child (⩽5 years)	126	588	(21)	398	2655	(15)	<0·001
Adult (>60 years)	55	588	(9)	69	2655	(3)	<0·001
Female	280	609	(46)	1304	2734	(48)	0·40
Hospitalized	412	578	(71)	2020	2652	(76)	0·01
Died	1	561	(<1)	4	2529	(<1)	>0·99
Vaccinated within 5 years before illness onset	7	494	(1)	112	1994	(6)	<0·001
Multidrug-resistant isolate*†	7	356	(2)	257	1669	(15)	<0·001
Nalidixic acid-resistant isolate*	48	356	(13)	1006	1669	(60)	<0·001

* Minimum inhibitory concentrations were interpreted by using the Clinical and Laboratory Standards Institute criteria when available: ampicillin (⩾32); chloramphenicol (⩾32); trimethoprim-sulfamethoxazole (⩾4/76); nalidixic acid (resistance breakpoint, ⩾32).

† Resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.

‡ χ^2 test or Fisher's exact test (when expected cell frequencies were <5).

(two larger clusters each included two distinct outbreaks based on PFGE patterns and epidemiological information). The 19 remaining clusters consisted of 17 non-outbreaks and two possible outbreaks. Space–time clusters that were classified as outbreaks often included more cases (median 4 *vs.* 2), fewer counties (median 3 *vs.* 4), and were shorter (median 2 months *vs.* 5 months) than those classified as non-outbreaks. The positive predictive value of our space–time scan approach to outbreak detection was 58% [95% confidence interval (CI) 42–72] (26 space–time clusters including at least one outbreak in 45 space–time clusters detected); when the two possible outbreaks were included, the positive predictive value was 62% (95% CI 47–76) (28/45). Sensitivity was 70% (95% CI 35–92) (7/10 reported or published outbreaks were detected) (Table 4). Specificity was 62% (95% CI 47–76) [Specificity is 1 minus probability of false positive, which was 38% (95% CI 24–53)]. When analysis was limited to space–time clusters with *P* values <0·05, the positive predictive value and specificity increased to 78% (95% CI 59–97) and 89% (95% CI 74–100), respectively, but the sensitivity decreased to 50% (95% CI 19–81) and 12 fewer outbreaks were detected.

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Table 2. *Reported domestically acquired and travel-associated typhoid fever cases and crude rates by state, National Typhoid and Paratyphoid Fever Surveillance, United States, 1999–2010*

	Domestically acquired typhoid fever ($N = 610$)			Travel-associated typhoid fever ($N = 2761$)		
State	No. of cases	%	Crude rate (per million)	No. of cases	%	Crude rate (per million)
California	180	30	0·42	656	24	1·54
New York	80	13	0·35	459	17	1·99
Florida	37	6	0·18	103	4	0·49
New Jersey	29	5	0·28	211	8	2·05
Minnesota	26	4	0·43	32	1	0·52
Texas	25	4	0·09	141	5	0·51
Virginia	21	3	0·23	105	4	1·17
Washington	19	3	0·25	58	2	0·77
Maryland	18	3	0·27	69	2	1·04
Georgia	17	3	0·16	92	3	0·85
Other states*	158	26	—	835	30	—

* Twenty-nine states for domestically acquired cases and 40 states for travel-associated cases.

Characteristics of domestically acquired typhoid outbreaks

Sixteen of the 28 outbreaks were linked to a confirmed or suspected carrier, two were linked to imported frozen mamey fruit pulp [21, 22], one was linked to Gulf Coast oysters [23], and five occurred in two household contacts with an unknown source. None were identified as waterborne. The number of epidemiologically linked cases in these outbreaks ranged from 2 to 15 (median 2, IQR 2–4), and the duration ranged from 4 to 250 days (median 19·5, IQR 10–45 days).

Three outbreaks had $\geqslant 2$ different *Xba*I PFGE patterns in the epidemiologically linked cases. One outbreak that occurred in restaurant patrons was linked to a food handler who was a suspected carrier. Isolates from these patients had three different PFGE patterns, with the largest difference of two bands (Fig. 3*a*). The second outbreak occurred in two brothers diagnosed 1·5 months apart. The patterns from their isolates differed by two bands (Fig. 3*b*). Their grandmother was identified as a *S.* Typhi carrier, but her isolate was not available for subtyping. The patients involved in the third outbreak were a 74-year-old woman and a 17-year-old boy living in the same household. They had illness onset within 2 days of each other, and their isolates differed by one band (Fig. 3*c*).

Three outbreaks published in the literature or reported to CDC outbreak surveillance systems were not detected (Table 4): one, because none of the outbreak-associated cases were reported to NTPFS; another, because only two cases were reported to NTPFS in an area with a high background rate of typhoid fever; and the third, because only one case was reported to NTPFS. The remaining 21 outbreaks detected by our approach had not been reported to CDC or published as outbreaks, but information from NTPFS forms or follow-up calls indicated that epidemiological links in cases were known to state health departments.

In three outbreaks that had previously been published or reported, the number of cases detected in the space–time cluster matched the number in the publication or report (Table 4). In three other outbreaks, the number of cases in the space–time cluster was smaller than the number of cases in outbreak reports, either because some of the outbreak-associated cases were not in the NTPFS database, or some of the outbreak-associated cases were spatially or temporally dispersed and not detected by the space–time scan statistic method. In one outbreak, the number of cases in the space–time cluster was larger than the number of cases in the outbreak report. This space–time cluster crossed a state line; while the outbreak report only discussed cases in one state, three additional cases occurred in an adjacent state during the same time period. Although PFGE data were not available for these additional cases, it is possible that these cases were linked to the outbreak and that the association was not recognized.

In addition, we identified two possible outbreaks in the detected space–time clusters. One was a cluster of two cases. These two cases had been part of a cluster of six cases recognized and investigated by the state

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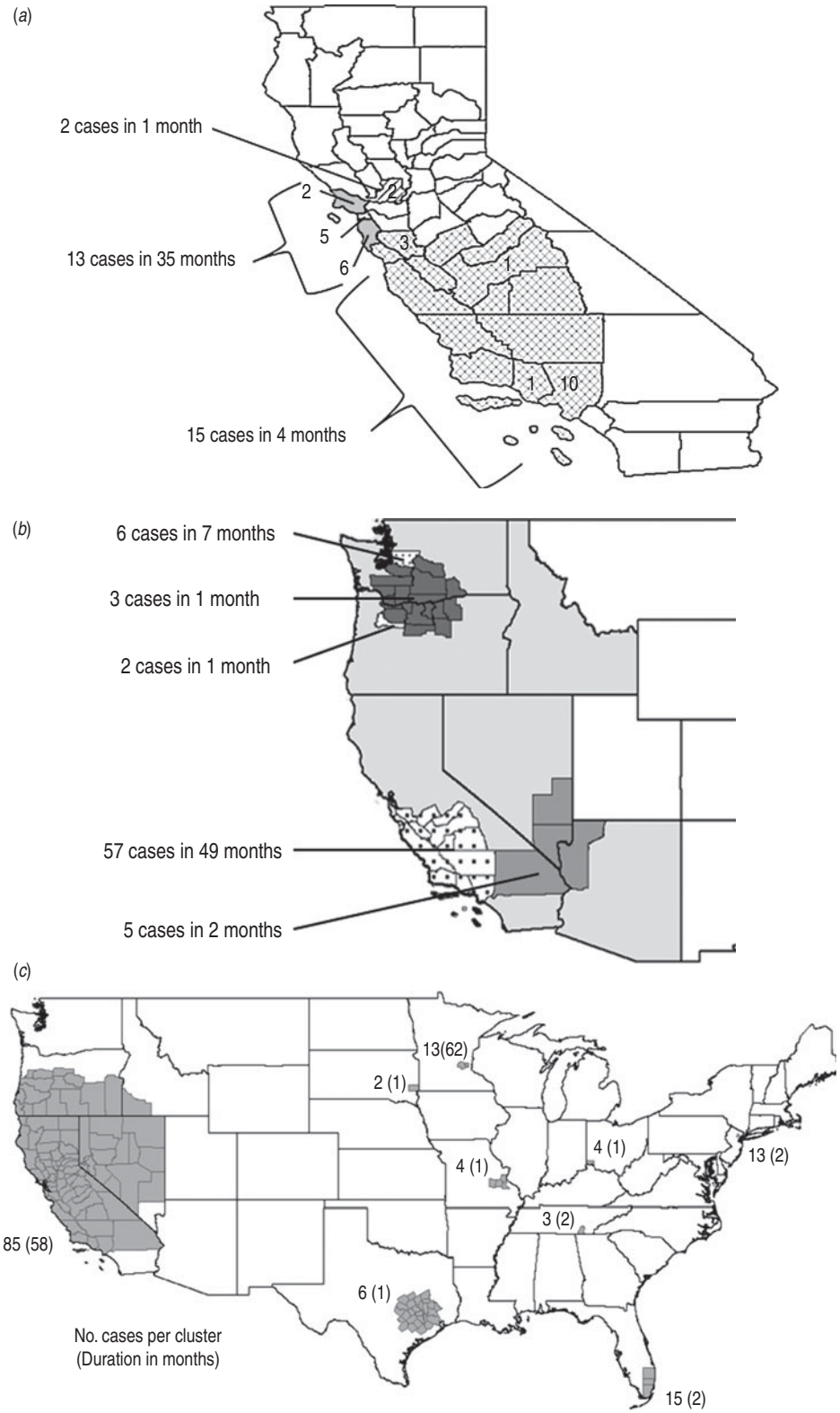

Fig. 2. Space–time clusters of domestically acquired typhoid-typhoid fever* by number of cases per cluster and time between first and last case detected in: (*a*) California, 1999–2010 (number of cases per county also shown); (*b*) a region in western United States, 1999–2010; and (*c*) continental United States, 1999–2010. (* Space–time clusters were identified in cases reported to the National Typhoid and Paratyphoid Fever Surveillance.)

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Table 3. *Proportion of outbreaks in statistically significant and non-significant space–time clusters of domestically acquired typhoid fever, United States, 1999–2010**

	Space–time clusters		
	$P < 0{\cdot}05$	$P > 0{\cdot}05$	Total
No. of detected clusters	18	27	45
No. (%) outbreaks in clusters	14 (78%)	12 (44%)	26 (58%)
No. (%) outbreaks and possible outbreaks in clusters	16 (89%)	12 (44%)	28 (62%)

* Space–time clusters were identified in cases reported to the National Typhoid and Paratyphoid Fever Surveillance.

health department (the other four cases were not reported to NTPFS); no epidemiological link was identified. The other cluster included five domestically acquired typhoid cases reported in one county during 1999–2001. No PFGE data or isolates were available. The state health department had no record of this cluster having been detected or investigated, and each case report was completed by different public health officials, suggesting this cluster had not been recognized as a possible outbreak.

DISCUSSION

Although typhoid fever is rare in the United States, domestically acquired typhoid fever cases continue to occur, causing occasional small outbreaks as well as substantial morbidity in affected patients. More than half of the detected outbreaks had been linked to a carrier. Due to potential contamination of food and water sources by an infected individual and the resulting public health impact, every case of typhoid fever acquired in a country where the disease is not endemic warrants thorough investigation. Our study found that most possible outbreaks in the United States had been detected and investigated using traditional analysis of surveillance data. However, space–time scan statistics shows promise as a useful additional analytic tool for public health.

Domestically acquired typhoid cases differ from travel-associated cases in some characteristics. While most of travel-associated typhoid patients were young to middle-aged adults, domestically acquired typhoid patients included a higher proportion of infants and young children, and adults aged >60 years. This may be explained by the demographics of travellers to typhoid-endemic countries. Isolates from domestically acquired cases were significantly less likely to be multidrug resistant or nalidixic acid resistant. Resistance to nalidixic acid has been shown to correlate with decreased susceptibility to ciprofloxacin [24, 25]. Antimicrobial resistance in *S.* Typhi strains has increased markedly during the past ~25 years, especially in Asia [4, 26–28]. Lower rates of drug resistance in infections acquired in the United States may be due in part to the source of some domestically acquired typhoid infections being chronic carriers who acquired the infection before widespread establishment of resistant strains or who came from areas where drug resistance is less common. This difference also suggests that travel-associated cases are not the major source of infections for domestically acquired typhoid cases; this is also compatible with the modest differences in the observed geographical distribution and crude rates of domestically acquired and travel-associated cases by state.

We explored the use of a space–time scan statistic as a screening tool for detecting outbreaks in domestically acquired typhoid fever cases because typhoid fever outbreaks caused by asymptomatic carriers can be small, prolonged, and therefore difficult to detect by routine surveillance. We did not limit our analysis to the clusters with statistical significance, because domestically acquired typhoid fever cases are rare and finding previously undetected outbreaks is likely to require an approach with high sensitivity, even if the positive predictive value is compromised. The method detected seven of the ten outbreaks previously published in the literature or reported to CDC outbreak surveillance systems. Two outbreaks were not detected because none or only one case was reported to the typhoid fever case surveillance system. This highlights a major limitation of our approach, i.e. reliance on cases being reported to the surveillance system. The third outbreak was not detected because it was masked by the presence of a concurrent large space–time cluster in neighbouring counties.

We also explored whether a space–time scan statistic could identify previously unrecognized outbreaks. We detected one possible outbreak that may not have been recognized previously; however, in all the other outbreaks detected by our approach, epidemiological links in cases were already known to state health departments. These outbreaks were not reported, perhaps because until 2009 only foodborne and waterborne disease outbreaks were reported through CDC

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Table 4. *Outbreaks of domestically acquired typhoid fever published in the literature or reported to CDC outbreak surveillance systems and cases in space–time clusters, United States, 1999–2010**

Year	Vehicle or common exposure	Number of cases in outbreak report	Number of cases in space–time cluster	Reference for outbreak
1999–2000	Imported frozen mamey	15	15	[21]; CDC†
2000	Sexual transmission between men; linked to carrier	7	4	[32]
2000	Restaurant; linked to suspected carrier	9	13	[33]; additional unpublished data from NYC DHMH
2000	Temple	16	6	CDC†
2001	Carrier	3	Not detected‡	CDC†
2002	Restaurant; linked to carrier	4	Not detected§	CDC†
2003	Gulf coast oyster	6	6	[23]; CDC†
2005	Congregation meeting; linked to returned traveller	2	Not detected¶	[34]
2009	Unknown (occurred in children)	3	3	CDC†
2010	Imported frozen mamey	12	5	[22], CDC†

NTPFS, National Typhoid and Paratyphoid Fever Surveillance; NYC DHMH, New York City Department of Health and Mental Hygiene.

* Space–time clusters were identified in cases reported to the NTPFS.

† Reported to CDC outbreak surveillance systems comprised of the Foodborne Disease Outbreak Surveillance System, Waterborne Disease and Outbreak Surveillance System, and the National Outbreak Reporting System.

‡ None of the cases were in NTPFS.

§ Two of the cases were in NTPFS, but the cluster occurred in an area with high background rate of typhoid fever.

¶ Only one of the cases was in NTPFS.

outbreak surveillance systems. Before 2009, if the mode of transmission in a typhoid fever outbreak was unclear or determined to be not foodborne or waterborne, the outbreak might not have been reported. This limitation was eliminated with the advent of NORS in 2009, a national surveillance system to which outbreaks with various modes of transmission or an indeterminate mode of transmission can be reported. Several clusters that met the outbreak definition involved household contacts. Because CDC outbreak surveillance systems are passive surveillance systems, there is variability in reporting practices in states; while some local and state health departments report household clusters to the outbreak surveillance system, others do not. We relied on available data and state health departments for outbreak classification: misclassification of outbreaks (e.g. true outbreaks misclassified as non-outbreaks when multiple PFGE patterns were present and epidemiological data were missing) may have affected our ability to accurately evaluate the space–time scan approach.

This study also highlighted possible limitations of current surveillance for typhoid fever outbreaks, which consists of local epidemiological investigation and a search for *S.* Typhi isolates with matching PFGE patterns in PulseNet from cases that occurred within a 60-day period. Since typhoid fever is uncommon, most confirmed cases are followed-up by local health departments and reported to state health departments, and eventually to NTPFS. While some space–time clusters of domestically acquired typhoid cases detected in our study crossed state lines, state health departments may not be aware of other typhoid fever cases in neighbouring states. As the purpose of NTPFS is to monitor trends and risk factors, case report forms are currently not collected in a manner that allows real-time outbreak detection. Not all *S.* Typhi isolates are submitted to PulseNet and possible associations between uploaded isolates may be missed if they occurred >60 days apart. Timely collection of case report forms and routine linking of NTPFS and PulseNet may improve outbreak surveillance by allowing PulseNet to focus on domestically acquired cases and expand the surveillance period from the current 60 days. We also detected three outbreaks involving multiple PFGE patterns in isolates from epidemiologically linked cases. A single chronic carrier can simultaneously shed *S.* Typhi variants with considerable genetic differences [29]. Microbiologically, it is plausible that genetic mutations

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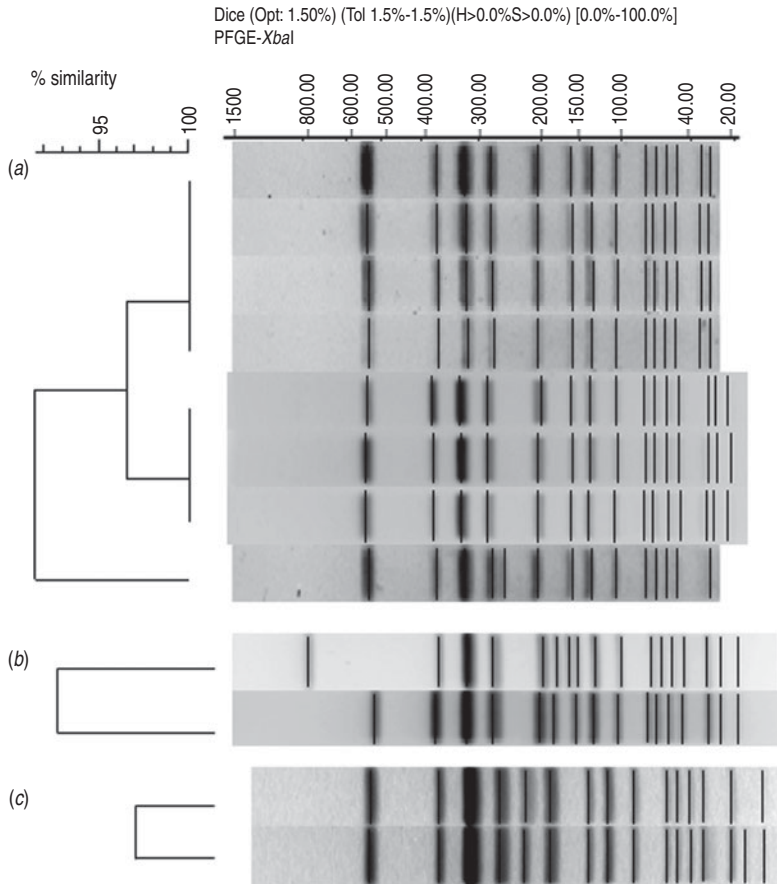

Fig. 3. Dendrogram of pulsed-field gel electrophoresis (PFGE)–*Xba*I patterns of the *Salmonella enteria* serotype Typhi strains from three outbreaks (*a*–*c*) involving more than one pattern, United States.

occur within a *S.* Typhi strain harboured by a chronic carrier over years. Further, since chronic carriers can shed the bacterium for many years, laboratory-based surveillance at local, state, and national levels should include review of subtyping data on isolates submitted over several years.

The study has some limitations beyond those discussed above. This was a retrospective analysis of passive surveillance data collected over 12 years; some cases and outbreaks were not reported to the surveillance system and some outbreaks were difficult to confirm because epidemiological or isolate data were missing. Many of the cases occurred >5 years earlier; additional epidemiological data could not be obtained, and isolates often had not been stored. Moreover, we may have misclassified travel-associated cases as domestic cases if the incubation period was over 30 days. Because no common identification system existed in the databases, we often had to rely on demographic data to merge databases, which limited our ability to accurately link isolate data to surveillance data in some cases. We used county of residence as a proxy for the location of exposure; some cases may have acquired infection in another county or even in another state. We also faced limitations inherent to the space–time scan statistic. Outbreaks widely dispersed in space or time, small outbreaks in areas with high background rates of typhoid or large populations, and separate outbreaks with overlapping areas may have escaped detection by our approach. Clusters with overlapping areas may be detected as one large cluster if they occurred during the same time period. Separate clusters that overlapped in space, but not in time would not be detected based on the 'no spatial overlap' setting we used for our space–time scans. In addition, purely temporal scans might also have been effective for detecting outbreaks that were spatially diffuse.

In conclusion, although they may be small, outbreaks of typhoid fever continue to occur in the United States. Our approach using a space–time scan statistic detected most reported or published outbreaks. Although it did not definitively identify any previously unrecognized outbreaks, it showed the

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potential to detect outbreaks that may escape detection by routine analysis of surveillance data, including a potential outbreak that extended across jurisdictional lines and a potential outbreak involving multiple PFGE patterns. To improve detection of domestically acquired typhoid fever outbreaks, we recommend that state and local health departments investigate and report all domestically acquired typhoid fever cases and identified outbreaks. Although the United States does not have national guidelines, detailed guidelines for management and investigation of typhoid and paratyphoid cases are outlined in a document published in England [30, 31]. We recommend CDC continue to explore the use of space–time scan statistics using different parameters and settings or use of the retrospective space–time permutation scan statistic [8] for identification of domestically acquired typhoid fever clusters that may represent undetected outbreaks retrospectively and for prospective real-time or periodic disease surveillance. Moreover, CDC should explore ways to improve timeliness of the typhoid fever surveillance system and to enable linking of the databases more easily. Space–time scan statistics may be a promising tool for outbreak detection, when used together with molecular subtyping and shoe-leather epidemiology.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814003021.

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DECLARATION OF INTEREST

None.

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