



Published in final edited form as:

Infect Dis (Lond). 2026 January ; 58(1): 108–125. doi:10.1080/23744235.2025.2553665.

Epidemiology and antimicrobial resistance of *Salmonella enterica* serotype Infantis in the United States: infections and emergence of a multidrug-resistant strain during 1979–2022

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Disclosure statement

The authors report there are no competing interests to declare.

Disclaimers

The opinions expressed by authors contributing to this report do not necessarily reflect the opinions of the Centers for Disease Control and Prevention.

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Abstract

Background: *Salmonella* infections are a major cause of human illness in the United States. *Salmonella enterica* serotype Infantis has re-emerged as a leading serotype with the emergence of a multidrug-resistant *S. Infantis* strain, designated as REPJFX01 by the Centers for Disease Control and Prevention (CDC). REPJFX01, which typically contains a megaplasmid of emerging *Salmonella* Infantis (pESI) harboring multiple resistance genes and a chromosomal *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin, has caused human infections linked to chicken consumption.

Objective: The study aimed to describe the epidemiology and antimicrobial resistance of human *S. Infantis* infections, including the emergence of REPJFX01, in the United States.

Methods: The study used data from five CDC surveillance systems, with combined years from 1979 through 2022. Negative binomial and logistic regression models were used in the multivariable analyses of surveillance data.

Results: In 10 active surveillance sites, the mean annual incidence of human *S. Infantis* infections was twice as high during 2013–2022 vs. 2003–2012 (adjusted rate ratio=1.96, 95% CI 1.75–2.20). REPJFX01 infections accounted for nearly one-third of *S. Infantis* infections during 2018–2022 (vs. 2013–2017, adjusted odds ratio=2.09, 95% CI 1.56–2.79). *S. Infantis* infections were more likely among persons who were ≥45 years old, female, from racial and ethnic minority groups, and had *Salmonella* isolated from urine, than infections with other common serotypes.

Conclusion: The increase in *S. Infantis* infections during 2013–2022 was likely driven by an increase in REPJFX01 infections. Public health strategies to reduce *Salmonella* contamination of chicken could help prevent human infections.

Keywords

Salmonella ; Infantis; pESI; REPJFX01; multidrug resistance; antimicrobial resistance; incidence

Background

Nontyphoidal *Salmonella* infections are a major cause of human illness in the United States, resulting in ~1.35 million illnesses annually, with ~25% attributed to poultry sources (1,2). Twenty serotypes cause most human infections. *Salmonella enterica* serotype Infantis (*S. Infantis*) has re-emerged as a leading serotype with the emergence of a multidrug-resistant strain (3–5). Although most *Salmonella* infections result in self-limited gastrointestinal illness, antimicrobial agents, particularly fluoroquinolones (e.g., ciprofloxacin) and third-generation cephalosporins (e.g., ceftriaxone), are recommended for patients with severe infections (e.g., bloodstream infections) (6,7). Azithromycin is a treatment option, particularly when resistance to fluoroquinolones and third-generation cephalosporins is a concern (7,8).

The multidrug-resistant *S. Infantis* strain, now designated as “REPJFX01,” was first identified in the United States from a retail chicken sample collected in 2014; it had a rare extended-spectrum β -lactamase gene, *bla*_{CTX-M-65}, conferring resistance to ceftriaxone and other β -lactams (9–11). Subsequent investigations found that the earliest U.S. infections with this *S. Infantis* strain occurred in 2012 in travelers returning from Peru (12). REPJFX01 typically contains a megaplasmid of emerging *Salmonella* Infantis (pESI) harboring multiple resistance genes and a chromosomal *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin (11,13–17). Additional human infections have since been detected, including outbreaks linked to consumption of chicken (5,11,18). *S. Infantis* is now among the most common serotypes from U.S. poultry sources (5,15–17).

We describe the epidemiology and antimicrobial resistance of human *S. Infantis* infections in the United States, including the emergence of REPJFX01, using data from five surveillance and monitoring systems at the Centers for Disease Control and Prevention (CDC). Since 2020, CDC has used whole genome sequencing (WGS) to monitor reoccurring, emerging, or persisting (REP) strains of enteric bacteria, including REPJFX01 (10,11). These systems, varying in scope and methods and including surveillance for overall and outbreak-related *Salmonella* infections, provide data for an overview of *S. Infantis* and REPJFX01 infections at the national level and more in-depth analyses of infections in 10 active surveillance sites.

Methods

Data Sources and Definitions

PulseNet: PulseNet, the national molecular subtyping network for foodborne disease surveillance, monitors *Salmonella* strains to detect potential outbreaks; in 2019, PulseNet began using whole genome sequencing (WGS) as their gold standard for cluster detection (19). Public health laboratories (PHLs) analyzed sequence data using BioNumerics Software

(Applied Maths, <http://www.applied-maths.com>) and uploaded sequence information to the CDC PulseNet national database with isolate metadata. Routine PulseNet sequencing was performed using short read data (19,20).

Since 2020, CDC has monitored REPJFX01 as a persisting REP strain (10,11,19). REPJFX01 isolates are defined by PulseNet as *S. Infantis* isolates related by core genome multilocus sequence typing (cgMLST) within a range of 0–82 alleles, typically characterized by the presence of pESI and *gyrA87* mutation (11). All *S. Infantis* sequences available in PulseNet (as of 2/21/24), including those submitted before 2020, were screened for inclusion in REPJFX01. The presence of *IncFIB*(pN55391), a plasmid replicon sequence associated with pESI (pESI-like), and *gyrA87* mutation were assessed among REPJFX01 isolates (15–17). We looked at *IncFIB*(pN55391) but not necessarily for other genes associated with the plasmid.

Laboratory-Based Enteric Disease Surveillance (LEDS): PHLs serotype human *Salmonella* isolates received from clinical laboratories and report them to CDC through the LEDS system (21). In this report, the term *Salmonella* refers to nontyphoidal *Salmonella* (i.e., excluding serotypes Typhi and Paratyphi A, B [tartrate-negative], and C) (21,22). We determined the 20 most common serotypes among isolates collected during 1979–2018 and partitioned them into two categories: *S. Infantis* and other common serotypes (“other *Salmonella*”).

Foodborne Diseases Active Surveillance Network (FoodNet): FoodNet conducts population-based active surveillance for laboratory-confirmed *Salmonella* infections, representing ~15% of the U.S. population (3,4). FoodNet, established in 1996, gradually expanded until 2004 when it stabilized to its current 10-site catchment; it collects patient demographic, clinical, outcome, and exposure data (Table 1). We used 1996–2020 data to determine the 20 most common serotypes and also created *S. Infantis* and “other *Salmonella*” categories (Table 1). Using available PulseNet identifiers, we linked FoodNet cases with PulseNet WGS data to identify REPJFX01 infections.

National Antimicrobial Resistance Monitoring System (NARMS): NARMS, established in 1996, monitors resistance among *Salmonella* (22–24). PHLs in 50 state and 4 local health departments submit every 20th *Salmonella* isolate from human infections that are received from clinical laboratories to CDC for antimicrobial susceptibility testing. Laboratory methods and interpretive criteria have been described in previous reports (22–24). Since 2015, the NARMS laboratory and PHLs participating in PulseNet have more routinely sequenced *Salmonella* isolates.

To assess antimicrobial resistance among *S. Infantis* isolates, we determined “predicted” resistance from WGS data based on the presence of resistance determinants, including genes and mutations, in the isolate’s genome. We categorized isolates with resistance to at least one antimicrobial as resistant to the drug class (as defined by the Clinical and Laboratory Standards Institute [CLSI]) (25). We used data from 2012–2022.

National Outbreak Reporting System (NORS): CDC has received reports of foodborne disease outbreaks electronically since 1998. The reporting platform NORS launched in 2009 to integrate outbreak reporting and includes data on all foodborne and waterborne outbreaks and enteric disease outbreaks transmitted by contact with environmental sources, infected persons or animals, or unknown modes. (Table 1) (26). State, local, and territorial public health agencies submit reports to CDC, including PulseNet identifiers for outbreak-associated clinical isolates. We used available PulseNet identifiers to link NORS isolate records with WGS data and identify outbreaks that included ≥ 1 REPJFX01 infection. We included *S. Infantis* outbreaks reported during 1998–2021.

Additional Description of Data Sources and Methods

Each of the five surveillance systems had unique and complementary contributions to our study. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.

To calculate incidence of *S. Infantis* infections each year, we used 1979–2018 data from LEDS and 1996–2022 data from FoodNet; annual incidence rates were calculated per 100,000 persons using U.S. Census population data (27). We included “historical” data from LEDS to describe longer-term changes. For an overall side-by-side comparison, we visually inspected incidence trend lines of *S. Infantis* infections in LEDS and FoodNet for the 23 years (1996–2018) with available data from both surveillance systems. However, we did not make formal comparisons between changes in incidence observed in the two systems. They differed in population coverage and type of surveillance. LEDS involved laboratory-based passive surveillance with limited patient information collected for isolates reported in 50 states, while FoodNet conducted active surveillance of infections in 10 sites (3,4,21). For ascertained infections, FoodNet collects data on patient demographics, specimen source, hospitalization, deaths, international travel in the 7 days before illness onset (since 2004), outbreak association, symptoms (since 2011), and history of selected comorbidities (since 2018).

For comparisons of average incidence rates, we categorized time periods by dividing study years equally (Table 1). Using negative binomial models, we assessed changes in incidence of *S. Infantis* infections by comparing average annual incidence rates for two 10-year periods during the 20 most recent available years: 2009–2018 vs. 1999 vs. 2008 in LEDS and 2013–2022 vs. 2003–2012 in FoodNet; the latter included 19 years (2004–2022) with stable 10-site catchment in FoodNet. The models were adjusted for site (50 states in LEDS, 10 sites in FoodNet).

We used logistic regression models in the multivariable analyses of FoodNet data to assess patient and other characteristics of *S. Infantis* and REPJFX01 infections, including isolate sources (e.g., blood suggesting bloodstream infections) (Tables 1, 2 and 4). We included years when most variables were routinely collected or WGS data were available in FoodNet and PulseNet. For example, because PHLs started sequencing more isolates in 2015 and FoodNet began collecting PulseNet WGS identifiers in 2018 (followed by retrospective collection for the earlier years), we included data for the five most recent available years, 2016–2020, in the analysis of REPJFX01 infections. Using PulseNet WGS identifiers, we

identified REPJFX01 infections by linking PulseNet and FoodNet data. In the analysis of overall *S. Infantis* infections, we included infections ascertained in FoodNet during 2006–2020; all variables were routinely collected and PulseNet linking was not necessary for this analysis. In the multivariable models, we considered variables that were significant in the univariable analyses or associated with *Salmonella* infections in previous studies (28–30) (Tables 2, 4, Supplemental Tables 1–3).

Using logistic regression, we assessed changes in REPJFX01 among sequenced *S. Infantis* isolates in PulseNet by comparing average annual percentages for two five-year periods, 2018–2022 vs. 2013–2017, during the 10 most recent available years; the models were adjusted for region. We used the 4 U.S. Census regions to categorize the submitting PHLs (27). We described predicted antimicrobial resistance among sequenced isolates using WGS data in NARMS for isolates received from PHLs (as part of every 20th submission for testing at CDC) and isolate sequences uploaded by PHLs to the CDC PulseNet database that were captured in the NARMS data system. To provide an overview of *S. Infantis* outbreaks, we used data from outbreak reports received by NORS for 1998–2021.

Results

LEDS: Incidence of *S. Infantis* infections (1979–2018)

S. Infantis was the sixth most common *Salmonella* serotype and accounted for 35,771 (3.0%) of 1,201,630 isolates representing the 20 most common serotypes. Typhimurium and Enteritidis, the two leading serotypes, accounted for 52% of total isolates of other common serotypes. Newport, Heidelberg, and Javiana were other common serotypes, ranked 3rd, 4th, and 5th, respectively.

The mean annual incidence of *S. Infantis* infections per 100,000 persons was 0.37 (95% CI 0.29–0.46) during 2009–2018, higher than that for 1999–2008 (0.18, 95% CI 0.17–0.20) and 1989–1998 (0.23, 95% CI 0.19–0.27), and lower than during 1979–1988 (0.54, 95% CI 0.48–0.59) (Figure 1). The adjusted incidence rate ratio (RR) increased significantly during 2009–2018 vs. 1999–2008 (RR=1.88, 95% CI 1.76–2.01).

The annual incidence of other *Salmonella* infections was stable during the past two decades (Figure 1). The mean incidence per 100,000 was 9.74 (95% CI 9.29–10.19) during 2009–2018 and 9.06 (95% CI 8.78–9.33) during 1999–2008.

FoodNet: Incidence and characteristics of infections

Overall *S. Infantis* incidence (1996–2022): *S. Infantis* was the 10th most common serotype and accounted for 3,036 (2.6%) of 117,064 isolates representing the 20 most common serotypes. The annual incidence of *S. Infantis* infections increased over the past two decades; rates (per 100,000) were stable (0.12–0.22) during 2003–2009, started increasing in 2010, and have remained at ≥ 0.30 since 2013 (Figure 2, Supplemental Figure 1). Mean annual rates for 2013–2022 and 2003–2012 were 0.44 (95% CI 0.39–0.49) and 0.23 (95% CI 0.20–0.26), respectively. The adjusted RR (1.96, 95% CI 1.75–2.20) increased significantly during 2013–2022 vs. 2003–2012; results were similar when excluding international travel-related infections.

From visual inspection of *S. Infantis* incidence by year for an overall side-by-side comparison with LEDS data, annual rates from the two systems appeared to align for most of the overlapping years from 1996 through 2018 (Supplemental Figure 1).

Characteristics of *S. Infantis* infections (2006–2020): FoodNet sites reported 2,363 *S. Infantis* infections. Among persons with these infections, 72.0% were adults (≥ 18 years), 58.0% were female, 59.4% were non-Hispanic (NH) White, 9.3% reported international travel, and 26.8% were hospitalized (Tables 2, 3; Supplemental Table 4).

S. Infantis infections were more likely than other *Salmonella* infections among persons who were 45–64 years (adjusted odds ratio [aOR]=1.29, 95% CI 1.11–1.50) and ≥ 65 years old (aOR=1.32, 95% CI 1.12–1.56); female (aOR 1.14, 95% CI 1.04–1.26); NH Asian or Pacific Islander (Asian/PI) (aOR=3.65, 95% CI 3.09–4.30), of multiple or other/unknown race/ethnicity (aOR=1.59, 95% CI 1.22–2.07), and Hispanic or Latino (1.31, 95% 1.13–1.51); and those who had an isolate from urine (aOR=2.06, 95% 1.75–2.42) and an outbreak-associated infection (aOR=1.20, 95% CI 1.03–1.39) (Table 2). *S. Infantis* infections were less likely among persons who had an isolate from blood (aOR=0.64, 95% CI 0.50, 0.83). In the univariable analysis, persons with *S. Infantis* infections were less likely to present with fever (OR=0.59, 95% CI 0.53–0.66), diarrhea (OR=0.61, 95% CI 0.52–0.72), and bloody diarrhea (OR=0.61, 95% CI 0.54–0.69), and more likely to report diabetes (OR=2.14, 95% CI 1.55–2.96); history of diabetes was unknown in 40.0% among *S. Infantis* and 39.2% among other *Salmonella* infections (Table 3, Supplemental Table 4). Persons with *S. Infantis* infections had a lower proportion hospitalized than other *Salmonella* infections (26.8% vs. 29.0%; OR=0.90, 95% CI 0.82–0.98). However, the difference was not statistically significant after adjusting for covariates in the multivariable model with hospitalization as dependent variable; isolation from blood and age ≥ 65 years were the strongest predictors of hospitalization among *S. Infantis* infections (Table 3, Supplemental Table 3).

Characteristics of REPJFX01 infections (2016–2020): FoodNet sites reported 1,001 *S. Infantis* infections; 703 (70.2%) were linked to PulseNet WGS data, of which 248 (35.3%) were REPJFX01. Among persons with the REPJFX01 infections, 86.3% were adults (≥ 18 years), 70.0% were female, 71.2% were NH White, 30.6% were hospitalized, 2 (0.8%) died, and 10.8% reported international travel (Tables 4, 5). Of 23 persons with known travel destination, the Dominican Republic (45.5%) and Ecuador or Peru (40.9%) were reported most often (Supplemental Table 5).

REPJFX01 infections were more likely than other *Salmonella* infections among persons who were 45–64 years (aOR=1.95, 95% CI 1.08–3.51) and ≥ 65 years old (aOR=2.34, 95% CI 1.28–4.27); female (aOR=1.46, 95% CI 1.06–2.00); and those who had an isolate from urine (aOR=4.82, 95% CI 3.35–6.92) and other sources (aOR=3.20, 95% CI 1.67–6.13) (Table 4). In the univariable analysis, persons with REPJFX01 infections were less likely to present with fever (OR=0.47, 95% CI 0.36–0.62), diarrhea (OR 0.28, 95% CI 0.20–0.40), and bloody diarrhea (OR=0.38, 95% CI 0.27–0.55), and more often reported diabetes (OR=4.44, 95% CI 2.85–6.91); history of diabetes was unknown in 42.8% among REPJFX01 and 39.2% among other *Salmonella* infections (Table 5, Supplemental Table 6). The proportion

of patients with REPJFX01 infections (30.6%) that were hospitalized was comparable with that among other *Salmonella* infections (30.1%). The difference was also not statistically significant after adjusting for covariates in the multivariable model with hospitalization as dependent variable; isolation from blood and age ≥ 65 years were the strongest predictors of hospitalization among REPJFX01 infections compared with other *Salmonella* infections. (Table 5, Supplemental Table 3).

We also compared REPJFX01 with non-REPJFX01 *S. Infantis* infections. The difference by sex was not statistically significant in the multivariable analysis. REPJFX01 infections were less likely among NH Asian/PI persons (aOR=0.19, 95% CI 0.05–0.70) (Supplemental Table 2); 3 (1.3%) isolates from NH Asian/PI persons were REPJFX01. In the univariable analysis, REPJFX01 infections had a higher likelihood of hospitalization than non-REPJFX01 infections (30.6% vs. 22.7%; OR=1.50, 95% CI 1.06–2.14) (Supplemental Table 2). However, the difference was not significant after adjusting for covariates in the multivariable model with hospitalization as dependent variable; isolation from blood and age ≥ 65 years were also the strongest predictors of hospitalization among REPJFX01 infections compared with non-REPJFX01 infections (Supplemental Table 3).

Other associations: Compared with other *Salmonella* infections, *S. Infantis* infections were less likely in the South; REPJFX01 infections were more likely in the Northeast and less likely in the South (Tables 2, 4). We found potential interaction between race-ethnicity and region and report aORs for race-ethnicity among *S. Infantis* infections stratified by region (Supplemental Table 7).

PulseNet and NARMS: Overall *S. Infantis* and REPJFX01 by state and year (2012–2022)

In PulseNet, REPJFX01 was first detected in 2012. All 50 states uploaded *S. Infantis* isolates to PulseNet during 2012–2022 (Supplemental Figure 2). Among 9,917 sequenced *S. Infantis* isolates from U.S. cases in PulseNet, 2,839 (28.6%) were REPJFX01. There were <50 isolates sequenced per year before 2014, and ≥ 100 isolates per year since 2015. Peak submissions were in the summer months for most years (Figure 3). REPJFX01 was detected in 10.1%–17.5% of isolates during 2014–2016, increased to 31.2% in 2018, peaked at 34.3% in 2019, and remained high through 2022 (Figure 4). The average percentage of REPJFX01 isolates during 2018–2022 (30.8%) was significantly higher than the average (20.8%) during 2013–2017 (aOR=2.09, 95% CI 1.56–2.79).

In NARMS, REPJFX01 was also first detected in 2012 among sequenced isolates; there was a similar increase in REPJFX01, which peaked at 34.3% in 2020 (Supplemental Figure 3). Because there were few REPJFX01 isolates before 2017, we did not use a multivariable model to compare 2018–2022 with 2013–2017.

PulseNet and NARMS: Molecular characteristics of REPJFX01 isolates and predicted antimicrobial resistance among *S. Infantis* isolates (2012–2022)

Of the *S. Infantis* isolates sequenced in PulseNet and NARMS, 6,542 were analyzed for predicted resistance; 2,778 (42.5%) were REPJFX01. The presence of pESI-like plasmid and *gyrA87* mutation were detected in 97% and 99.8% of REPJFX01 isolates, respectively.

Predicted resistance to 8 antimicrobial classes was higher among REPJFX01 than among non-REPJFX01 isolates ($p < 0.01$): quinolones (99.9%), aminoglycosides (96.8%), folate pathway inhibitors (94.3%), tetracyclines (90.2%), penicillins (60.9%), cephalosporins (60.7%), phenicols (56.9%), and fosfomycin (25.5%) (Table 6). Nearly half (49.6%) of REPJFX01 isolates were resistant to ≥ 7 classes, compared with 0.7% of non-REPJFX01 isolates ($p < 0.01$). Predicted resistance to azithromycin was low among REPJFX01 (0.4%) and *S. Infantis* overall (0.3%).

NORS: *S. Infantis* outbreaks (1998–2021)

Of 122 outbreaks with *S. Infantis* infections, multiple serotypes were reported in 18. The 104 *S. Infantis*-only outbreaks caused 2,953 illnesses, 460 hospitalizations, and 5 deaths; 19 (18.3%) were multistate (Table 7). The primary modes of transmission included 69 (66.3%) foodborne and 14 (13.5%) animal contact. Of the 69 foodborne outbreaks, 20 (29.0%) were linked to a single food category, including consumption of pork (7) and chicken (4).

The 14 animal contact outbreaks were linked to a single animal category: live chicken and other poultry (13) and dry dog food (1). The dog-associated outbreak, which included cases in 2011–2012, was the first detected since reporting of animal contact outbreaks began in 2009. Poultry-associated outbreaks linked to animal contact were first reported in 2012.

All 17 *S. Infantis* outbreaks linked to a single food or animal category that were associated with chicken consumption or live poultry exposure occurred during 2012–2021, accounting for 73.9% of 23 outbreaks during this period; 63.6% of 11 outbreaks that occurred before 2012 were linked to pork or other meat (Table 7, Supplemental Figure 4). A large outbreak of REPJFX01 infections in 2018–2019 was linked to consumption of raw chicken products, causing 129 illnesses, 25 hospitalizations, and 1 death (5, 11.18).

Discussion

S. Infantis has re-emerged as a major serotype causing *Salmonella* infections in the United States. In FoodNet, *S. Infantis* has been among the 10 most commonly reported serotypes since 2013 and increases in incidence have been described in previous annual reports (3,4). We estimate that the average annual incidence of *S. Infantis* infections was almost twice as high during 2013–2022 as it was during 2003–2012.

An increase in *S. Infantis* infections during the more recent 10-year period was likely driven by an increase in REPJFX01 *S. Infantis*, which accounted for nearly one-third of overall *S. Infantis* infections during 2018–2022. The acquisition of pESI could have allowed *S. Infantis* to proliferate in U.S. poultry production settings and drive an increase in human infections (5), similar to the spread of *S. Infantis* in the European poultry production system (13,14,31). The emergence of REPJFX01, typically containing pESI carrying multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin, is concerning. Nearly all REPJFX01 isolates had predicted decreased susceptibility to ciprofloxacin, and more than half had predicted resistance to ceftriaxone, limiting first-line treatment options and increasing the likelihood of treatment failures for severe salmonellosis (6–8,22,25). Blood cultures and antimicrobial susceptibility testing

(AST) are recommended to tailor the choice of antimicrobial treatment. Because of the low rates of predicted resistance to azithromycin among REPJFX01 and *S. Infantis* overall, this drug remains a viable treatment option (7–8). However, clinical breakpoints using traditional AST methods to determine resistance to azithromycin among nontyphoidal *Salmonella* serotypes have not been established by the Clinical and Laboratory Standards Institute (8,25,32,33). Our findings underscore the need for further research on clinical outcomes and other data to support establishing clinical breakpoints for azithromycin and continued monitoring of resistance genes and mechanisms conferring resistance to antimicrobial agents recommended for invasive *Salmonella* infections (8,32,33).

Comparing *S. Infantis* with other *Salmonella* infections, we found differences in demographic and other patient characteristics. These associations appeared to be stronger when we compared the subset of *S. Infantis* infections caused by REPJFX01 with other *Salmonella* infections—reflected in higher proportions that were female, ≥ 45 years (particularly ≥ 65), had isolates from urine, and reported diabetes, while fever and diarrheal illness were less represented among REPJFX01 infections. These findings suggest that increased urinary isolates among *S. Infantis* and REPJFX01 infections could represent increased urinary tract infections (UTIs), versus asymptomatic bacteriuria or specimen contamination from feces (34–37), compared with other *Salmonella* infections. Previous studies support these findings that infections with *Salmonella* isolated from urine were predominantly among older adults, female patients, and those with underlying conditions (e.g., diabetes) (34–37). There is a growing body of literature on foodborne transmission of pathogens causing UTIs, including a study of *Salmonella* UTIs using foodborne outbreak data; a small survey of patients from the study documented that consumption of contaminated food occurred before the illnesses (34). In addition to *S. Infantis*, other serotypes have been isolated more often from urine than serotypes belonging to commonly reported *Salmonella* groups, suggesting that these serotypes could have a predilection for invading the urinary tract (35, 36). A better understanding of the uropathogenicity of *S. Infantis* can help clarify mechanisms of *Salmonella* UTIs (36).

S. Infantis infections were more likely than other *Salmonella* infections among persons from racial and ethnic minority groups, particularly NH Asian/PI. REPJFX01 infections were more likely than other *Salmonella* infections in the Northeast. However, *S. Infantis* infections among NH Asian/PI persons were less likely to be due to REPJFX01. The reasons for these associations are unknown, but may reflect differences in exposures (e.g., meat and other food consumption, food preparation, animal contact) and warrant further investigation of potential interactions between race-ethnicity and region.

There were notable findings from the unadjusted analyses of hospitalization among patients with *S. Infantis* and REPJFX01, although they were not significant in the multivariable analyses and need to be interpreted with caution. Patients with *S. Infantis* infections had a lower proportion hospitalized than that for other *Salmonella* infections. This could be related to *S. Infantis* being less likely to be isolated from blood and more likely from urine than other *Salmonella* infections, which include infections caused by Typhimurium and Enteritidis; strains of these two most common serotypes have been associated with multidrug resistance or invasive illness (8,38,39). Patients with REPJFX01 infections had

a higher proportion hospitalized than those with non-REPJFX01 infections, suggesting that REPJFX01 can cause more severe illness than non-REPJFX01. This association could be related to the presence of virulence genes associated with pESI. Genomic analyses have shown diversity in *S. Infantis* subpopulations, and further research is needed to identify *Salmonella* genes associated with severe illness (40–43). In the multivariable analyses with hospitalization as the dependent variable, adjusted for the serotype (*S. Infantis* vs. other *Salmonella*) or strain category (REPJFX01 vs other *Salmonella* and vs. non-REPJFX01), the strongest predictors were blood isolation (indicating bloodstream infection or severe illness) and older age (≥ 65 years). Associations between these clinical predictors and hospitalization have been described in previous studies on salmonellosis (8,32,39,44). Hospitalization was not predictable from the serotype or strain category, after adjusting for other factors, including specimen source and patient's age.

In addition to travel to South America (Ecuador and Peru), which was associated with early U.S. cases (12), travel to the Dominican Republic was reported among patients with REPJFX01 infections. This highlights the need for continued monitoring of international travel destinations that could be associated with increased risk of REPJFX01 infections.

Poultry-associated outbreaks, first reported to NORS in 2012, accounted for most *S. Infantis* outbreaks linked to a single food or animal category during 2012–2021 (5,11,26,45). *S. Infantis* was one of three serotypes classified as high burden and increased trajectory from a 2012–2021 study of *Salmonella* outbreaks associated with consumption of chicken and other meat (46). These findings underscore that strategies for preventing or reducing *Salmonella* contamination of chicken and other poultry, such as poultry vaccines and other on-farm prevention measures, could help prevent *S. Infantis* infections, including those caused by REPJFX01 (5,11,26,46–51). Live poultry-associated outbreaks highlight the need for strategies involving partners in human, animal, and environmental health (51,52).

Our analysis had limitations. LEDS and NORS are passive surveillance systems in 50 states and underreporting likely occurs and varies by state and year (21,45). In FoodNet, which conducts active surveillance in 10 sites, the regional differences may not be generalized to the U.S. population but were important considerations in adjusting for potential confounding in the multivariable analyses. We used *S. Infantis* incidence data from LEDS and FoodNet but did not make formal comparisons between changes in incidence observed in the two systems. Despite differences in population coverage and type of surveillance, incidence rates from LEDS and FoodNet appeared to align, which supports our findings of increased incidence of *S. Infantis* infections during the more recent period. Associations of *S. Infantis* and REPJFX01 infections with reported diabetes are notable but should be interpreted with caution because of high percentages of missing data. The proportions of missingness from the comparisons, *S. Infantis* and REPJFX01 vs. other *Salmonella* infections, were similar. However, there is potential for bias, particularly if the data were not missing completely at random. Collection of data on diabetes and other comorbidities in FoodNet started in 2018, and thus, we only included such data in the univariable analyses. Despite the limitations, we highlighted the findings on reported history of diabetes from the univariable analyses, which are interesting and consistent with previous studies (34–37). Further investigation to evaluate the pattern of missingness and explore methods, such as multiple imputations or

sensitivity analyses, might be appropriate to better understand these associations. Inferences can be affected by the choice of time periods and estimates of significant changes between periods can reflect year-to-year variation within periods rather than sustained trends (22,53). Confidence intervals from the negative binomial models to assess changes in incidence are likely too narrow because of unaccounted sources of uncertainty (e.g., dependence between cases in large multi-year or multi-state outbreaks). That said, our findings of increased incidence of *S. Infantis* infections were observed in both LEDS and FoodNet and were consistent with other observations (3,4,54). Therefore, although our comparisons were subject to greater uncertainties, these findings have important public health implications. Although our methods and research questions differed from those used by Powell and Williams, which assessed coincident trends from two separate data streams, we found a similar increase in *S. Infantis* incidence in FoodNet sites (54). In PulseNet, completeness of WGS submissions can vary by state, sequencing was limited before 2015, and use of WGS to identify potential outbreaks started in 2019; similarly, there was variability in completeness of state reporting of PulseNet identifiers in NORS. Therefore, earlier clusters of REPJFX01 may have been difficult to detect. We did not use co-localization, contig analysis, or other supporting methods to assess the linkage of resistance genes to pESI-like plasmids, which was inferred solely on the presence of the *IncFIB(pN55391)* replicon. Although this approach served as a useful proxy, particularly for screening of pESI-like plasmids among *S. Infantis* isolates designated as REPJFX01 using the PulseNet definition (i.e., related by cgMLST within a range of 0–82 alleles), we recognize the potential for multiple plasmids to be present in a single isolate and for resistance genes to be chromosomally integrated. Given the size of this plasmid and that routine PulseNet sequencing was performed using short read data, association of specific resistance genes can be challenging, particularly at scale. In NARMS, WGS was limited in earlier years and the 1 in 20 submission scheme yielded a much smaller number of isolates (23,24). Not all *S. Infantis* outbreaks were captured in NORS, including two live poultry-associated outbreaks that occurred before reporting of animal contact outbreaks began in 2009 (26,51).

The proliferation of *S. Infantis* in U.S. poultry is likely related to the presence of pESI, conferring selective advantage—including enhanced antimicrobial resistance, resistance to disinfectants, stress tolerance, and virulence; pESI has also shown ability to conjugate into other serotypes (5,13–16,31,40–43,47). Therefore, prevention efforts in poultry production could be critical to limit not only proliferation of *S. Infantis* and REPJFX01 strains but also the spread of pESI to other serotypes, reports of which are concerning (16,31,47–50). Further research to characterize virulence genes in REPJFX01 isolates from human infections and chicken products, and to assess disinfectant resistance in *S. Infantis* strains from poultry production environments, could offer important insights into the pathogenic potential of REPJFX01 and the persistence of *S. Infantis* in food production settings (40–43, 47,48). Because plasmids carrying multidrug resistance may be maintained by selection pressure from use of agents for which there is resistance, judicious antimicrobial use in humans and food animal production is crucial to prevent the emergence and spread of multidrug-resistant *Salmonella* strains (55). As fluoroquinolone use in U.S. poultry has been prohibited since 2005, other potential drivers of REPJFX01 need to be explored, including use of antimicrobials from other drug classes, particularly those linked to high rates

of resistance among REPJFX01 (e.g., aminoglycosides, sulfonamides, tetracyclines), and resistance to commonly used disinfectants in poultry production (47,48,56). Additionally, studies have shown that once resistance-conferring mutations, such as those in *gyrA*, are established, they can persist in bacterial populations even in the absence of selective pressure due to minimal associated fitness cost. This may help explain the continued presence of fluoroquinolone resistance in *Salmonella* despite the discontinued use of this drug in poultry (57). International collaboration and a One Health approach can advance the identification and implementation of strategies for addressing this food safety concern in the poultry industry (13,47–50).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank state and local health departments and their public health laboratories for their contributions to the Foodborne Diseases Active Surveillance Network (FoodNet), Laboratory-Based Enteric Disease Surveillance (LEDS), National Antimicrobial Resistance Monitoring System (NARMS), National Outbreak Reporting System (NORS), and PulseNet. We acknowledge Taylor Eisenstein and Logan Ray for their assistance with NORS and FoodNet data. We are grateful to our NARMS and other colleagues from the Food and Drug Administration Center for Veterinary Medicine and the U.S. Department of Agriculture Food Safety Inspection Service for their comments.

Funding and support

This work was supported by the Centers for Disease Control and Prevention.

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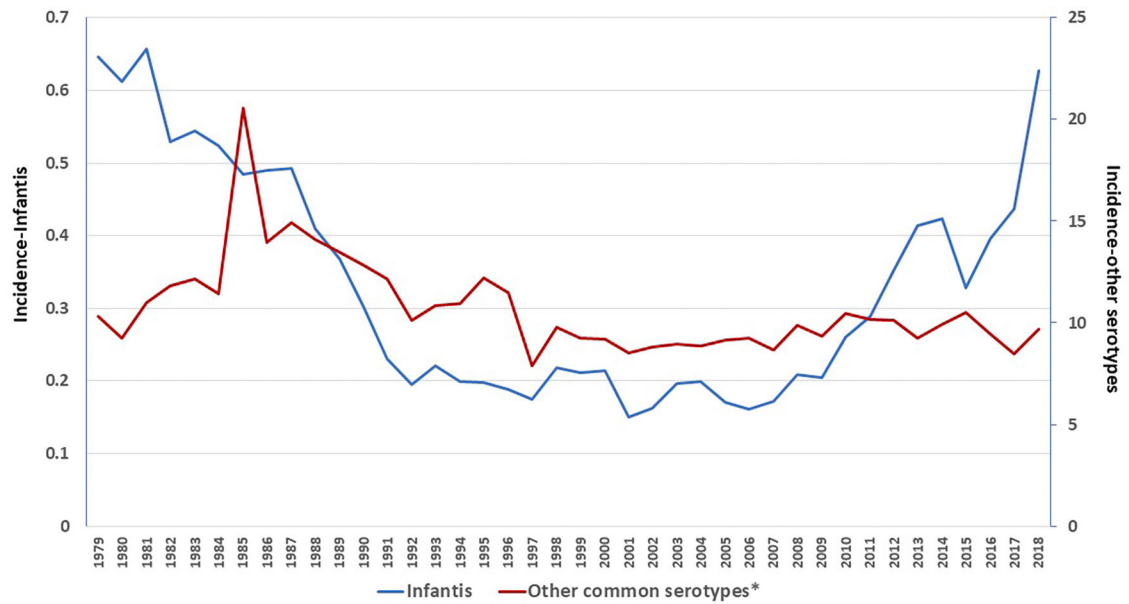


Figure 1: Annual incidence (per 100,000 persons) of *Salmonella* ser. *Infantis* and other *Salmonella* infections—Laboratory-Based Enteric Disease Surveillance (LEDS), 1979–2018.

The 20 most common serotypes were determined from culture-confirmed infections reported to LEDS and included *S. Infantis* and other common serotypes: Typhimurium, Enteritidis, Newport, Heidelberg, Javiana, Montevideo, Muenchen, Saintpaul, Agona, Hadar, I 4, [5],12:i:-, Oranienburg, Thompson, Braenderup, Mississippi, Paratyphi B var. L(+) tartrate+, Berta, Poona, Anatum. Typhimurium and Enteritidis were the two leading serotypes, accounting for 52% of isolates from other *Salmonella* infections.

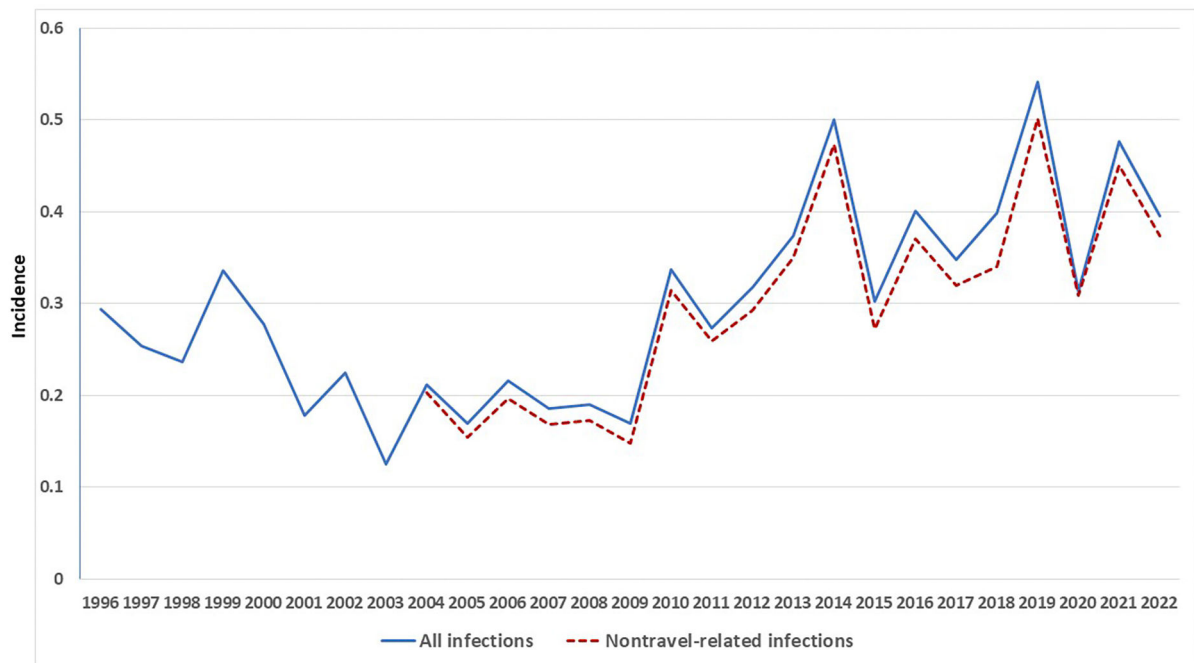


Figure 2: Annual incidence (per 100,000 persons) of *Salmonella* ser. Infantis infections—Foodborne Diseases Active Surveillance Network (FoodNet), 1996–2022.

FoodNet began active surveillance for laboratory-confirmed *Salmonella* infections in 5 sites in 1996 and gradually expanded until 2004 when it stabilized to its current 10-site catchment (CA, CO, CT, GA, MD, MN, NM, NY, OR, TN). Nontravel-related infections exclude infections among persons who reported international travel (i.e., travel outside the United States) in the 7 days before illness onset. FoodNet has collected international travel history since 2004.

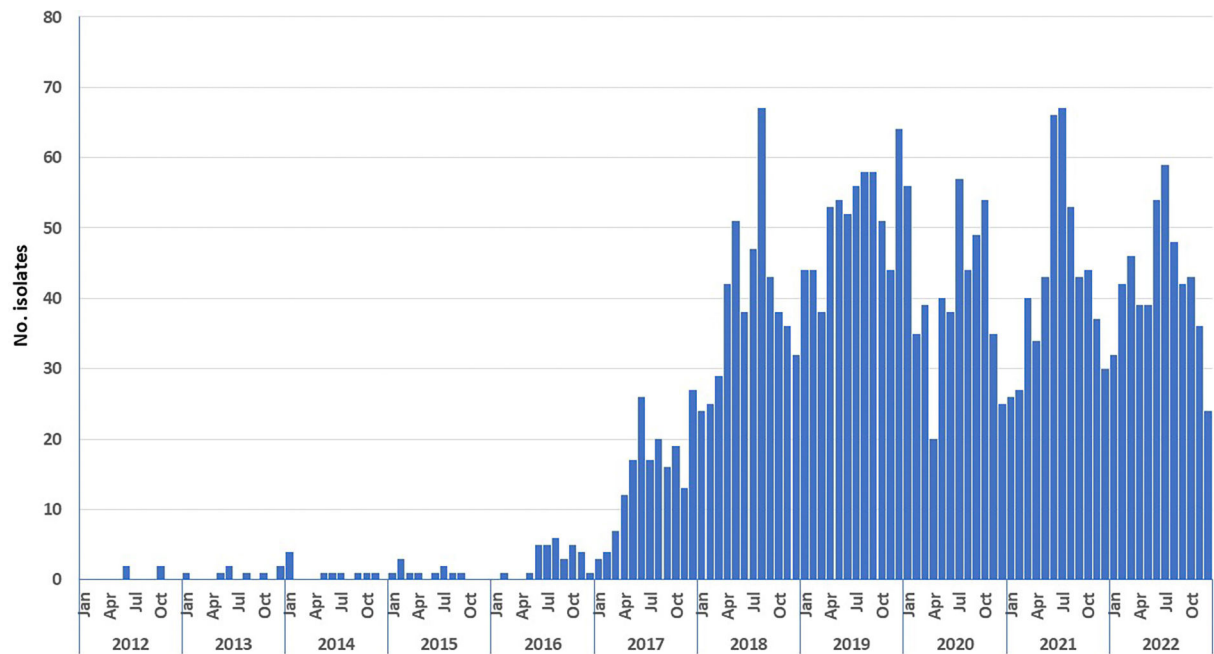


Figure 3: Number of REPJFX01 isolates, by month and year—PulseNet, 2012–2022.

REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin. Isolation date was used to assign month and year when available. REPJFX01 isolates (n=2,839) from the 50 U.S. states were included.

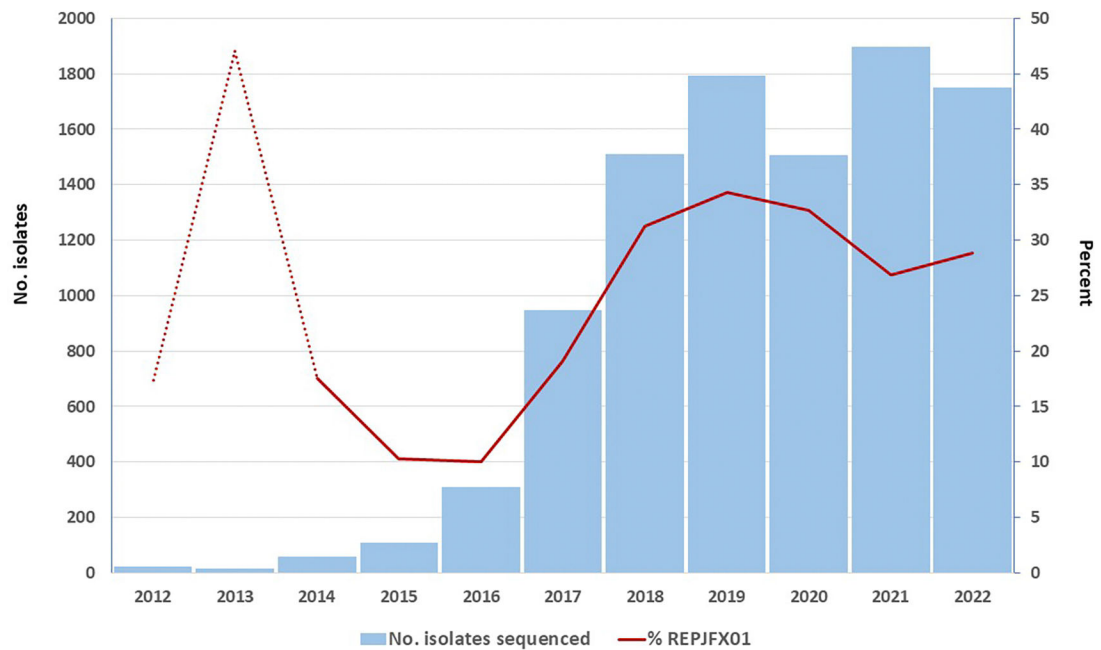


Figure 4: Number of sequenced *Salmonella* ser. *Infantis* isolates and percentage of REPJFX01 isolates, by year—PulseNet, 2012–2022.

REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin. *S. Infantis* isolates (n=9,917) from the 50 U.S. states were included. Only 1 isolate from each *S. Infantis* infection was typically sequenced; however, some *S. Infantis* infections could have >1 isolate sequenced and uploaded to PulseNet. Percentages of REPJFX01 for 2012 and 2013 (<50 isolates sequenced) are shown in dotted line.

Table 1:

Description of statistical methods for analysis

Data sources* (available data years)	Purpose	Multivariable model†	Analysis approach	Years included or time periods compared*
LEDS (1979–2018)	Assess changes in annual incidence of <i>S. Infantis</i> infections	Negative binomial, adjusted for state (50 states)	Compared average annual incidence for 2 time periods	2009–2018 vs. 1999–2008
FoodNet‡ (1996–2022)	Assess changes in annual incidence of <i>S. Infantis</i> infections	Negative binomial, adjusted for site (10 sites)	Compared average annual incidence for 2 time periods	2013–2022 vs. 2003–2012
FoodNet‡ (1996–2020)	Assess demographic and other factors associated with <i>S. Infantis</i> and REPJFX01 infections§	Logistic regression, <i>S. Infantis</i> and REPJFX01 as dependent variables, adjusted for selected variables¶	Compared demographic and clinical characteristics of <i>S. Infantis</i> and REPJFX01 vs. other <i>Salmonella</i> infections, and REPJFX01 vs. non-REPJFX01 infections§¶	2006–2020 for <i>S. Infantis</i> , 2016–2020 for REPJFX01
FoodNet‡ (1996–2020)	Assess association between hospitalization and <i>S. Infantis</i> , REPJFX01 infections§	Logistic regression, hospitalization as dependent variable, adjusted for selected variables¶	Compared hospitalization among <i>S. Infantis</i> and REPJFX01 vs. other <i>Salmonella</i> infections, and among REPJFX01 vs. non-REPJFX01s infections§¶	2006–2020 for <i>S. Infantis</i> , 2016–2020 for REPJFX01
PulseNet (1998–2022)	Assess changes in annual percentage of REPJFX01§ among <i>S. Infantis</i> isolates	Logistic regression, REPJFX01 as dependent variable, adjusted for region (4 U.S. Census regions)	Compared average annual percentage of REPJFX01 among <i>S. Infantis</i> isolates for 2 time periods	2012–2022 (percentage by year), compared 2018–2022 vs. 2013–2017
NARMS (1996–2022)	Describe antimicrobial resistance (AR) among <i>S. Infantis</i> isolates		Descriptive analysis of AR among <i>S. Infantis</i> based on predicted resistance**	2012–2022
NORS†† (1998–2021)	Describe sources and characteristics of <i>S. Infantis</i> outbreaks		Descriptive analysis of <i>S. Infantis</i> outbreak data††	1998–2021

* Sources of surveillance data include the Laboratory-Based Enteric Disease Surveillance (LEDS) system, Foodborne Diseases Active Surveillance Network (FoodNet), PulseNet (national molecular subtyping network for foodborne disease surveillance), National Antimicrobial Resistance Monitoring System (NARMS), and National Outbreak Reporting System (NORS).

† Negative binomial models included a log link function and a log offset for the population of each site each year. Population data from the U.S. Census Bureau were used. Rate ratios from negative binomial models and odds ratios from logistic regression models that do not include 1.0 in the 95% confidence intervals were considered statistically significant.

‡ FoodNet collects data on patient demographics, specimen source, hospitalization, deaths, international travel in the 7 days before illness onset, outbreak association, symptoms (since 2011), and selected comorbidities (since 2018). The 10 sites were grouped using the 4 U.S. Census regions in some analyses: Midwest (MN), Northeast (CT, NY), South (GA, MD, TN), and West (CA, CO, NM, OR).

§ REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin.

¶ Some results from multivariable analyses are shown in supplemental tables.

** Predicted resistance was based on the presence of resistance determinants, including genes and mutations, in the isolate's genome.

†† CDC has received reports of foodborne disease outbreaks to the Foodborne Disease Outbreak Surveillance System (FDOSS) electronically since 1998. The reporting platform NORS launched in 2009 to integrate outbreak reporting and includes data on all foodborne and waterborne outbreaks and enteric disease outbreaks transmitted by contact with environmental sources, infected persons or animals, or unknown modes. Information on outbreaks of human enteric illness linked to contact with animals or their environments has been collected through the Animal Contact Outbreak Surveillance System (ACOSS) (<https://www.cdc.gov/nors/about/acoss.html>) since 2009. NORS isolate records with available WGS identifiers were linked to PulseNet WGS data to identify *Infantis* outbreaks that included REPJFX01 isolates.

Table 2:

Demographic and other characteristics of *Salmonella* ser. Infantis infections compared with infections caused by other common *Salmonella* serotypes—Foodborne Diseases Active Surveillance Network (FoodNet), United States, 2006–2020

Characteristics*	S. Infantis n=2,363*	Other <i>Salmonella</i> † n=80,559*	Odds ratio (95% CI) ‡§	Adjusted odds ratio (95% CI)‡§
	No. (%)	No. (%)		
Age group (y)				
0–4	425 (18.0)	19,447 (24.1)	Ref	Ref
5–17	236 (10.0)	12,261 (15.2)	0.88 (0.75, 1.03)	0.71 (0.59, 0.85)§
18–44	697 (29.5)	21,398 (26.6)	1.49 (1.32, 1.68)§	1.10 (0.95, 1.27)
45–64	596 (25.2)	16,665 (20.7)	1.64 (1.44, 1.86)§	1.29 (1.11, 1.50)§
≥ 65	409 (17.3)	10,755 (13.4)	1.74 (1.52, 2.00)§	1.32 (1.12, 1.56)§
Sex				
Male	992 (42.0)	38,608 (48.0)	Ref	Ref
Female	1,368 (58.0)	41,794 (52.0)	1.27 (1.17, 1.38)§	1.14 (1.04, 1.26)§
Race and ethnicity				
White, non-Hispanic (NH)	1,218 (59.4)	44,469 (66.5)	Ref	Ref
Black, NH	219 (10.7)	9,822 (14.7)	0.81 (0.70, 0.94)§	1.03 (0.87, 1.23)
Asian, Pacific Islander, NH	228 (11.1)	2,266 (3.4)	3.67 (3.17, 4.26)§	3.65 (3.09, 4.30)§
Native American, NH	17 (0.8)	520 (0.8)	1.19 (0.73, 1.94)	0.92 (0.54, 1.55)
Multiple, other, unknown race, NH	71 (3.5)	1,941 (2.9)	1.34 (1.05, 1.70)§	1.59 (1.22, 2.07)§
Hispanic or Latino	296 (14.4)	7,891 (11.8)	1.37 (1.20, 1.56)§	1.31 (1.13, 1.51)§
Specimen source				
Stool	1,964 (83.3)	70,737 (88.2)	Ref	Ref
Blood	80 (3.4)	4,246 (5.3)	0.68 (0.54, 0.85)§	0.64 (0.50, 0.83)§
Urine	264 (11.2)	4,014 (5.0)	2.37 (2.08, 2.70)§	2.06 (1.75, 2.42)§
Other	51 (2.2)	1,185 (1.5)	1.55 (1.17, 2.06)§	1.38 (0.98, 1.93)
Year				
2006–2010	509 (21.5)	27,007 (33.5)	Ref	Ref
2011–2015	853 (36.1)	27,950 (34.7)	1.62 (1.45, 1.81)§	1.66 (1.45, 1.89)§
2016–2020	1,001 (42.4)	25,602 (31.8)	2.08 (1.86, 2.31)§	2.01 (1.77, 2.29)§
Region and state of residence¶				
Midwest	384 (16.3)	8,619 (10.7)	Ref (region)	Ref (region)
MN	384 (16.3)	8,619 (10.7)		
Northeast	437 (18.5)	10,188 (12.6)	0.96 (0.84, 1.11)	1.07 (0.92, 1.25)
CT	213 (9.0)	4,933 (6.2)		

Characteristics*	S. Infantis n=2,363*	Other <i>Salmonella</i> † n=80,559*	Odds ratio (95% CI) ‡§	Adjusted odds ratio (95% CI)‡§
	No. (%)	No. (%)		
NY	224 (9.5)	5,255 (6.5)		
South	825 (34.9)	44,951 (55.8)	0.41 (0.36, 0.47)§	0.49 (0.42, 0.56)§
GA	422 (17.9)	25,837 (32.1)		
MD	126 (5.3)	8,931 (11.1)		
TN	277 (11.7)	10,183 (12.6)		
West	717 (30.3)	16,801 (20.9)	0.96 (0.84, 1.09)	0.90 (0.78, 1.04)
CA	354 (15.0)	4,972 (6.2)		
CO	119 (5.0)	3,509 (4.4)		
NM	83 (3.5)	3,628 (4.5)		
OR	161 (6.8)	4,692 (5.8)		
International travel*				
Yes	184 (9.3)	5,555 (8.9)	1.05 (0.90, 1.23)	0.86 (0.73, 1.02)
Outbreak associated*				
Yes	248 (10.5)	6,017 (7.5)	1.45 (1.27, 1.66)§	1.20 (1.03, 1.39)§

* The total number of infections (n) are shown for years included; the total number with known data was used as denominator to calculate the percentage of infections for each category. Missing data were excluded (shown in Supplemental Table 4) in the univariable and multivariable analyses. Infections were categorized as “missing race-ethnicity” if ethnicity was missing, regardless of race data. International travel was defined as travel outside the United States within the 7 days before illness onset. The infection was categorized as outbreak associated if the case-patient was part of a recognized outbreak. “No” was the referent (Ref) category for international travel and outbreak associated.

† The 20 most common serotypes were determined from culture-confirmed infections reported during 1996–2020 and included *S. Infantis* and other *Salmonella* serotypes (in descending order): Enteritidis, Typhimurium, Newport, Javiana, I 4,[5],12:i:-, Heidelberg, Muenchen, Montevideo, Saintpaul, Braenderup, Oranienburg, Thompson, Mississippi, Bareilly, Agona, I 13,23:b:-, Paratyphi B var. L(+) Tartrate+, Hadar, and Poona.

‡ Seven variables (age group, sex, race-ethnicity, specimen source, year group, region, and outbreak-associated) that were significant in the univariable analysis and international travel, which has been associated with *Salmonella* strains in previous studies, were considered in the multivariable model. The final model included the 8 variables.

§ Odds ratios that do not include 1.00 in the 95% confidence intervals (CIs) were considered statistically significant.

¶ The 10 sites in FoodNet were grouped using the 4 U.S. Census regions.

Table 3:

Clinical characteristics of *Salmonella* ser. Infantis infections compared with infections caused by other common *Salmonella* serotypes—Foodborne Diseases Active Surveillance Network (FoodNet)^{*}, United States, 2006–2020

Characteristics (years included), total no. infections (n) [†]	<i>S. Infantis</i>	Other <i>Salmonella</i> [‡]	Odds ratio (95% CI)
Hospitalized[*] (2006–2020), n[†]	2,363	80,559	
Yes	608 (26.8)	22,518 (29.0)	0.90 (0.82, 0.98) [§]
Died (2006–2020)	2,363	80,559	
Yes	6 (0.3)	351 (0.5)	0.58 (0.26, 1.31)
History of comorbidities (2018–2020), n[†]	630	15,034	
Abdominal surgery	12 (3.7)	196 (2.3)	1.63 (0.90, 2.95)
Cancer	15 (3.9)	392 (4.3)	0.92 (0.54, 1.56)
Diabetes	45 (11.9)	542 (5.9)	2.14 (1.55, 2.96) [§]
Symptoms (2011–2020), n[†]	1,854	53,552	
Fever	784 (55.1)	25,950 (67.5)	0.59 (0.53, 0.66) [§]
Diarrhea	1,367 (89.0)	38,754 (93.0)	0.61 (0.52, 0.72) [§]
Bloody diarrhea	388 (27.4)	14,795 (38.2)	0.61 (0.54, 0.69) [§]
Antimicrobial use[*] (2017–2020), n[†]	803	20,274	
Yes	302 (65.8)	6,489 (62.6)	1.15 (0.94, 1.40)

^{*}The 10 sites in FoodNet include CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN.

[†]Values are no. (%) unless indicated and the total number of infections (n) are shown for years included; the total number with known data was used as denominator to calculate the percentage of infections for each category. Missing data were excluded (shown in Supplemental Table 4) in the univariable analysis. “No” was the referent category for all variables. Hospitalization was reported if the case-patient was hospitalized within 7 days of specimen collection. Antimicrobial use was defined as use within the 7 days before illness onset. History of selected comorbidities within the 6 months before illness onset was defined for the following: abdominal surgery (e.g., removal of appendix or gallbladder, any surgery of the stomach or large intestine); diagnosis or treatment for cancer (including leukemia/lymphoma); and diagnosis or treatment for diabetes. Odds ratios from the multivariable analysis with hospitalization as dependent variable are shown in Supplemental Table 3.

[‡]The 20 most common serotypes were determined from culture-confirmed infections reported during 1996–2020 and included *S. Infantis* and other *Salmonella* serotypes (in descending order): Enteritidis, Typhimurium, Newport, Javiana, I 4,[5],12:i:-, Heidelberg, Muenchen, Montevideo, Saintpaul, Braenderup, Oranienburg, Thompson, Mississippi, Bareilly, Agona, I 13,23:b:-, Paratyphi B var. L(+), Tartrate+, Hadar, and Poona.

[§]Odds ratios that do not include 1.00 in the 95% confidence intervals (CIs) were considered statistically significant.

Table 4:

Demographic and other characteristics* of REPJFX01 infections compared with infections caused by other common *Salmonella* serotypes—Foodborne Diseases Active Surveillance Network (FoodNet), United States, 2016–2020

Characteristics*	REPJFX01 [†] (n=248)* No. (%)	Other <i>Salmonella</i> [‡] (n=25,602)* No. (%)	Odds ratio (95% CI) ^{§¶}	Adjusted odds ratio (95% CI) ^{§¶}
Age group (y)				
0–4	18 (7.3)	5,456 (21.3)	Ref	Ref
5–17	16 (6.5)	3,358 (13.1)	1.44 (0.74, 2.84)	0.93 (0.44, 1.97)
18–44	64 (25.8)	6,730 (26.3)	2.88 (1.71, 4.87) [¶]	1.44 (0.79, 2.61)
45–64	76 (30.7)	5,837 (22.8)	3.95 (2.36, 6.61) [¶]	1.95 (1.08, 3.51) [¶]
≥ 65	74 (29.8)	4,221 (16.5)	5.31 (3.17, 8.91) [¶]	2.34 (1.28, 4.27) [¶]
Sex				
Male	74 (30.0)	12,044 (47.2)	Ref	Ref
Female	173 (70.0)	13,484 (52.8)	2.09 (1.59, 2.75) [¶]	1.46 (1.06, 2.00) [¶]
Race and ethnicity				
White, non-Hispanic (NH)	161 (71.2)	15,497 (67.1)	Ref	Ref
Black, NH	37 (16.4)	3,175 (13.8)	1.12 (0.78, 1.61)	1.35 (0.87, 2.10)
Asian, Pacific Islander, NH	3 (1.3)	724 (3.1)	0.40 (0.13, 1.25)	0.53 (0.17, 1.70)
Native American, NH	1 (0.4)	183 (0.8)	0.53 (0.07, 3.78)	0.55 (0.07, 4.08)
Multiple, other, unknown race, NH	5 (2.2)	706 (3.1)	0.68 (0.28, 1.67)	0.54 (0.17, 1.72)
Hispanic or Latino	19 (8.4)	2,794 (12.1)	0.66 (0.41, 1.06)	0.71 (0.41, 1.22)
Specimen source				
Stool	160 (64.5)	21,986 (86.0)	Ref	Ref
Blood	8 (3.2)	1,485 (5.8)	0.74 (0.36, 1.51)	0.74 (0.34, 1.62)
Urine	65 (26.2)	1,464 (5.7)	6.10 (4.55, 8.18) [¶]	4.82 (3.35, 6.92) [¶]
Other	15 (6.0)	632 (2.5)	3.26 (1.91, 5.67) [¶]	3.20 (1.67, 6.13) [¶]
Year				
2016	5 (2.0)	5,328 (20.8)	Ref	Ref
2017	35 (14.1)	5,240 (20.5)	7.12 (2.79, 18.18) [¶]	7.36 (2.58, 20.99) [¶]
2018	63 (25.4)	5,686 (22.2)	11.81 (4.75, 29.37) [¶]	12.58 (4.54, 34.87) [¶]
2019	88 (35.5)	5,143 (20.1)	18.23 (7.40, 44.92) [¶]	18.47 (6.72, 50.72) [¶]
2020	57 (23.0)	4,205 (16.4)	14.44 (5.79, 36.06) [¶]	12.80 (4.55, 36.00) [¶]
Region and state of residence**				
Midwest	36 (14.5)	3,013 (11.8)	Ref (region)	Ref (region)
<i>MN</i>	<i>36 (14.5)</i>	<i>3,013 (11.8)</i>		

Characteristics [*]	REPJFX01 [†] (n=248) [*] No. (%) [*]	Other <i>Salmonella</i> [‡] (n=25,602) [*] No. (%) [*]	Odds ratio (95% CI) ^{§¶}	Adjusted odds ratio (95% CI) ^{§¶}
Northeast	103 (41.5)	3,181 (12.4)	2.71 (1.85, 3.97) [¶]	2.76 (1.78, 4.27) [¶]
CT	56 (22.6)	1,550 (6.1)		
NY	47 (19.0)	1,631 (6.4)		
South	63 (25.4)	14,091 (55.0)	0.37 (0.25, 0.57) [¶]	0.41 (0.25, 0.67) [¶]
GA	21 (8.5)	8,080 (31.6)		
MD	16 (6.4)	2,748 (10.7)		
TN	26 (10.5)	3,263 (12.7)		
West	46 (18.6)	5,317 (20.8)	0.72 (0.47, 1.12)	0.77 (0.46, 1.30)
CA	7 (2.8)	1,326 (5.2)		
CO	16 (6.4)	1,198 (4.7)		
NM	5 (2.0)	1,159 (4.5)		
OR	18 (7.3)	1,634 (6.4)		
International travel[*]				
Yes	23 (10.8)	2,222 (10.5)	1.03 (0.67, 1.60)	1.09 (0.68, 1.74)

^{*} The total number of infections (n) are shown for years included; the total number with known data was used as denominator to calculate the percentage of infections for each category. Missing data were excluded (shown in Supplemental Table 6) in the univariable and multivariable analyses. Infections were categorized as missing race-ethnicity if ethnicity was missing regardless of race data. International travel was defined as travel outside the United States within the 7 days before illness onset. "No" was the referent (Ref) category for international travel.

[†] REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin.

[‡] The 20 most common serotypes were determined from culture-confirmed infections reported during 1996–2020 and included *S. Infantis* and other *Salmonella* serotypes (in descending order): Enteritidis, Typhimurium, Newport, Javiana, I 4,[5],12:i:-, Heidelberg, Muenchen, Montevideo, Saintpaul, Braenderup, Oranienburg, Thompson, Mississippi, Bareilly, Agona, I 13,23:b:-, Paratyphi B var. L(+) Tartrate+, Hadar, and Poona.

[§] Five variables (age group, sex, specimen source, year, and region) that were significant in the univariable analysis, and race-ethnicity and international travel, which have been associated with *Salmonella* strains in previous studies, were considered in the multivariable model. The final model included the 7 variables.

[¶] Odds ratios that do not include 1.00 in the 95% confidence intervals (CIs) were considered statistically significant.

^{**} The 10 sites in FoodNet were grouped using the 4 U.S. Census regions.

Table 5:

Clinical characteristics of REPJFX01 infections compared with infections caused by other common *Salmonella* serotypes—Foodborne Diseases Active Surveillance Network (FoodNet)^{*}, United States, 2016–2020

Characteristics (years included), total no. infections (n) [†]	REPJFX01 [‡]	Other <i>Salmonella</i> [§]	Odds ratio (95% CI) [¶]
Hospitalized (2016–2020), n[†]	248	25,602	
Yes	74 (30.6)	7,440 (30.1)	1.02 (0.78, 1.35)
Died (2016–2020), n[†]	248	25,602	
Yes	2 (0.8)	135 (0.5)	1.54 (0.38, 6.24)
Comorbidities (2018–2020), n[†]	208	15,034	
Abdominal surgery	3 (3.8)	196 (2.3)	1.63 (0.51, 5.22)
Cancer	6 (5.1)	392 (4.3)	1.21 (0.53, 2.77)
Diabetes	26 (21.8)	542 (5.9)	4.44 (2.85, 6.91) [¶]
Symptoms (2016–2020), n[†]	248	25,602	
Fever	101 (47.6)	14,038 (66.0)	0.47 (0.36, 0.62) [¶]
Diarrhea	175 (81.0)	20,719 (93.8)	0.28 (0.20, 0.40)
Bloody diarrhea	36 (18.1)	7,701 (36.6)	0.38 (0.27, 0.55) [¶]
Antimicrobial use[*] (2017–2020), n[†]	243	20,274	
Yes	108 (73.5)	6,489 (62.6)	1.65 (1.14, 2.39) [¶]
Outbreak associated[*] (2016–2020), n[†]	248	25,602	
Yes	28 (11.3)	2,316 (9.0)	1.28 (0.86, 1.90)

^{*}The 10 sites in FoodNet include CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN.

[†]Values are no. (%) unless indicated and the total number of infections (n) are shown for years included; the total number with known data was used as denominator to calculate the percentage of infections for each category. Missing data were excluded (shown in Supplemental Table 6) in the univariable analysis. “No” was the referent category for all variables. Hospitalization was reported if the case-patient was hospitalized within 7 days of specimen collection. History of selected comorbidities within the 6 months before illness onset was defined for the following: abdominal surgery (e.g., removal of appendix or gallbladder, any surgery of the stomach or large intestine); diagnosis or treatment for cancer (including leukemia/lymphoma); and diagnosis or treatment for diabetes. The infection was categorized as outbreak associated if the case-patient was part of a recognized outbreak. Antimicrobial use, defined as use within the 7 days before illness onset, was excluded from the multivariable analysis; it was not routinely collected until 2017 and missing data accounted for 39.5% of REPJFX01 and 48.9% of other *Salmonella* infections.

[‡]REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin.

[§]The 20 most common serotypes were determined from culture-confirmed infections reported during 1996–2020 and included *S. Infantis* and other *Salmonella* serotypes (in descending order): Enteritidis, Typhimurium, Newport, Javiana, I 4,[5],12:i:-, Heidelberg, Muenchen, Montevideo, Saintpaul, Braenderup, Oranienburg, Thompson, Mississippi, Bareilly, Agona, I 13,23:b:-, Paratyphi B var. L(+) Tartrate+, Hadar, and Poona.

[¶]Odds ratios that do not include 1.00 in the 95% confidence intervals (CIs) were considered statistically significant.

Table 6:
Antimicrobial resistance among REPJFX01 and non-REPJFX01 isolates—National Antimicrobial Resistance Monitoring System and PulseNet, United States, 2012–2022

Predicted antimicrobial resistance *	REPJFX01 [†] (n=2,778)	Non-REPJFX01 (n=3,764)	All Isolates n=6,542
	No. (%)	No. (%)	No. (%)
Resistance by antimicrobial class *			
Quinolones *	2,775 (99.9)	92 (2.4)	2,867 (43.8)
Ciprofloxacin	2,775 (99.9)	92 (2.4)	2,867 (43.8)
Nalidixic acid	2,775 (99.9)	60 (1.6)	2,835 (43.3)
Aminoglycosides	2,690 (96.8)	197 (5.2)	2,887 (44.1)
Streptomycin	2,466 (88.8)	157 (4.2)	2,623 (40.1)
Gentamicin	1,875 (67.5)	101 (2.7)	1,976 (30.2)
Hygromycin	1,872 (67.4)	26 (0.7)	1,898 (29.0)
Tobramycin	1,799 (64.8)	25 (0.7)	1,824 (27.9)
Kanamycin	1,122 (40.4)	66 (1.8)	1,188 (18.2)
Folate pathway inhibitors	2,621 (94.3)	196 (5.2)	2,817 (43.1)
Sulfonamide	2,473 (89.0)	150 (4.0)	2,623 (40.1)
Trimethoprim	1,293 (46.5)	86 (2.3)	1,379 (21.1)
Co-trimoxazole	1,145 (41.2)	40 (1.1)	1,185 (18.1)
Tetracyclines	2,507 (90.2)	209 (5.6)	2,716 (41.5)
Tetracycline			
Penicillins	1,691 (60.9)	200 (5.3)	1,891 (28.9)
Ampicillin			
Cephalosporins	1,685 (60.7)	110 (2.9)	1,795 (27.4)
Ceftriaxone	1,685 (60.7)	108 (2.9)	1,793 (27.4)
Ceftiofur	1,684 (60.6)	108 (2.9)	1,792 (27.4)
Cefoxitin	6 (0.2)	80 (2.1)	86 (1.3)
Phenicol	1,581 (56.9)	99 (2.6)	1,680 (25.7)
Chloramphenicol			
Fosfomycin	709 (25.5)	15 (0.4)	724 (11.1)
Fosfomycin			
Macrolides[†]	10 (0.4)	9 (0.2)	19 (0.3)
Azithromycin			
β-Lactamase/inhibitors	6 (0.2)	80 (2.1)	86 (1.3)
Ampicillin/clavulanic acid			
Carbapenem	0 (0)	0 (0)	0 (0)

Predicted antimicrobial resistance*	REPJFX01 [†] (n=2,778)	Non-REPJFX01 (n=3,764)	All <i>Infantis</i> n=6,542
	No. (%)	No. (%)	No. (%)
Meropenem			
Resistance by number of classes			
No resistance detected	3 (0.1)	3,342 (88.8)	3,345 (51.1)
Resistance to ≥1 classes	2,775 (99.9)	422 (11.2)	3,197 (48.9)
Resistance to ≥3 classes	2,699 (97.2)	226 (6.0)	2,925 (44.7)
Resistance to ≥5 classes	1,968 (70.8)	56 (1.5)	2,024 (30.9)
Resistance to ≥7 classes	1,377 (49.6)	28 (0.7)	1,405 (21.5)

* Antimicrobial resistance was assessed by predicting resistance from WGS data based on the presence of resistance genes and mutations; for ciprofloxacin, the presence of resistance mechanisms conferring decreased susceptibility is reported as representing predicted quinolone resistance. Antimicrobial classes were defined using categories from the Clinical and Laboratory Standards Institute (CLSI).

[†] REPJFX01 was defined as *S. Infantis* isolates related by core genome multilocus sequence typing within a range of 0–82 alleles, typically characterized by the presence of pESI megaplasmid harboring multiple resistance genes and *gyrA87* mutation conferring decreased susceptibility to ciprofloxacin.

Table 7:

Characteristics of outbreaks caused by *Salmonella* ser. Infantis—National Outbreak Reporting System*, United States, 1998–2021

Characteristics	<i>S. Infantis</i> (n=104)* No. (%)
Multistate	19 (18.3)
Primary mode of transmission	
Foodborne (n=69, 66.3%)^{†‡}	
Single food category [†]	20 (29.0)
No single food category [‡]	14 (20.3)
No specific foods reported [‡]	35 (50.7)
Animal contact (n=14, 13.5%)[§]	
Single animal category [§]	14 (100.0)
Other (n=9, 8.7%)[¶]	
Person-to-person	8 (88.9)
Environmental (contamination other than food or water)	1 (11.1)
Unknown (n=12, 11.5%)*	
Food source, single food category[†] (n=20)	
Land animals (n=15, 75%)	
Pork	7 (35.0)
Chicken [†]	4 (20.0)
Beef and other meat [†]	4 (20.0)
Plants	3 (15.0)
Aquatic animals (fish)	2 (10.0)
Animal contact, single animal category (n=14)[§]	
Live poultry (chicken or baby chicks, ducks or ducklings)	13 (92.9)
Dog [§]	1 (7.1)
Clinical outcomes	
Total no. illnesses (median, range)	2,953 (9, 2–287)
Total no. hospitalizations (median, range)	460 (2, 0–58)
No. (%) outbreaks with ≥1 hospitalized cases (n=100 with reported outcome)	68 (68.0)
Total no. deaths (median, range)	5 (0, 0–2)
No. (%) outbreaks with ≥1 death (n=100 with reported outcome)	4 (4.0)

* CDC has received reports of foodborne disease outbreaks to the Foodborne Disease Outbreak Surveillance System (FDOSS) electronically since 1998. The reporting platform NORS launched in 2009 to integrate outbreak reporting and includes data on all foodborne and waterborne outbreaks and enteric disease outbreaks transmitted by contact with environmental sources, infected persons or animals, or unknown modes. Information on outbreaks of human enteric illness linked to contact with animals or their environments has been collected through the Animal Contact Outbreak Surveillance System (ACOSS) (<https://www.cdc.gov/nors/about/acoss.html>) since 2009. Of 122 Infantis outbreaks reported to CDC, 18 that were linked to multiple serotypes were excluded. Data for the remaining 104 Infantis-only outbreaks are shown. Values are no. (%) unless indicated.

[†]Major food groups or subcategories (for land and aquatic animals) from the Interagency Food Safety Analytics Collaboration (IFSAC) were used to categorize food sources (<https://www.cdc.gov/ifsac/php/projects/index.html>). The first single food category foodborne outbreak linked to poultry was detected in 2014. The 4 single food category outbreaks linked to beef and other meat include 3 with beef and 1 with lamb as the implicated food. A large outbreak that included REPJFX01 infections in 2018–2019 was linked to raw chicken products, causing 129 illnesses, 25 hospitalizations, and 1 death.

[‡]Three foodborne outbreaks that were not linked to a single food category or had no specific food reported included REPJFX01 infections, of which the first was detected in 2016.

[§]Outbreaks reported through NORS involving pet food, treats/chews, other, or unknown were classified based on the animal that is the intended recipient. The first animal contact outbreak was linked to dry dog food and included cases detected in 2011 and 2012. The first two poultry-associated outbreaks linked to animal contact were detected in 2012.

[¶]Of 8 outbreaks linked to person-to-person transmission, the settings included child day care (4 outbreaks), private home/residence (1), and unknown (2).