

Spatio-Temporal Distribution of Antimicrobial Resistance in Non-Typhi *Salmonella*, NARMS, 2003-2007

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Abstract (amended)

Background

Non-Typhi *Salmonella* (NTS) is estimated to cause 1.4 million illnesses a year resulting in over 100,000 office visits, 16,000 hospitalizations, and 400 deaths. Antimicrobial resistant strains of NTS are more likely to cause invasive infections and result in hospitalization, which increase the burden of illness and health care costs.

Methods

From 2003-2007, the National Antimicrobial Resistance Monitoring System received every 20th NTS isolate submitted to 50 states and 3 local public health laboratories. At CDC, isolates were susceptibility tested by broth microdilution. MICs were determined for 15 antimicrobial agents and interpreted using CLSI criteria when available. ArcGIS 9.3 was used to map the spatio-temporal distribution of resistance in NTS. We calculated *Shannon* conditional entropy values for the distribution of resistance patterns by geography.

Results

From 2003-2007, 3.5% of NTS were resistant to ceftiofur, 2.6% to nalidixic acid, 7.0% to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline (ACSSuT), 2.3% to at least ACSSuT, amoxicillin-clavulanic acid, and ceftiofur (MDRAmpC). The prevalence of ACSSuT and MDRAmpC has declined since 2003: highest resistances were observed in the northern Midwest. Highest level of resistance to ceftiofur was noted in some northern Midwest states. Nalidixic acid resistance ranged from 2.3% to 3.0% from 2003-2007. In *Salmonella* serotype Typhimurium, 22.8% were ACSSuT from 2003-2007; a decline was noted since 2003 and highest resistance prevalence rates remained in the Midwest and South. In serotype Newport, 13.3% were MDRAmpC from 2003-2007; a decline was observed since 2003 and highest resistance rates remained in the Midwest.

Conclusion

Highest rates of several resistance patterns in NTS were found in Midwestern states. A spatio-temporal view allows monitoring of trends across space and time to better understand the emergence and spread of resistance.

Methods

- Isolate submission scheme
 - NARMS received every 20th NTS isolate submitted to 50 states by clinical laboratories.
 - Typhimurium var. O:5- is categorized with Typhimurium.
- Antimicrobial susceptibility testing
 - All isolates were tested using broth microdilution (Sensititre) to determine minimum inhibitory concentrations (MICs) for 15 agents.
 - MICs were interpreted using criteria from the Clinical and Laboratory Standards Institute (CLSI) when available.
 - Clinically important resistances in NTS and specific serotypes are discussed in this study
- Spatio-temporal analysis
 - ArcGIS 9.3 was used to map the spatio-temporal distribution of resistance in NTS.
 - States were categorized by Census division.³
 - We calculated *Shannon* conditional entropy values for the distribution of resistance patterns by geography using the census divisions.

$$\text{Entropy} = -(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$$

- Entropy provides an ordering; low entropy distributions showing concentration of higher values in a smaller area.

Results

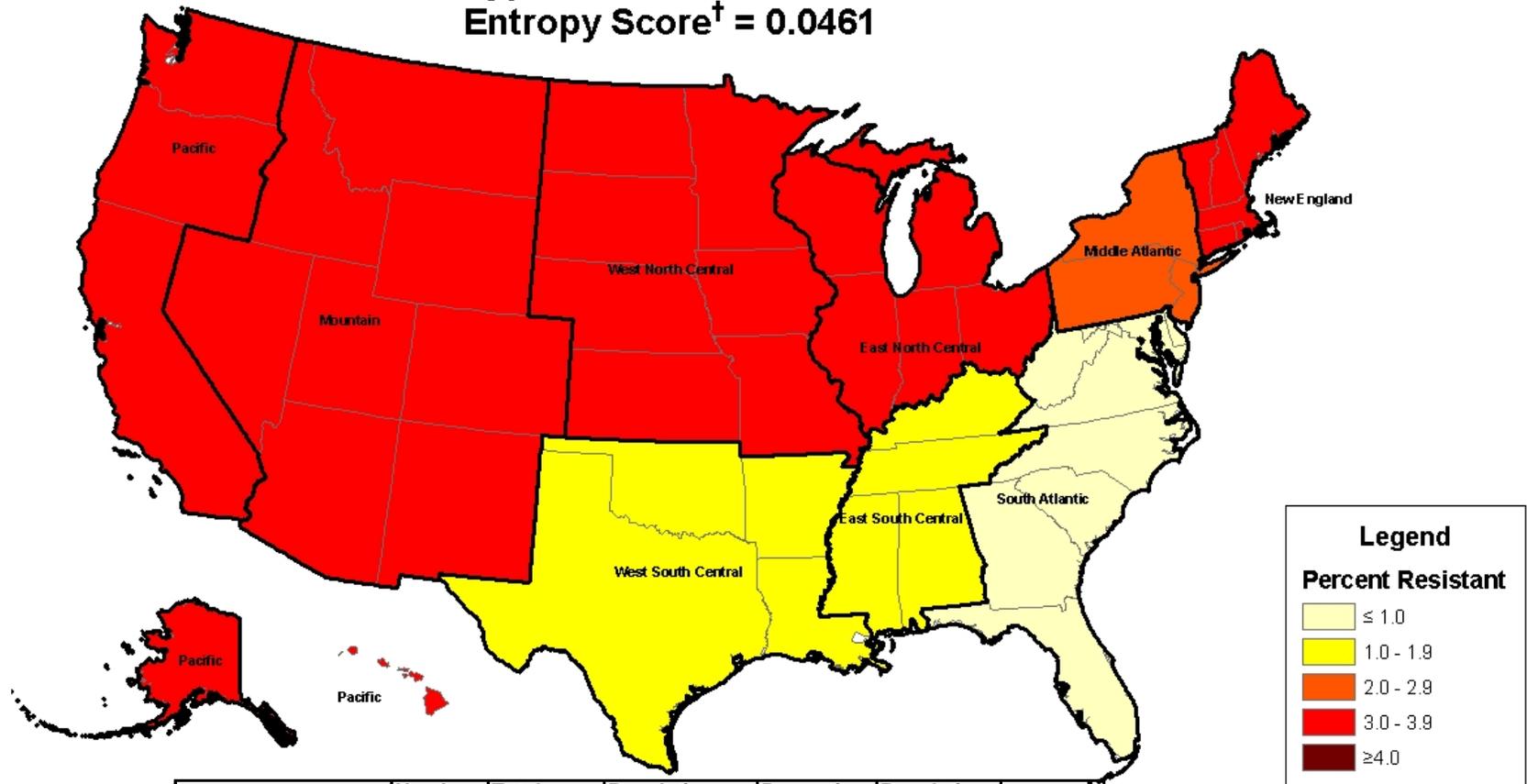
Results 2003-2007

- Non-Typhi *Salmonella*
 - 3.5% resistant to ceftiofur.
 - 2.6% resistant to nalidixic acid.
 - 7.0% resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline (ACSSuT).
 - 2.3% resistant to at least ACSSuT, amoxicillin-clavulanic acid, and ceftiofur (MDRAmpC).
 - ACSSuT and MDRAmpC declined since 2003
 - ACSSuT declined from 9.3% in 2003 to 6.3% in 2007
 - MDRAmpC declined from 3.2% in 2003 to 2.1% in 2007
 - Highest ACSSuT resistances were observed in the northern Midwest: MT, 6 (25%); ID, 8 (17.4%); IA, 13 (14.9%); ND, 2 (11.8%); NE, 9 (14.3%); SD, 5 (10.6%).
 - Highest level of resistance to ceftiofur was noted in some northern Midwest states: MT, 4 (16%); MI, 13 (6.2%); ND, 1 (5.9%); WI, 12 (5.4%).
 - Nalidixic acid resistance ranged from 2.3% to 3.0% from 2003-2007.
- *Salmonella* serotype Typhimurium
 - 22.8% were ACSSuT from 2003-2007; a decline was noted since 2003.
 - ACSSuT declined from 26.1% in 2003 to 22.8% in 2007
 - Highest ACSSuT resistance prevalence rates remained in Midwest and Southern states: ID, 7 (46.7%); IA, 9 (39.1%); GA, 33, (34.7%); FL, 9 (34.6%); VA, 28 (34.6%); SC, 10 (34.5%); KS, 2 (33.3%); ND, 1 (33.3%); LA, 7 (31.8%).
- *Salmonella* serotype Newport
 - 13.3% were MDRAmpC from 2003-2007; a decline was observed since 2003.
 - MDRAmpC declined from 22.8% in 2003 to 7.7% in 2007
 - Highest MDRAmpC resistance rates remained in the Midwest: NE, 1 (100%); MI, 10 (58.8%); WI, 11 (52.4%); NV, 2 (40%).

Entropy Score Results

- MDRampC resistance in NTS - most resistance lies in the west and northern divisions (Figure 1).
- Nalidixic acid resistance in NTS - lower resistance proportions are found in the West South Central and East South Central divisions (Figure 2).
- Ceftiofur resistance in NTS - most resistance lies in the west and northern divisions (Figure 3).
- Nalidixic acid resistance in *Salmonella* Enteritidis - lower resistance proportions are found in the southern divisions (Figure 4).
- ACSSuT resistance in NTS - The highest resistance proportion was found in the West North Central division (Figure 5).
- Ceftiofur resistance in *Salmonella* Heidelberg - highest proportion of resistance was found in the Middle Atlantic and East South Central divisions (Figure 6).
- MDRampC resistance in *Salmonella* Newport - lower resistance proportions are found in the southern divisions (Figure 7).
- Ceftiofur resistance in *Salmonella* Newport - lower resistance proportions are found in the southern divisions (Figure 8).
- ACSSuT resistance in *Salmonella* Typhimurium - High resistance proportions were found across all divisions (Figure 9).

Figure 1: Spatial Distribution by Census Division of MDRampC* Resistance in Non-Typhi *Salmonella*, 2003-2007
Entropy Score[†] = 0.0461



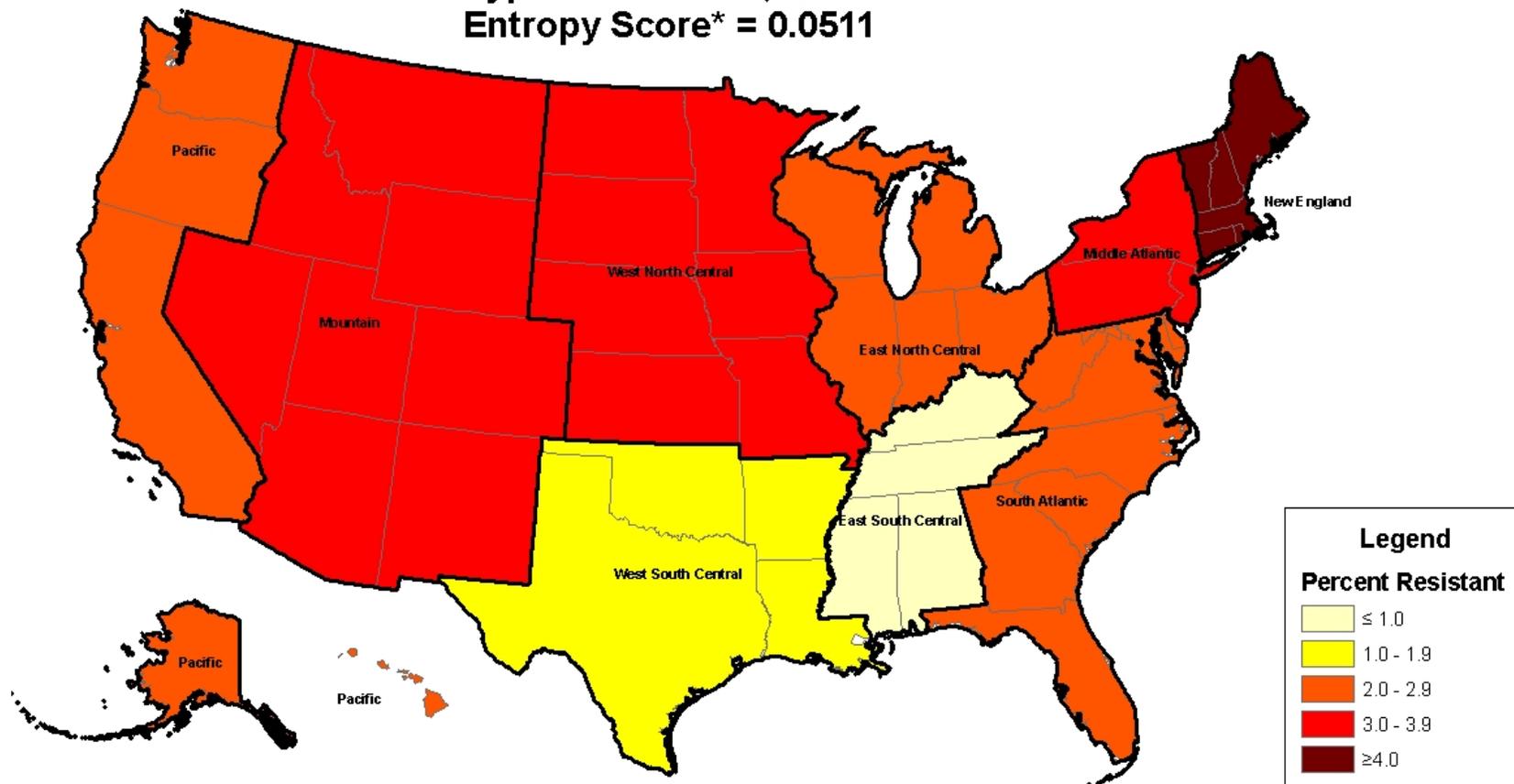
Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [‡]
East North Central	46	1384	46338216	0.033	0.15363052	0.009676
East South Central	8	838	17944829	0.01	0.0594946	0.001447
Middle Atlantic	33	1406	40416441	0.023	0.13399737	0.006372
Mountain	25	668	21360990	0.037	0.0708206	0.004869
New England	19	597	14264185	0.032	0.04729173	0.002909
Pacific	54	1497	48735960	0.036	0.16158004	0.010878
South Atlantic	13	2072	57860260	0.006	0.19183091	0.003056
West North Central	24	700	18276008	0.034	0.06059259	0.003905
West South Central	10	895	34649697	0.011	0.1148782	0.003021

*MDRampC: Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline, amoxicillin-clavulanic acid, ceftiofur and decreased susceptibility to ceftriaxone (MIC \geq 2 μ g/L)

[†]Sum of entropy scores by region

[‡]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant}))$

Figure 2: Spatial Distribution by Census Division of Nalidixic acid Resistance in Non-Typhi *Salmonella*, 2003-2007
Entropy Score* = 0.0511

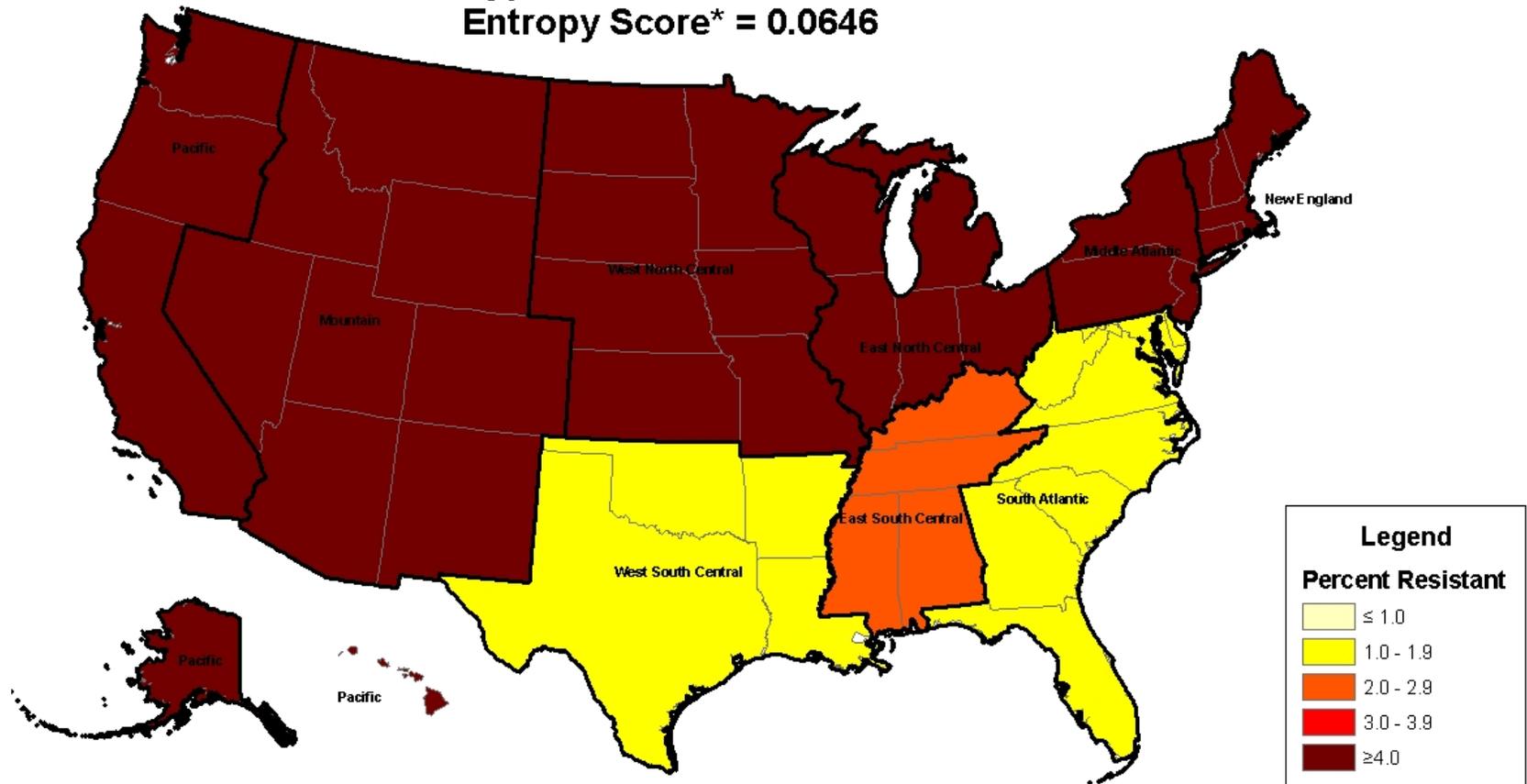


Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [†]
East North Central	30	1384	46338216	0.022	0.15363052	0.0071
East South Central	6	838	17944829	0.007	0.0594946	0.0011
Middle Atlantic	55	1406	40416441	0.039	0.13399737	0.0096
Mountain	20	668	21360990	0.03	0.0708206	0.0041
New England	24	597	14264185	0.04	0.04729173	0.0034
Pacific	41	1497	48735960	0.027	0.16158004	0.0087
South Atlantic	55	2072	57860260	0.027	0.19183091	0.0103
West North Central	24	700	18276008	0.034	0.06059259	0.0039
West South Central	9	895	34649697	0.01	0.1148782	0.0028

*Sum of entropy scores by region

[†]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant}))$

Figure 3: Spatial Distribution by Census Division of Ceftiofur Resistance in Non-Typhi *Salmonella*, 2003-2007
Entropy Score* = 0.0646

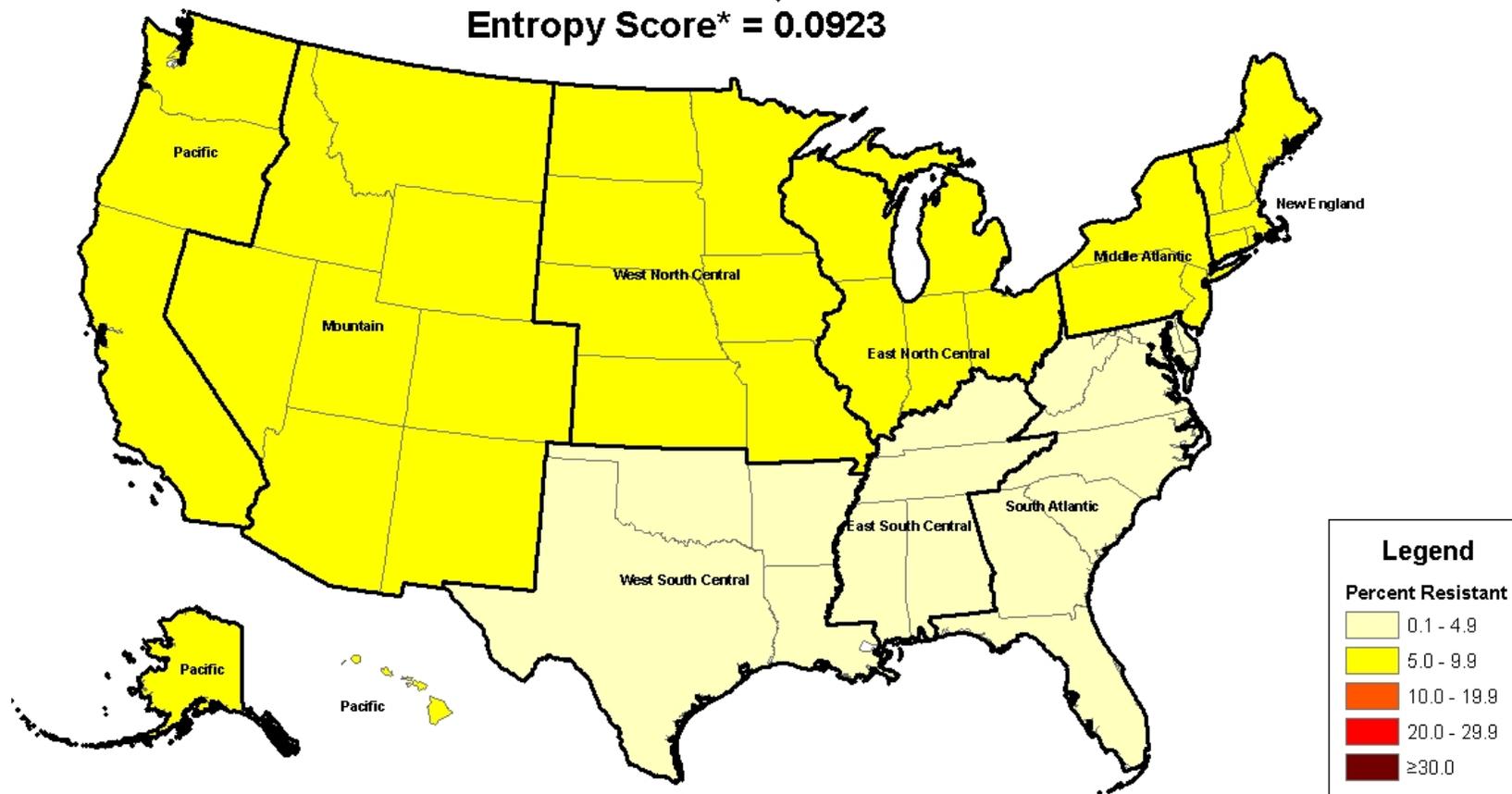


Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [†]
East North Central	60	1384	46338216	0.043	0.15363052	0.0118
East South Central	18	838	17944829	0.021	0.0594946	0.0026
Middle Atlantic	67	1406	40416441	0.048	0.13399737	0.0112
Mountain	30	668	21360990	0.045	0.0708206	0.0056
New England	28	597	14264185	0.047	0.04729173	0.0039
Pacific	70	1497	48735960	0.047	0.16158004	0.0133
South Atlantic	33	2072	57860260	0.016	0.19183091	0.0068
West North Central	31	700	18276008	0.044	0.06059259	0.0047
West South Central	16	895	34649697	0.018	0.1148782	0.0045

*Sum of entropy scores by region

[†]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$

Figure 4: Spatial Distribution by Census Division of Nalidixic acid Resistance in *Salmonella* Enteritidis, 2003-2007
Entropy Score* = 0.0923

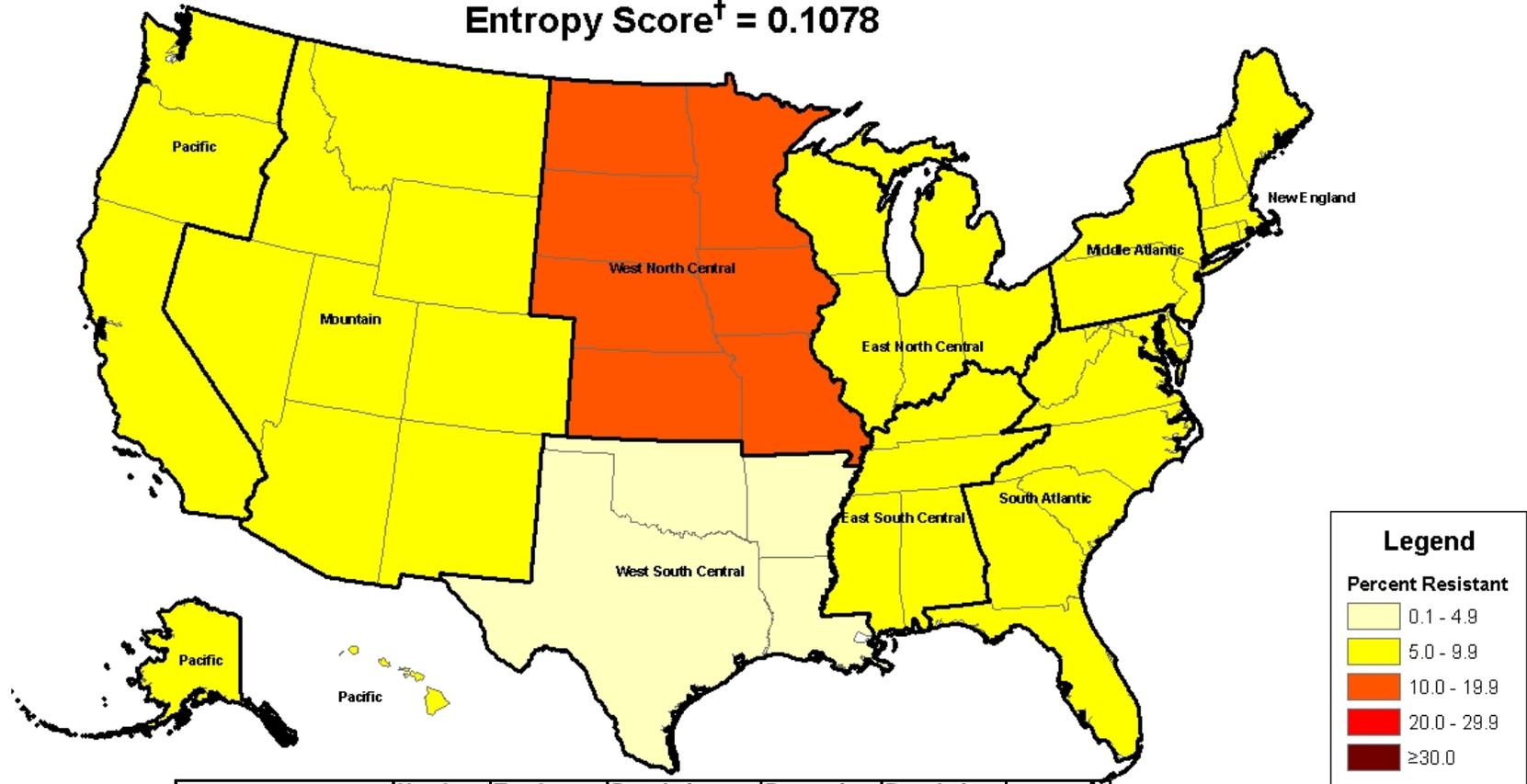


Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [†]
East North Central	14	270	46338216	0.052	0.15363052	0.013635
East South Central	3	72	17944829	0.042	0.0594946	0.004502
Middle Atlantic	18	358	40416441	0.05	0.13399737	0.011552
Mountain	6	67	21360990	0.09	0.0708206	0.009305
New England	11	142	14264185	0.077	0.04729173	0.005574
Pacific	20	278	48735960	0.072	0.16158004	0.01816
South Atlantic	15	342	57860260	0.044	0.19183091	0.015034
West North Central	10	107	18276008	0.093	0.06059259	0.008143
West South Central	2	72	34649697	0.028	0.1148782	0.006372

*Sum of entropy scores by region

[†]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$

Figure 5: Spatial Distribution by Census Division of ACSSuT* Resistance in Non-Typhi *Salmonella*, 2003-2007
Entropy Score[†] = 0.1078



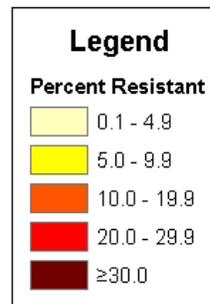
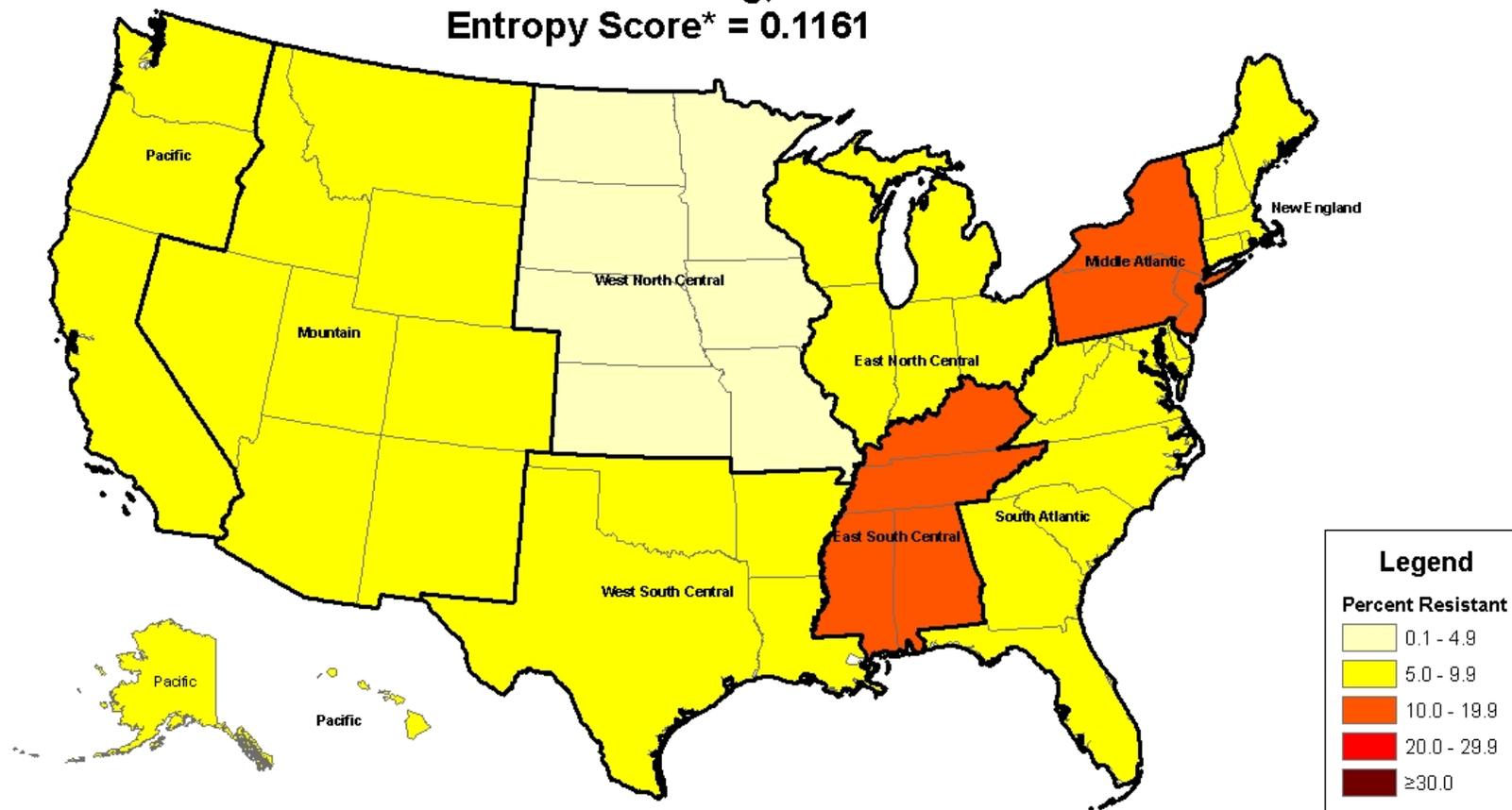
Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [‡]
East North Central	105	1384	46338216	0.076	0.15363052	0.017941
East South Central	42	838	17944829	0.05	0.0594946	0.005129
Middle Atlantic	90	1406	40416441	0.064	0.13399737	0.013841
Mountain	57	668	21360990	0.085	0.0708206	0.008945
New England	36	597	14264185	0.06	0.04729173	0.004662
Pacific	122	1497	48735960	0.081	0.16158004	0.019733
South Atlantic	143	2072	57860260	0.069	0.19183091	0.020915
West North Central	70	700	18276008	0.1	0.06059259	0.008555
West South Central	34	895	34649697	0.038	0.1148782	0.008059

*ACSSuT: Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline

[†]Sum of entropy scores by region

[‡]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$

Figure 6: Spatial Distribution by Census Division of Ceftiofur Resistance in *Salmonella* Heidelberg, 2003-2007
Entropy Score* = 0.1161

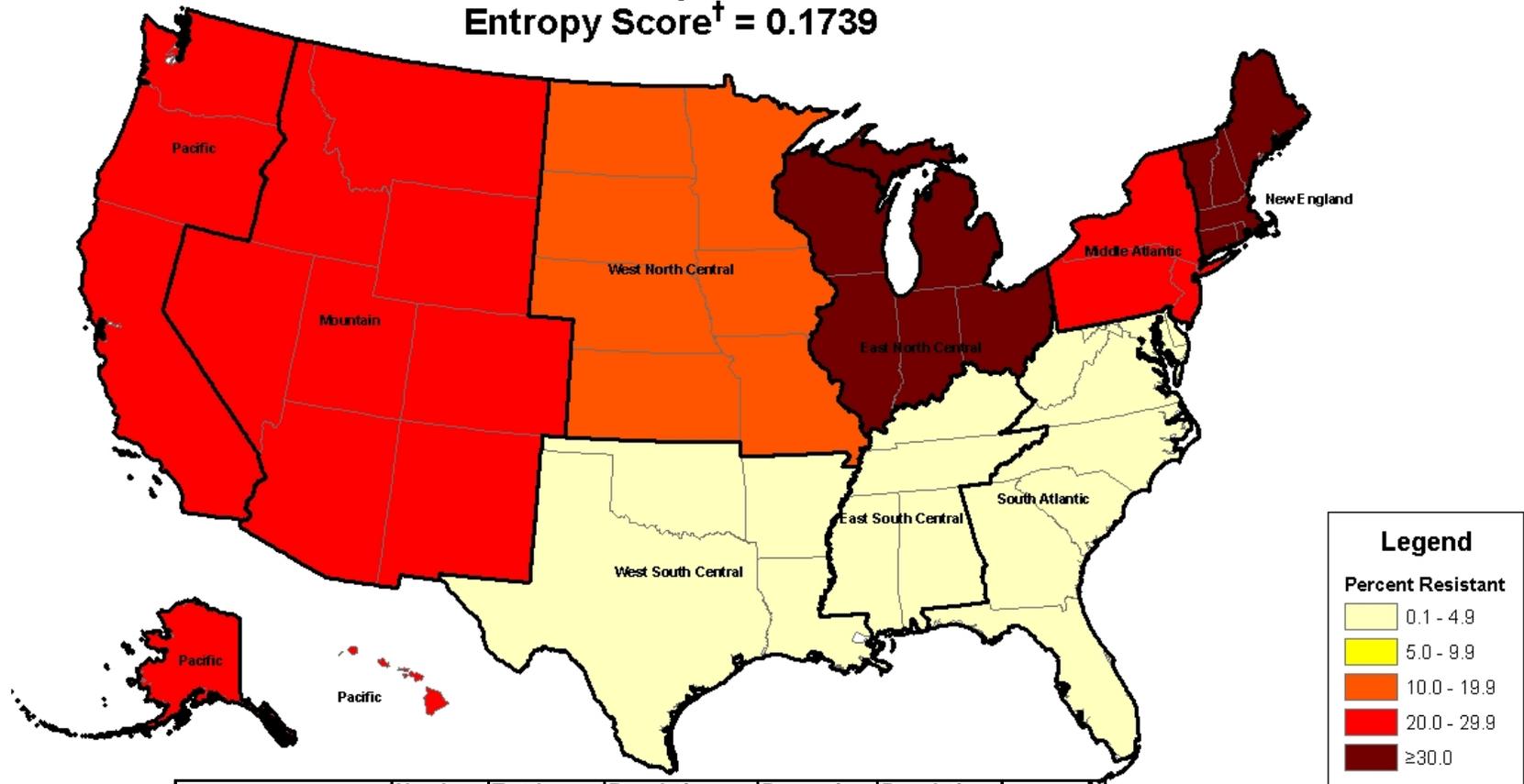


Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [†]
East North Central	6	76	46338216	0.079	0.15363052	0.018436
East South Central	5	36	17944829	0.139	0.0594946	0.010417
Middle Atlantic	13	99	40416441	0.131	0.13399737	0.022596
Mountain	2	39	21360990	0.051	0.0708206	0.006196
New England	2	32	14264185	0.062	0.04729173	0.004774
Pacific	7	107	48735960	0.065	0.16158004	0.016877
South Atlantic	4	62	57860260	0.065	0.19183091	0.020037
West North Central	1	37	18276008	0.027	0.06059259	0.003267
West South Central	2	26	34649697	0.077	0.1148782	0.013539

*Sum of entropy scores by region

[†]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$

Figure 7: Spatial Distribution by Census Division of MDRampC* Resistance in *Salmonella* Newport, 2003-2007
Entropy Score[†] = 0.1739



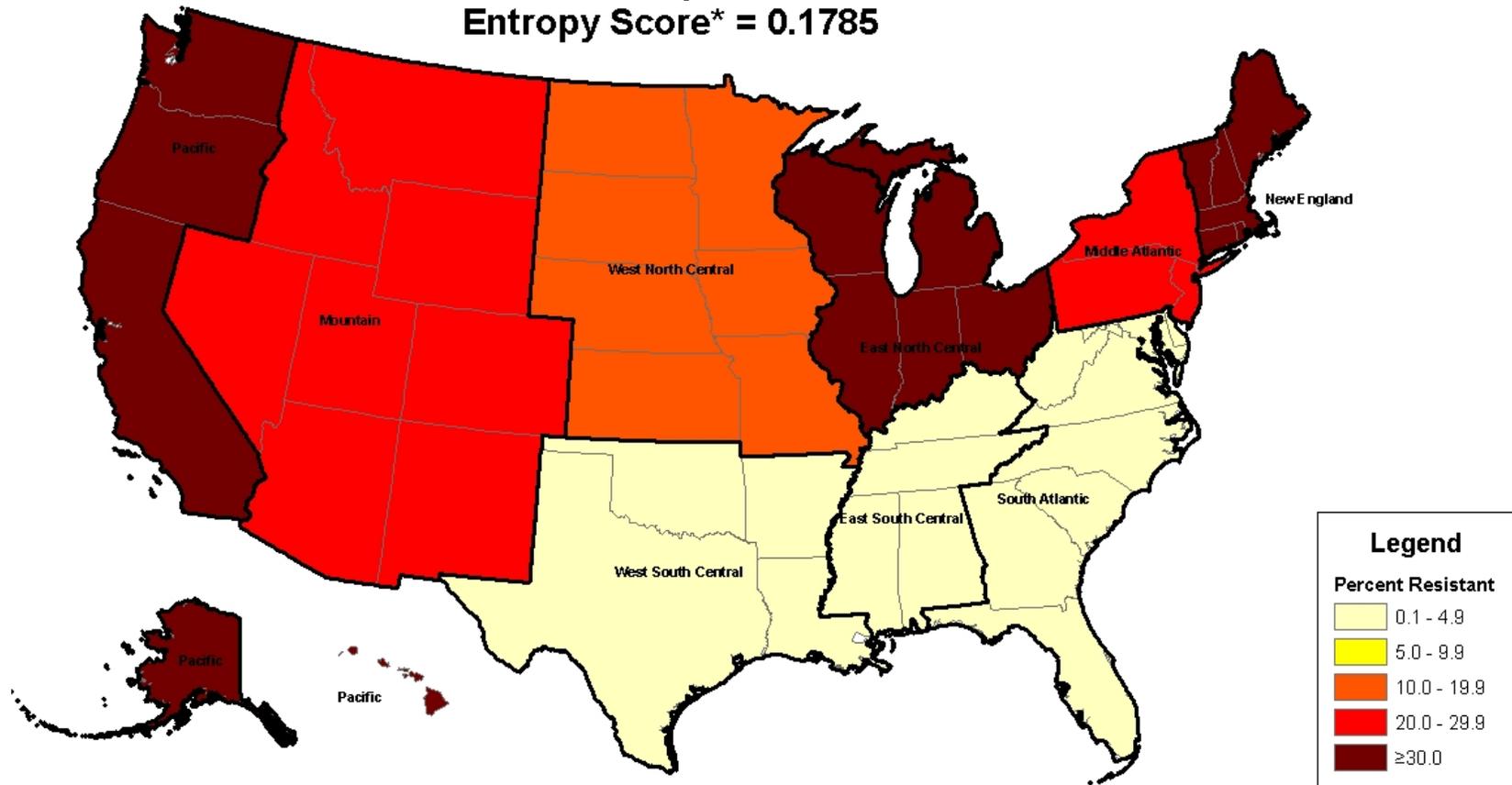
Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [‡]
East North Central	32	99	46338216	0.323	0.15363052	0.041975
East South Central	3	101	17944829	0.03	0.0594946	0.003481
Middle Atlantic	26	103	40416441	0.252	0.13399737	0.032852
Mountain	11	55	21360990	0.2	0.0708206	0.015391
New England	15	46	14264185	0.326	0.04729173	0.012966
Pacific	33	120	48735960	0.275	0.16158004	0.041274
South Atlantic	9	297	57860260	0.03	0.19183091	0.011226
West North Central	10	61	18276008	0.164	0.06059259	0.011743
West South Central	2	176	34649697	0.011	0.1148782	0.003021

*MDRampC: Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline, amoxicillin-clavulanic acid, ceftiofur and decreased susceptibility to ceftriaxone (MIC₂ ≥ 2 µg/L)

[†]Sum of entropy scores by region

[‡]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant}))$

Figure 8: Spatial Distribution by Census Division of Ceftiofur Resistance in *Salmonella* Newport, 2003-2007
Entropy Score* = 0.1785

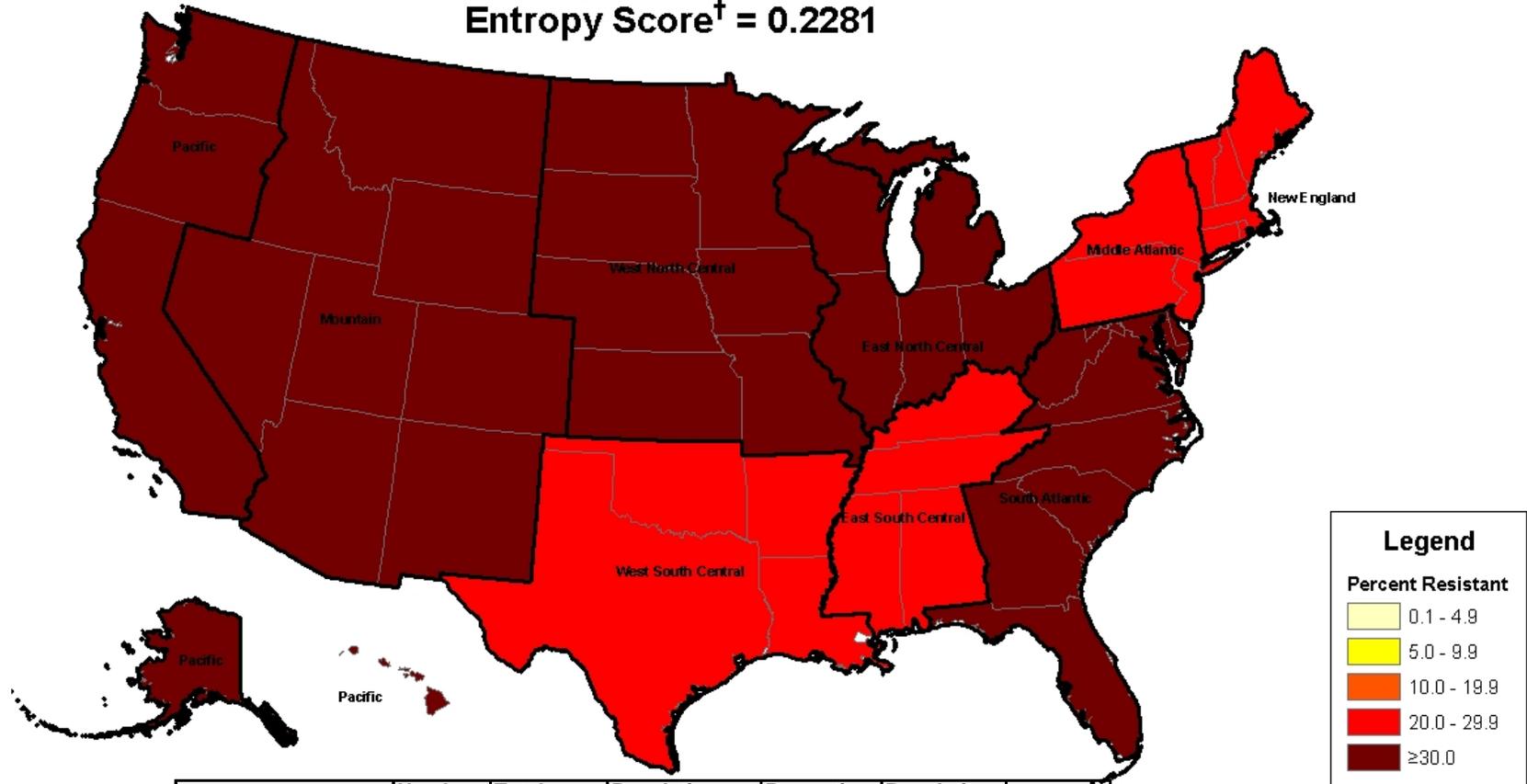


Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [†]
East North Central	32	99	46338216	0.323	0.15363052	0.041975
East South Central	3	101	17944829	0.03	0.0594946	0.003481
Middle Atlantic	26	103	40416441	0.252	0.13399737	0.032852
Mountain	12	55	21360990	0.218	0.0708206	0.016128
New England	16	46	14264185	0.348	0.04729173	0.013272
Pacific	36	120	48735960	0.3	0.16158004	0.042866
South Atlantic	11	297	57860260	0.037	0.19183091	0.013187
West North Central	10	61	18276008	0.164	0.06059259	0.011743
West South Central	2	176	34649697	0.011	0.1148782	0.003021

*Sum of entropy scores by region

[†]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant}))$

Figure 9: Spatial Distribution by Census Division of ACSSuT* Resistance in *Salmonella* Typhimurium, 2003-2007
Entropy Score[†] = 0.2281



Division	Number resistant	Total Submitted	Population Estimates	Proportion Resistant	Population Proportion	Entropy [‡]
East North Central	59	281	46338216	0.21	0.15363052	0.034292
East South Central	33	171	17944829	0.193	0.0594946	0.012675
Middle Atlantic	55	277	40416441	0.199	0.13399737	0.02904
Mountain	33	114	21360990	0.289	0.0708206	0.018493
New England	17	107	14264185	0.159	0.04729173	0.008996
Pacific	64	295	48735960	0.217	0.16158004	0.036707
South Atlantic	125	443	57860260	0.282	0.19183091	0.049556
West North Central	49	194	18276008	0.253	0.06059259	0.014884
West South Central	28	156	34649697	0.179	0.1148782	0.023442

*ACSSuT: Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline

[†]Sum of entropy scores by region

[‡]Entropy = $-(\text{PopulationProportion}) * ((\text{ProportionResistant} * \text{LOG}(\text{ProportionResistant}) + (1 - \text{ProportionResistant}) * \text{LOG}(1 - \text{ProportionResistant})))$

Key Findings/Conclusions

- Resistance in *Salmonella* Typhimurium is more widely distributed, entropy score = 0.2281.
- Ceftiofur resistance in *Salmonella* Newport follows a similar pattern to MDRampC.
- Ceftiofur resistance in *Salmonella* Heidelberg seems to be more widely distributed.
- Resistance rates in *Salmonella* Enteritidis are low, more data is needed to see if the distribution is regional.
- High rates of several resistance patterns in NTS were found in Western and Central states.
- A spatio-temporal view allows monitoring of trends across space and time to better understand the emergence and spread of resistance.

Acknowledgements

- 50 state and 3 local health departments and their public health laboratories
- U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention