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Outbreak of Multidrug-Resistant *Salmonella* Heidelberg Infections Linked to Dairy Calf Exposure, United States, 2015–2018

Megin Nichols,[1] Lauren Gollarza,[1] Donald Sockett,[2] Nicole Aulik,[2] Elisabeth Patton,[3] Louise K. Francois Watkins,[1] Kelly J. Gambino-Shirley,[1] Jason P. Folster,[1] Jessica C. Chen,[1] Kaitlin A. Tagg,[1,4] Gregory Sean Stapleton,[1,5,i] Eija Trees,[6] Zachary Ellison,[1] Jason Lombard,[7] Brenda Morningstar-Shaw,[8] Linda Schlater,[8] Lina Elbadawi,[9] and Rachel Klos[9]

Abstract

In August 2016, the Wisconsin Department of Health Services notified the U.S. Centers for Disease Control and Prevention of multidrug-resistant (MDR) *Salmonella enterica* serovar Heidelberg infections in people who reported contact with dairy calves. Federal and state partners investigated this to identify the source and scope of the outbreak and to prevent further illnesses. Cases were defined as human *Salmonella* Heidelberg infection caused by a strain that had one of seven pulsed-field gel electrophoresis (PFGE) patterns or was related by whole genome sequencing (WGS), with illness onset from January 1, 2015, through July 2, 2018. Patient exposure and calf purchase information was collected and analyzed; calves were traced back from the point of purchase. Isolates obtained from animal and environmental samples collected on-farm were supplied by veterinary diagnostic laboratories and compared with patient isolates using PFGE and WGS. Antimicrobial susceptibility testing by standardized broth microdilution was performed. Sixty-eight patients from 17 states were identified. Forty (63%) of 64 patients noted cattle contact before illness. Thirteen (33%) of 40 patients with exposure to calves reported that calves were sick or had died. Seven individuals purchased calves from a single Wisconsin livestock market. One hundred forty cattle from 14 states were infected with the outbreak strain. WGS indicated that human, cattle, and environmental isolates from the livestock market were genetically closely related. Most isolates (88%) had resistance or reduced susceptibility to antibiotics of ≥5 antibiotic classes. This resistance profile included first-line antibiotic treatments for patients with severe salmonellosis, including ampicillin, ceftriaxone, and ciprofloxacin. In this outbreak, MDR *Salmonella* Heidelberg likely spread from sick calves to humans, emphasizing the importance of illness surveillance in animal populations to prevent future spillover of this zoonotic disease.

Keywords: antimicrobial resistance, zoonotic disease, food safety, calves, *Salmonella*, One Health

[1]Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
[2]Wisconsin Veterinary Diagnostic Laboratory, Madison, Wisconsin, USA.
[3]Wisconsin Department of Agriculture, Trade and Consumer Protection, Madison, Wisconsin, USA.
[4]Weems Design Studio, Inc., Suwanee, Georgia, USA.
[5]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee, USA.
[6]Association of Public Health Laboratories, Silver Spring, Maryland, USA.
[7]Animal and Plant Health Inspection Service, Veterinary Services, United States Department of Agriculture, Fort Collins, Colorado, USA.
[8]Animal and Plant Health Inspection Service, Veterinary Services, National Veterinary Services Laboratories, United States Department of Agriculture, Fort Collins, Colorado, USA.
[9]Wisconsin Department of Health Services, Madison, Wisconsin, USA.
[i]ORCID ID (https://orcid.org/0000-0002-1784-6577).

Introduction

Nontyphoidal *Salmonella* causes an estimated 1.35 million infections and 26,500 hospitalizations in the United States annually (CDC, 2019). Infection often results from consumption of contaminated food or from contact with animals or their environments (Fey *et al.*, 2000; Lynch *et al.*, 2009; Gieraltowski *et al.*, 2016). Livestock infected with *Salmonella* can shed the pathogen in feces and may not demonstrate clinical signs (McGuirk *et al.*, 2003). Human symptoms include diarrhea (sometimes bloody), fever, and abdominal cramps and may depend on the immune status of the infected person (Molbak, 2005; CDC, 2015).

Some *Salmonella* infections can spread to the bloodstream, increase complications and disease severity, and require treatment with antimicrobials. Ciprofloxacin, ceftriaxone, or azithromycin is used as first-line treatment for severe *Salmonella* infections pending culture results (Shane *et al.*, 2017; American Academy of Pediatrics, 2021). Clinically significant antimicrobial resistance in *Salmonella* can be predicted from the presence of certain genetic factors in the bacterial genome (McDermott *et al.*, 2016). Multidrug-resistant (MDR) strains of *Salmonella* have been associated with increased risk of bloodstream infections and hospitalization; as a result, MDR *Salmonella* strains are a serious human health threat (Varma *et al.*, 2005; CDC, 2019).

Salmonella enterica serovar Heidelberg was initially discovered in 1933 after a human outbreak in Heidelberg, Germany (Habbs, 1933). A *Salmonella* Heidelberg illness outbreak was reported in the United Kingdom in the 1960s, attributed to ingestion of contaminated milk from dairy cattle (Davies *et al.*, 1962; Knox *et al.*, 1963). More recently, *Salmonella* Heidelberg caused a multistate MDR illness outbreak linked to poultry consumption (Gieraltowski *et al.*, 2016), and in 2017, *Salmonella* Heidelberg was among the *Salmonella* serotypes most commonly linked to human infection (Marder *et al.*, 2018). *Salmonella* Heidelberg isolated from live animals and food products in the United States commonly demonstrates resistance to multiple antimicrobials, including tetracycline, streptomycin, kanamycin, and ampicillin (Lynne *et al.*, 2009).

On August 3, 2016, the Wisconsin Veterinary Diagnostic Laboratory (WVDL) notified the Wisconsin Division of Public Health (WDPH) of an isolate of *Salmonella* Heidelberg cultured from an ill dairy bull calf submitted to the WVDL by a farm experiencing a recurrent *Salmonella* outbreak among calves, which was associated with unusually high calf mortality. Initial query of PulseNet, the national molecular subtyping network for foodborne disease surveillance, identified isolates from ill people matching those of the index calf.

Antimicrobial susceptibility testing (AST) of the calf's isolate revealed resistance, as defined by the Clinical and Laboratory Standards Institute (CLSI), to multiple antimicrobials (CLSI, 2021). Consultation with the CDC National Antimicrobial Resistance Monitoring System (NARMS) team indicated that the AST resistance phenotype had not been previously reported to NARMS among human *Salmonella* Heidelberg isolates and included antimicrobials used for first-line treatment of salmonellosis (CDC, 2020a). Whole genome sequencing (WGS) demonstrated close genetic relatedness of a *Salmonella* isolate from an ill worker from the index farm and the calf's isolate.

An investigation involving human and animal health and laboratory entities was initiated to identify additional illnesses and determine relatedness of the human and animal *Salmonella* Heidelberg isolates. This article describes the actions taken to investigate this outbreak of *Salmonella* Heidelberg with a novel MDR pattern in humans and animals and ongoing activities to disseminate information to prevent *Salmonella* Heidelberg illnesses.

Materials and Methods

This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy.*

The initial case definition was a laboratory-confirmed *Salmonella* Heidelberg human infection with one of six pulsed-field gel electrophoresis (PFGE) patterns reported through PulseNet with illness onset on or after January 1, 2016. These PFGE patterns were found in cattle isolates and in isolates from ill people who reported contact with cattle. The case definition was subsequently expanded to encompass cases with illness onset on or after January 1, 2015, after case finding conducted using PulseNet identified seven additional clinical *Salmonella* Heidelberg isolates from 2015.

Case identification continued throughout 2018, and an additional PFGE pattern was identified with close genetic similarity (based on WGS analysis) to the outbreak strain causing illness in humans with reported calf exposure. The final case definition was a laboratory-confirmed *Salmonella* Heidelberg human infection with an isolate with one of seven implicated PFGE patterns, or related by WGS, with illness onset from January 1, 2015, through July 2, 2018.

To identify potential sources of infection and other epidemiologic linkages between cases, state and local public health officials interviewed ill people about food and environmental exposures occurring in the week before illness onset. Based on initial reports of exposure to dairy cattle and calves and identification of samples from dairy calves owned by an ill person with a related *Salmonella* Heidelberg isolate, ill people were asked more detailed questions on the type of contact with cattle, health status of cattle, date and location of purchase of cattle (purchase records), and cattle rearing and management practices.

Calf purchase records obtained from ill people were used by federal and state health and agriculture officials to examine and trace interstate movement of cattle from purchasers to livestock markets and transport companies or haulers. Trace back activities helped to inform environmental testing at a single livestock market. Health and agriculture departments in states that received cattle from these markets were informed of the outbreak.

The WVDL serotyped *Salmonella* isolates from cattle and calves submitted for necropsy and from fecal or environmental samples submitted for culture from farms experiencing animal morbidity or mortality consistent with *Salmonella* infection. Animal isolates identified as *Salmonella* Heidelberg were submitted to the Wisconsin State Laboratory of Hygiene (WSLH) for additional characterization, including PFGE and WGS; these data were submitted to PulseNet to determine genetic relatedness of human and

*See, for example, 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

cattle isolates. Additionally, some ill people who owned cattle granted investigators permission to collect samples from cattle.

Environmental sampling was conducted at a livestock market that voluntarily permitted investigation to determine if *Salmonella* Heidelberg could be isolated from locations where commingled calves were housed. Animal samples from 14 states were submitted to USDA-APHIS National Veterinary Services Laboratories (NVSL), WVDL, state veterinary diagnostic laboratories, or public health laboratories where culture for *Salmonella*, PFGE, and WGS analysis were performed. During this investigation, PulseNet was transitioning from using PFGE to WGS to monitor and track disease outbreaks; thus, both methods were utilized during this investigation (Kubota *et al.*, 2019).

PFGE was performed following the PulseNet protocol for *Salmonella* (Ribot *et al.*, 2006). Patterns were analyzed using BioNumerics 6.6 (Applied Maths, Sint-Martens-Latem, Belgium) and uploaded to the national database at CDC for comparison and pattern naming. WGS was performed using the Nextera XT library preparation kit (Illumina, San Diego, CA), followed by sequencing on the Illumina MiSeq platform. Sequences were shared with CDC for high-quality single-nucleotide polymorphism analysis and core genome multilocus sequence typing (Katz *et al.*, 2017). All sequences have been submitted to the National Center for Biotechnology Information (NCBI) bioproject PRJNA230403.

The WSLH and NARMS laboratory performed AST by broth microdilution on select human clinical isolates using a Sensititre® panel (Trek Diagnostics, Westlake, OH) with 14 drugs: amoxicillin–clavulanic acid, ampicillin, azithromycin, cefoxitin, ceftriaxone, chloramphenicol, ciprofloxacin, gentamicin, meropenem, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim–sulfamethoxazole (CDC, 2018b). Breakpoints established by the CLSI were used to define susceptible, intermediate, and resistant ranges when available; otherwise, NARMS-established breakpoints were used (CDC, 2018b; CLSI, 2021). *De novo* assemblies from sequenced isolates were produced using shovill, v.1.0.4 (https://github.com/tseemann/shovill).

Screening of assemblies for resistance determinants was performed using staramr, v. 0.4.0, which employs the ResFinder database (updated July 30, 2020) using thresholds of 90% identity and 50% gene coverage and the PointFinder scheme for *Salmonella* spp. (updated August 30, 2019) (Tagg *et al.*, 2020). A predicted resistance pattern was assigned based on the presence of resistance determinants in genome assemblies (McDermott *et al.*, 2016). Multidrug resistance was defined as resistance to at least one antimicrobial in three or more drug classes (Magiorakos *et al.*, 2012).

Results

Sixty-eight human cases of *Salmonella* Heidelberg infection were identified from 17 states; of these, 18 (26%) cases were reported from Wisconsin (Fig. 1). Estimated onset dates of infection in patients ranged from August 1, 2015, through July 2, 2018 (Fig. 2). The median patient age was 14 years, with a range of <1–89 years. Thirty-nine (57%) patients were 18 years old or younger (Fig. 3). Twenty-one (35%) patients were hospitalized. Median age of hospitalized patients was 24 years. No deaths were reported.

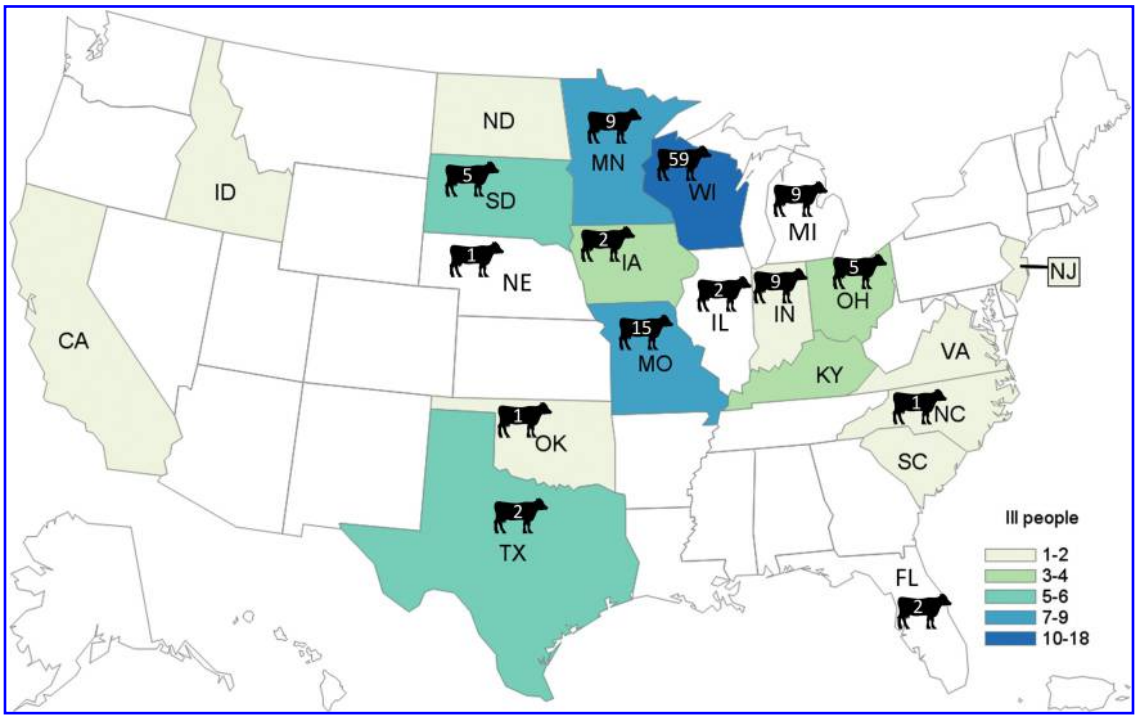

FIG. 1. Human cases of *Salmonella* Heidelberg by state. A total of 17 states were associated with human cases in this outbreak. The highest number of cases (18) occurred in Wisconsin. Cattle icons denote states in which isolates positive for the *Salmonella* Heidelberg outbreak strain were detected in samples from cattle, and the corresponding number of positive isolates is indicated. Color images are available online.

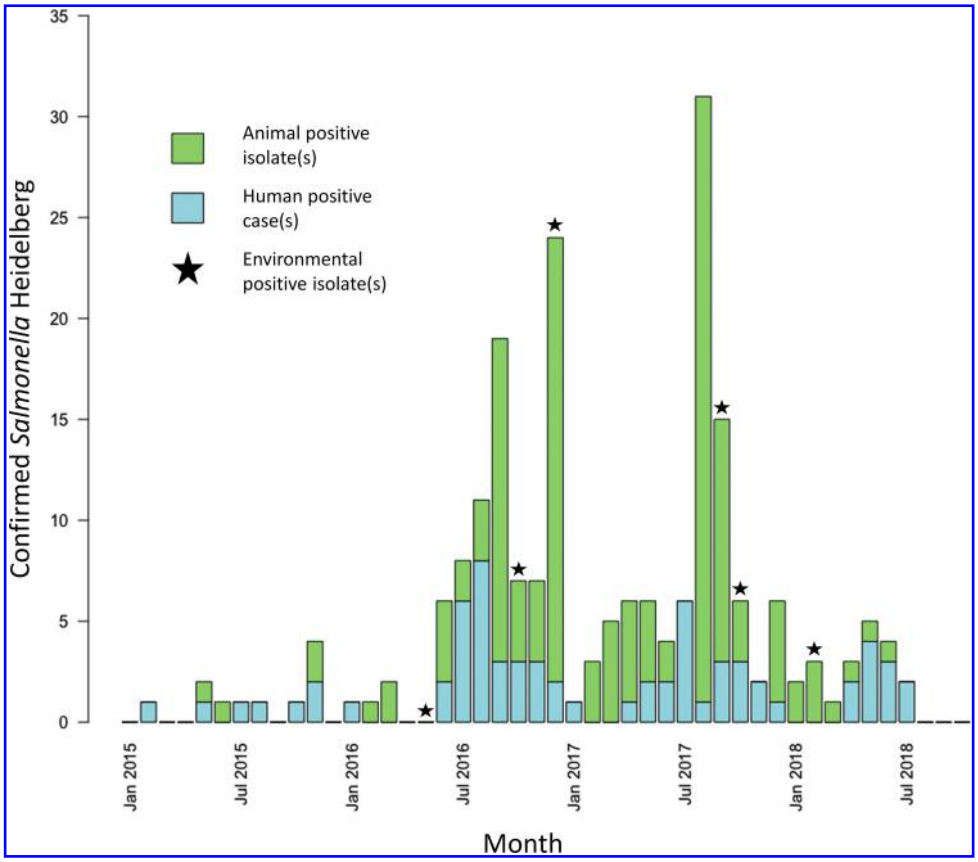

FIG. 2. Epidemiologic curve of human *Salmonella* Heidelberg cases and animal isolates from January 1, 2015, to July 2, 2018. Seven human patients matching the outbreak case definition had estimated onset dates of *Salmonella* Heidelberg in 2015; 28 in 2016; 22 in 2017; and 11 in 2018. Animal isolates reflect dates when *Salmonella* Heidelberg was isolated through laboratory testing rather than animal illness onset date. Star icons indicate months in which *Salmonella* Heidelberg was isolated through environmental testing. Color images are available online.

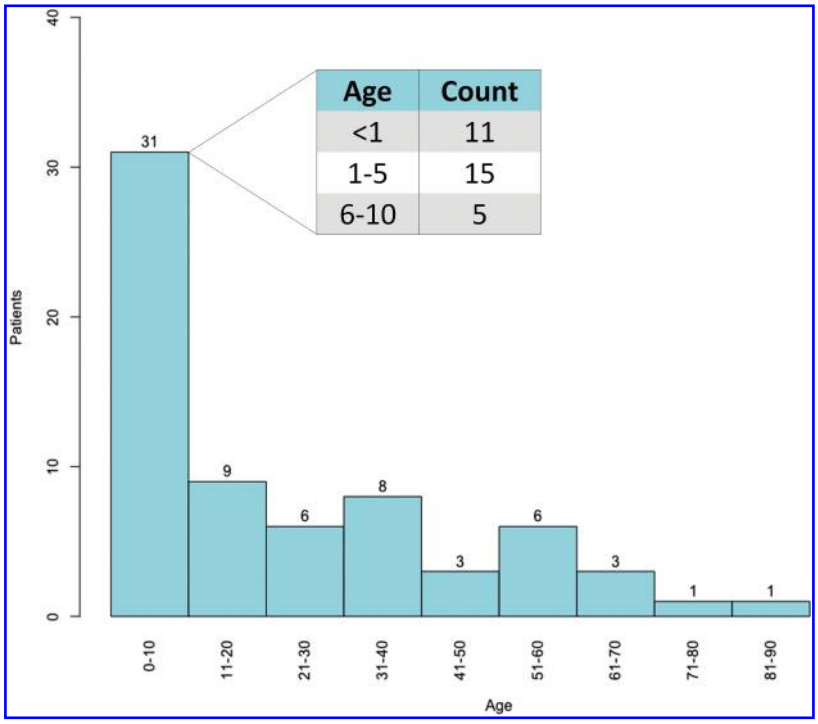

FIG. 3. Age distribution of *Salmonella* Heidelberg human patients. The median age of human patients meeting the *Salmonella* Heidelberg outbreak case definition was 14 (range <1–89 years). Color images are available online.

Forty (63%) of 64 patients with available information reported exposure to cattle. Twenty-four (60%) of those 40 patients were 18 years old or younger. Eleven (28%) of the 40 patients reported contact with calves specifically, and 5 (13%) patients with cattle exposure lived on farms where calves were present. Two people indicated their reason for purchasing calves, and both reported purchasing for the purpose of youth agriculture club activities. *Salmonella* Heidelberg was also plausibly transmitted from person to person among family members in households with cattle; among five members of a single family infected with *Salmonella* Heidelberg with a single PFGE pattern, two were children below the age of 1 year who did not have direct cattle contact.

Thirteen (33%) of the 40 patients with cattle exposure reported that the cattle were sick. Eight (20%) specified that cattle or calves were sick with diarrhea, which is the most common illness affecting young calves (Lorenz *et al.*, 2011). Ten (77%) of 13 patients who reported owning or caring for sick cattle specified that the sick animals were calves and reported calf mortality. Recent purchase of cattle or calves before illness onset was reported for 23 (58%) of 40 patients with cattle exposure. One patient reported owning a goat that was housed with sick cattle. This goat became ill and died, and the outbreak strain was isolated from samples collected from the goat (Fig. 4 and Supplementary Fig. S1).

Calves linked to seven patients in six states (Wisconsin, Iowa, Minnesota, Missouri, Oklahoma, and South Dakota) had purchase records from a single livestock market (Market A) in Wisconsin. Purchase record and trace back information was more complete for calves sold from Wisconsin to other states than calves sold intrastate, as calves sold intrastate were not required to have the same level of identification as cattle moving between states (e.g., ear tags or brands). Market A was supplied with calves from multiple source farms in Wisconsin.

One hundred and seventy-five nonhuman isolates with PFGE patterns matching the human patients were identified either through sampling as part of the outbreak investigation or by review of PFGE results obtained during routine surveillance activities (Supplementary Fig. S1). Matching nonhuman isolates were collected from May 28, 2015, through June 19, 2018 (Fig. 2), in 14 states. Animal isolates accounted for 140 (80%) of 175 nonhuman isolates. Thirty-three (92%) of the 35 environmental isolates were obtained from sources in Wisconsin.

WGS analysis of isolates resulting from bacterial culture of Market A samples indicated that 10 environmental isolates were genetically closely related to human- and bovine-origin isolates identified in this investigation (Fig. 4). Animal transport vehicles for Market A were sampled and yielded isolates matching the outbreak strain of *Salmonella* Heidelberg.

Thirteen human isolates were submitted to CDC's NARMS laboratory for phenotypic AST. All were MDR strains, with nonsusceptibility in up to 11 of the 14 antimicrobial agents tested (Table 1). Whole genome sequences from 59 human and 117 animal isolates revealed resistance determinants consistent with the phenotypic AST results; a

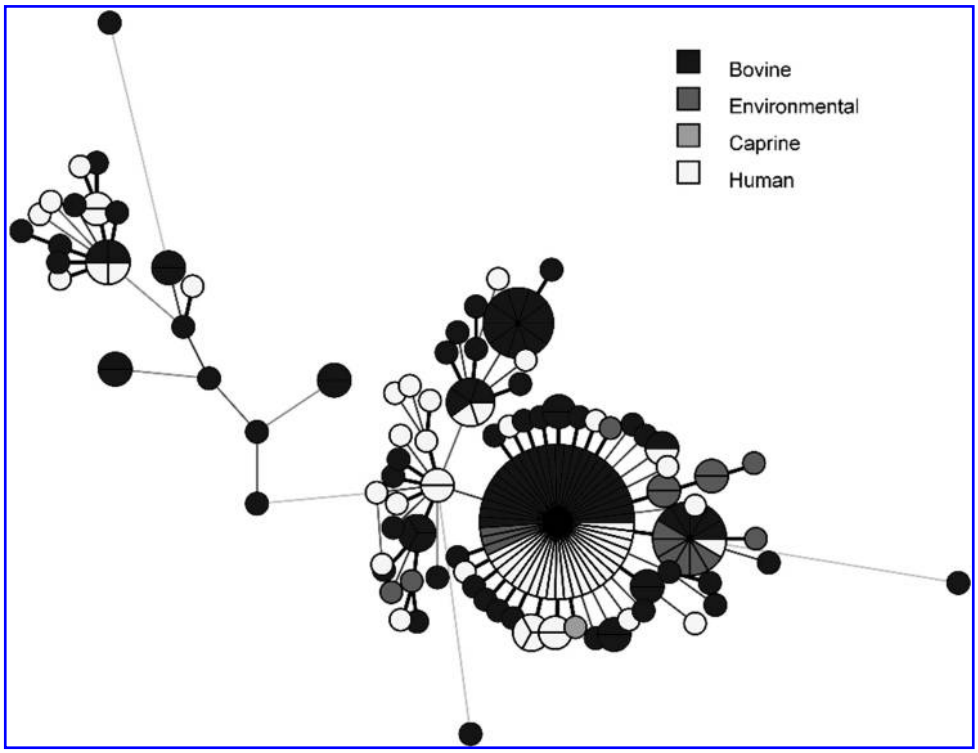

FIG. 4. Minimum spanning tree diagraming genetic relatedness of human, animal, and environmental isolates. All sequences have an allele difference range of 0–35 alleles. The length of the lines indicates the allele difference between individual sequences. Line length is proportionally scaled, and the longer the line, the greater the allele difference is between the sequences. Isolates with no allelic variation are represented as slices of the same circle. The single caprine isolate was obtained from a goat that became infected with the outbreak strain, following housing with infected cattle. Color images are available online.

Table 1. Antimicrobial Resistance[a] of Human and Bovine *Salmonella* Heidelberg Outbreak Isolates from January 1, 2015, Through July 2, 2018

Drug[b]	*Human* N = *59* n *(%)*	*Bovine* N = *117* n *(%)*	*Total* N = *176* n *(%)*
Ampicillin	55 (93)	101(86)	156 (88)
Amoxicillin–clavulanic acid	55 (93)	101 (86)	156 (88)
Azithromycin	0 (0)	0 (0)	0 (0)
Cefoxitin	55 (93)	101 (86)	156 (88)
Ceftriaxone	55 (93)	101 (86)	156 (88)
Chloramphenicol[c]	25 (42)	44 (38)	69 (39)
Ciprofloxacin[d]	59 (100)	111 (95)	170 (97)
Gentamicin	0 (0)	2 (1.7)	2 (1.1)
Meropenem	0 (0)	0 (0)	0 (0)
Streptomycin	57 (97)	101 (86)	158 (90)
Sulfisoxazole	57 (97)	97 (83)	154 (88)
Tetracycline	57 (97)	97 (83)	154 (88)
Trimethoprim–sulfamethoxazole	56 (95)	96 (82)	152 (86)
Kanamycin[e]	45 (76)	90 (77)	135 (77)
Fosfomycin[e]	59 (100)	117 (100)	176 (100)
Resistance to ≥5 antimicrobial classes	55 (93)	101 (86)	156 (88)

[a]Resistance was determined by AST for 13 isolates; resistance was predicted based on whole genome sequencing for the remaining 163 isolates.
[b]Resistance to nalidixic acid is not shown. Most (150/176) isolates contained the *qnrB19* gene; 9/12 *qnrB19*(+) isolates tested phenotypically showed resistance to nalidixic acid.
[c]Eighty-four out of 153 *floR(+)* isolates had an interruption in the *floR* gene, resulting in predicted loss of chloramphenicol resistance.
[d]Includes intermediate susceptibility.
[e]AST was not performed for these agents.
AST, antimicrobial susceptibility testing.

majority of isolates from all sources contained the plasmid-mediated resistance genes, *aadA1*, *aph(3′)-Ia*, bla_{CMY-2}, *floR*, *fosA7*, *qnrB19*, *strA*, *strB*, *sul1*, *sul2*, *tet(A)*, *tet(B)*, and *tet(O)*, and a novel gene *dfrA34*.

Following isolation of *Salmonella* Heidelberg from environmental sampling at Market A, education and cleaning and disinfection information were provided to the livestock market management and staff by investigators from Wisconsin and USDA. A recommendation was made to discontinue the use of a power washer that had been used to remove visible debris before disinfection to mitigate dissemination of bacteria throughout the facility. Records from the veterinary diagnostic laboratories indicated that ill calves originated from numerous farms and moved through multiple different livestock markets other than Market A.

Information on the *Salmonella* Heidelberg outbreak and preventive biosecurity measures was mailed to all licensed truckers, dealers, and livestock markets in Wisconsin. Additionally, this information was also provided to licensed veterinarians and producer groups. The CDC issued a public warning through a web posting in November 2016, with multiple updates through 2018 (CDC, 2018a). The outbreak notice included advice for livestock handlers and veterinarians and a section for health care providers regarding the MDR strain.

Discussion

The present study describes the first documented multistate outbreak of MDR *Salmonella* Heidelberg in humans linked to cattle exposure. This human illness outbreak likely occurred as the result of a spillover of an epidemic of MDR *Salmonella* Heidelberg infections in calves and cattle; this is supported by the detection of ill calves in veterinary diagnostic laboratories before detection of human illness and reports from patients, indicating that calves became sick before the onset of human illness. Initially, calves were traced back to a single livestock market (Market A); however, further investigation demonstrated that additional livestock markets sold calves that were linked to human illness.

Calves came into livestock markets, including Market A, from multiple source farms. However, trace back of calves to source farms was limited as records were not available for all cattle purchases from livestock markets or from farms. Isolates resulting from sampling at Market A were genetically closely related to isolates obtained from ill people reporting contact with this market through purchase of calves (Fig. 4). It is possible that additional livestock markets could have also yielded the outbreak strain had they been sampled.

The MDR *Salmonella* Heidelberg strain causing this outbreak might have been disseminated to many different farms, sale locations, and livestock markets through movement and commingling of calves and conveyance equipment, including livestock trailers. Trace back through calf purchase records collected from ill people, laboratory sampling, and WGS results indicated that interstate movement of cattle likely contributed to the geographic spread of the outbreak.

During the process of transportation over long distances, cattle commingle and share pathogens through direct contact with one another or contaminated conveyance equipment such as livestock trailers. Thus, infectious agents might spread over a wide geographic area if the same equipment is used to move animals to multiple locations without cleaning and disinfection between shipments (Barham *et al.*, 2002; Arthur *et al.*, 2008; Dewell *et al.*, 2008). Stress of transportation has not been definitively proven to increase the rate at which *Salmonella* spp. are shed in feces of cattle, although studies have reported this finding (Corrier *et al.*, 1990; Barham *et al.*, 2002).

Increased shedding during shipment might increase the rate of contamination of animals themselves, which poses an additional risk of exposing animal handlers at the final destination, especially if trailers are not regularly cleaned (Barham *et al.*, 2002; Arthur *et al.*, 2008; Dewell *et al.*, 2008). The USDA Title 9 Code of Federal Regulations (9 CFR 91.6) specifies requirements for cleaning and disinfection of vehicles used for interstate movement of animals (USDA, 2019). The responsibility falls on individual livestock haulers to institute proper routine biosecurity measures for transportation equipment to mitigate the risk of disease transmission and on veterinarians and other accredited personnel certifying animal transportation to ensure transportation equipment is cleaned and disinfected between animal shipments.

The resistance profile in this outbreak had not previously been identified among *Salmonella* strains reported to NARMS. This phenotype is conferred by the presence of 14 plasmid-borne genes, 12 of which are carried on an IncC plasmid (NCBI accession MH760469.1) (Folster *et al.*, 2018; Tagg *et al.*, 2019). The prevalence of MDR in *Salmonella* has increased over time among humans in the United States, which poses the challenge of severe salmonellosis steadily becoming more difficult to treat as empirical antimicrobial selection becomes more limited (Molbak, 2005; CDC, 2018b).

Recent *Salmonella* Heidelberg isolates specifically have demonstrated a broadened resistance profile compared with isolates dating back to the 1980s (Antony *et al.*, 2018). In this outbreak, a high proportion of patients were hospitalized (35%), similar to previous outbreaks associated with MDR *Salmonella* Heidelberg (Folster *et al.*, 2012; Grinnel *et al.*, 2013; Gieraltowski *et al.*, 2016). Resistance has been previously associated with elevated virulence, possibly secondary to coselection of virulence traits with resistance mechanisms (Fluit, 2005; Molbak, 2005).

Genomic analysis of isolates from calves and humans involved in this outbreak identified a specific *safABCD* genetic operon encoding adhesive fimbriae that confer enhanced pathogenesis. These have been identified with some frequency in *Salmonella* Typhimurium, but are generally not detected in *Salmonella* Heidelberg (Łaniewski *et al.*, 2017; Antony *et al.*, 2018).

Resistant *Salmonella* bacteria can be acquired from numerous sources along the food production chain, and evidence indicates that new MDR variants of *Salmonella* are continuing to emerge in food-producing animals just as in this outbreak (CDC, 2015; Cohen *et al.*, 2020). Young age is a known risk factor for cattle carrying MDR *Salmonella* (Davidson *et al.*, 2018; Springer *et al.*, 2018). This might be from lack of competitive exclusion of resistant or pathogenic bacteria by the undeveloped intestinal microflora; however, more data are needed to substantiate this hypothesis (Davidson *et al.*, 2018).

Exposure to antimicrobial drugs can also elevate the risk of developing antimicrobial resistance. Waste milk (milk that cannot be sold for human consumption) collected from cattle that have been administered systemic antibiotics can contain drug residues that might interact with intestinal flora and preferentially select for resistant bacteria (Van Vleck Pereira *et al.*, 2016) when ingested by calves. Management practices that might have resulted in selection for and transmission of MDR *Salmonella* Heidelberg were not examined in this investigation, but were subsequently studied by state and federal partners (Lombard, 2017).

Treatment failures in humans and cattle were not assessed in this investigation. Case histories provided by practicing veterinarians to veterinary diagnostic laboratories mentioned the absence of any effective antimicrobial drug for treating calves infected with *Salmonella* Heidelberg and that sudden death in high-stressed calves occurred.

Of note, most infected patients in this outbreak were children (Fig. 3). Outbreaks of *Salmonella* Heidelberg in the United States have similarly reported a younger median patient age ranging from 14 to 23 years (CDC, 2012, 2014; Folster *et al.*, 2012; Grinnel *et al.*, 2013; Gieraltowski *et al.*, 2016). Young age is a known risk factor for human salmonellosis, likely linked to decreased immune function and hygiene practices (Graham, 2002). This raises the possibility that children living on farms or participating in agricultural activities might be at a greater risk of zoonotic salmonellosis and therefore caregivers must be diligent in monitoring direct contact with animals and enforcing proper hand washing practices (CDC, 2015; Conrad *et al.*, 2017).

During the active investigation, case frequency demonstrated a cyclical pattern in which the highest numbers of human cases were reported during the late spring and summer months (Fig. 2). It is well established that *Salmonella* excretion by cattle increases in the spring and summer months, which could contribute to farm contamination and human exposure (Davidson *et al.*, 2006; Lombard *et al.*, 2012; Abu Aboud *et al.*, 2016; Likavec *et al.*, 2016).

In this outbreak, this could also merely be an indicator of the time of year when humans were most likely to come in contact with cattle (e.g., calving season, petting zoos, and animal exhibits) (Conrad *et al.*, 2017; Daly *et al.*, 2017). *Salmonella* Heidelberg infections with this MDR strain continue to be monitored by CDC and state and local health departments.

Conclusions

This investigation highlights the importance of surveillance to identify disease outbreaks among animals, which can spillover or result in human illnesses. Understanding the complexity of animal movement within the industry was important to ensure broad dissemination of biosecurity information and infection prevention.

Early detection of emergence of MDR *Salmonella* strains, which are resistant to first-line antimicrobials used to treat severe human and animal infections, might help to prevent zoonotic and foodborne disease transmission through early implementation of disease prevention and control measures.

Author Contributions

M.N. oversaw epidemiologic data collection for the outbreak, analyzed outbreak data, and wrote and revised the manuscript. N.A. and D.S. provided consultation on project scope, contact with veterinarians, preparation of cleaning and disinfection protocols and questions for producers, and remitting data to involved parties. N.A. oversaw *Salmonella* cultures, serotyping, and antimicrobial susceptibility testing at the WVDL, as well as remitting isolates to the Wisconsin Department of Health and revision of the manuscript.

J.C.C., J.P.F., L.K.F.W., and K.A.T. analyzed antimicrobial resistance data and wrote and revised the manuscript. G.S.S. analyzed outbreak data and wrote and revised the manuscript. E.T. oversaw the WGS at CDC, coordinated the bioinformatic analyses, and revised the manuscript. B.M.S. and L.K. performed sample isolation and serotyping and revised the manuscript. Z.E. created the dendrogram and minimum spanning tree and revised the manuscript.

J.L. organized and moderated the meeting with Market A on biosecurity practices, worked with the Wisconsin Department of Agriculture, Trade and Consumer Protection on the investigation, and revised the manuscript. E.P. facilitated the meeting with Market A and USDA, sample collection, and manuscript revisions.

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Disclosure Statement

The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention (CDC).

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Supplementary Material

Supplementary Figure S1

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Address correspondence to:
Megin Nichols, DVM, MPH, DACVPM
Division of Foodborne, Waterborne, and Environmental Diseases
National Center for Emerging and Zoonotic Infectious Diseases
U.S. Centers for Disease Control and Prevention
1600 Clifton Road, MS-A38
Atlanta, GA 30333
USA

E-mail: gpg6@cdc.gov