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Nontyphoidal *Salmonella* infections in CT —Decreasing antibiotic susceptibility and increasing antibiotic use

The Centers for Disease Control and Prevention (CDC) has designated drug-resistant nontyphoidal *Salmonella* as a serious public health threat in their Antibiotic Resistance Threats in the United States, 2019 report *(1)* based on data from the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). NARMS was implemented in 1996 to monitor changes in antimicrobial susceptibility among enteric pathogens, including nontyphoidal Salmonella, by testing isolates from across the country *(2)*. These national data highlighted changes in susceptibility to commonly prescribed antibiotics including ciprofloxacin. Nationally, the proportion of nontyphoidal *Salmonella* isolates with decreased susceptibility to ciprofloxacin increased from 2% to 8% between 2009-2017*(1)*.

Since 1995, Connecticut has participated in the Foodborne Diseases Active Surveillance Network (FoodNet), a collaborative effort between CDC, 10 Emerging Infections Program (EIP) sites, the US Department of Agriculture (USDA), and the Food and Drug Administration (FDA), to monitor the burden of enteric diseases, including salmonellosis *(4)*. This has provided an opportunity to better understand severity of illness, potential exposures before infection, and history of antibiotic use. This is important in the context of antibiotic resistance. Pathogens with decreased susceptibility may lead to more severe disease, including hospitalization; overuse of antibiotic treatment can contribute to antibiotic resistance; and exposures known to be associated with decreased susceptibility or resistance can help narrow down treatment options if antibiotics are recommended*(1).* Treatment of nontyphoidal *Salmonella* infection with antibiotics is generally not recommended but may be recommended for case-patients who experience severe illness, are at least 65 years of age, or are immunocompromised *(5).*

Using both Connecticut NARMS and FoodNet case interview data, we evaluated trends in ciprofloxacin susceptibility among nontyphoidal *Salmonella* isolates and antibiotic use among salmonellosis case-patients. We also assessed associations between ciprofloxacin susceptibility and international travel and illness severity using hospitalization as a marker. NARMS susceptibility data on Connecticut nontyphoidal *Salmonella* surveillance isolates collected during 1996 -2020 were analyzed. Decreased susceptibility to ciprofloxacin (DSC) was defined according to the Clinical and Laboratory Standards Institute (CLSI). Isolates with minimum inhibitory concentration (MIC) values in the intermediate (MIC = 0.12–0.5 µg/ml) or resistant (MIC ≥1 µg/ml) range were considered to have decreased susceptibility*(3)*.FoodNet data on hospital admission and international travel among nontyphoidal *Salmonella* cases were available for 2010-2021 and on antibiotic usage for 2018-2021. Chi -square for trend tests were used to analyze yearly trends in the proportion of isolates with DSC and in antibiotic use among cases. The association between DSC and hospitalization status and international

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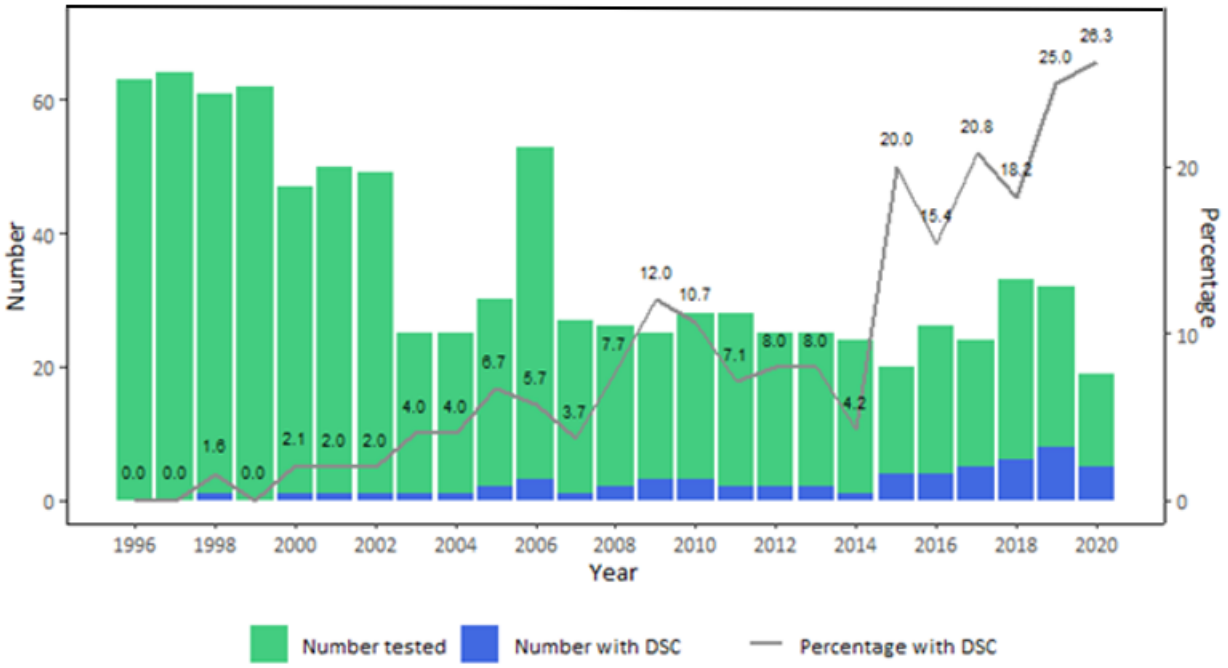
Figure 1: Decreased susceptibility to ciprofloxacin (DSC), CT, 1996 – 2020 Among nontyphoidal *Salmonella* isolates tested via AST



travel were assessed via the chi-square test.

Between 1996-2020, the proportion of isolates with DSC increased significantly from zero to 26.3% (chi square for trend = 58.97, p < 0.001) (Figure 1). Infections caused by *Salmonella* with DSC were found to be significantly associated with international travel, with 28.6% (10/35) of case patients with DSC infections having traveled within the seven days prior to illness onset, compared with 13.7% (25/183) of those with ciprofloxacin susceptible infections (chi square = 4.85, p<0.05). Among case-patients reporting international travel, most had traveled to Central America, South America or the Caribbean, although there was not a significant association between DSC and travel to any particular region. No significant association was found between infection with *Salmonella* with DSC and hospitalization status, with 38.2% (13/34) of those with DSC infection being hospitalized compared with 34.4% (64/186) of those with ciprofloxacin susceptible infection (p-value=0.67).

Connecticut FoodNet data from 2018-2021 were used to identify the proportion of salmonellosis case-patients that reported using antibiotics to treat their infection. Across all four years, the proportion treated with antibiotics was 50.4% (904/1795), increasing from 47.2% (236/500) in 2018 to 56.0% (241/430) in 2021 (chi square for trend = 5.87, p<0.05). Among those treated with antibiotics, 377 (41.7%) were hospitalized, 189 (20.9%) were 65 years or older, and 465 (51.4%) were either hospitalized, 65 years or older, or both. Ciprofloxacin was the most commonly reported antibiotic with 15.8% (n=283) of all case-patients and 31.3% of case-patients on antibiotics treated with it.

Editorial

Connecticut has seen a rise in levels of DSC among nontyphoidal *Salmonella* infections, increasing beyond the 2017 national level of 8% *(2).* In 2017, over 20% of nontyphoidal *Salmonella*

infections in Connecticut had DSC; this percentage increased to over 25% in 2020. This level of decreased susceptibility, and the trajectory of it, is concerning, especially when coupled with the fact that the most commonly prescribed antibiotic reported in Connecticut for nontyphoidal *Salmonella* infection from 2018-2021 was ciprofloxacin. However, given that fluoroquinolones are among the recommended first line therapies for empiric treatment of *Salmonella* infection, this is not surprising, and is in agreement with recommendations.

While we did not see increased hospitalization rates among DSC infections in Connecticut, further analysis is needed to explore other indicators of severe illness. Increasing rates of antibiotic treatment may be in response to increasing disease severity that is not reflected in hospitalization rates, however that is beyond the scope of this analysis. Analysis of Connecticut data shows an association between DSC and international travel. According to the 2018-2019 FoodNet Population Survey, international travel in the past 30 days was more commonly reported among Connecticut residents (5.0%) compared to the overall percentage among residents of all FoodNet sites (3.7%) (6). This suggests that international travel may play a role in the higher proportion of DSC in CT than in the US overall.

Healthcare providers should evaluate the need for antibiotics when caring for patients with nontyphoidal *Salmonella* infection, as treatment may not be recommended for all patients. This is of utmost importance as prudent use of antibiotics can help mitigate the serious public health threat of antibiotic resistance. Further recommendations can be found in the 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea *(7)*.

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Multisystem Inflammatory Syndrome in Children (MIS-C)—Connecticut, April 2020–December 2022

Multisystem inflammatory syndrome in children (MIS-C) is a delayed hyperinflammatory condition first recognized in April 2020 that can follow an infection with the SARS-CoV-2 virus (*1*). In May 2020, the Centers for Disease Control and Prevention (CDC) disseminated a health advisory requesting clinicians report suspected cases to local and state health departments using a clinical case definition. MIS-C was officially added to the List of Reportable Diseases, Emergency Illnesses and Health Conditions in Connecticut on January 1, 2021 (*2*). Beginning in January 2023, a new case definition for MIS-C standardized surveillance was adopted and is now referred to as the CSTE/CDC MIS-C surveillance case definition. Given the limited knowledge of MIS-C early on, the original clinical case definition was broad. The 2023 CSTE/CDC case definition has greater specificity allowing for the differentiation between MIS-C and other hyperinflammatory conditions, including Kawasaki disease and toxic shock syndrome. This article summarizes the MIS-C cases reported among Connecticut residents under 21 years of age between April 2020–December 2022 under the original clinical case definition and highlights updates to the CSTE/CDC MIS-C case definition for MIS-C moving forward.

Between April 2020–December 2022, 137 cases of MIS-C that met the clinical case definition were reported to the Connecticut Department of Public Health (CT DPH) (Table 1). Of these, 78 (57%) were male. The median age was eight years (range 10 months–19 years), with the highest incidence in children under the age of ten years old. MIS-C disproportionately impacted non-Hispanic Black populations, with an incidence rate of 36.77 cases per 100,000, and Hispanic/Latinx populations (17.69). This is consistent with national data (CDC, 2022). Cases were reported in all eight Connecticut counties with New Haven County having the highest incidence rate at 24.91 per 100,000, followed closely by Fairfield County at 21.18. Eighty-five percent of cases were not vaccinated against COVID-19 (Table 2). All cases had at least one positive SARS-CoV-2 test, with the majority having a positive SARS-CoV-2 IgG antibody test (n=85, 63%). There were no fatalities, but 30.66% of cases were admitted to the intensive care unit.

Table 1: *Demographics of MIS-C Cases April 2020 – December 2022*

Classification	Number (%)	IR per 100,000
All cases	n=137	
Age (years)		
<5	44 (32)	24.21
5-9	40 (29)	25.83
10-14	28 (20)	13.07
15-20	25 (18)	8.59
Race/Ethnicity		
Non-Hispanic White	40 (29)	8.25
Non-Hispanic Black	37 (27)	36.77
Hispanic/Latinx	36 (26)	17.69
Multiracial	5 (4)	11.08
Non-Hispanic Asian	2 (1)	4.45
Unknown	17 (12)	
Gender/Sex		
Male	78 (57)	17.35
Female	59 (43)	13.64
County of Residence		
Fairfield County	50 (37)	21.18
New Haven County	49 (36)	24.91
Hartford County	21 (15)	10.04
New London County	6 (4)	10.35
Middlesex County	3 (2)	9.30
Tolland County	3 (2)	8.65
Windham County	3 (2)	11.25
Litchfield County	2 (1)	5.53

**Percentages may not sum to 100 due to rounding*

Table 2: *Vaccine Status of Reported MIS-C Cases*

Classification	Number (%)
Vaccination Status (at time of hospitalization)	
Completed Vaccination	11 (8)
Partial Vaccination	10 (7)
Unvaccinated	116 (85)
Eligible	82
Not eligible*	34

**Percentages may not sum to 100 due to rounding*

Discussion

The 2023 CSTE/CDC MIS-C surveillance case definition was developed after a review of 2020–2022 data in consultation with MIS-C experts (*3*). This definition was created to reduce the risk of misclassification during public health surveillance. Changes to the clinical criteria include a focus on C-reactive protein as the laboratory marker of systemic inflammation and multiple changes to the organ systems, clinical signs and symptoms that are used to define a MIS-C case. Laboratory criteria changes include the extension from 30 to 60 days for having a positive SARS-CoV-2 test (viral or antibody) or close contact with a confirmed or probable case prior to hospitalization.

Limitations of this analysis based on the original clinical case definition include the potential for underreporting and the inclusion of hyperinflammatory conditions caused by multiple etiologies. However, with the updated 2023 surveillance case definition for MIS-C, there is an increased ability to differentiate MIS-C from other hyperinflammatory conditions.

Healthcare providers should remain alert to the possibility of MIS-C among their patients due to the potential severity. Additionally, providers should test for IgG antibodies in suspect MIS-C cases; less than 6% of cases had a positive viral test at the time of MIS-C diagnosis. Suspected cases of MIS-C should continue to be reported to the Connecticut DPH Epidemiology and Emerging Infections Program. Healthcare providers should complete the new CDC MIS-C case report form (https://www.cdc.gov/mis/pdfs/MIS-C_case-report-form.pdf) for each case identified and fax it to the CT DPH at (860)-629-6962 . For guidance on completing the updated case report form with the new definition, please view (https://www.cdc.gov/mis/pdfs/MIS-C_case-report-form-guidance-document.pdf). The updated CSTE/CDC MIS-C Surveillance Case Definition and the supporting evidence can be found here.

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