Non-Typhi *Salmonella* Infections

- A leading cause of foodborne illness in the United States
  - Estimated to cause 1.4 million infections, 15,000 hospitalizations, and 400 deaths annually[1]

- Most infections are self-limited but antimicrobial agents are essential to treat serious illness[2]
  - Fluoroquinolones and third-generation cephalosporins are commonly used for antimicrobial treatment

Multidrug Resistance

- Multidrug resistance (MDR) has been associated with increased morbidity in non-Typhi *Salmonella*[12-14]
  - Infections due to *Salmonella* Typhimurium definitive type 104 (DT 104) with resistance to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline (ACSSuT) have been found to be more invasive than infections due to other *Salmonella* Typhimurium strains[12]

- MDR complicates management of severe infections by limiting options for antimicrobial therapy
  - Resistance to quinolones and third-generation cephalosporins is of particular concern

- Currently there is no standard definition for MDR in bacterial pathogens

- MDR may be reported by quantifying resistance to classes of antimicrobial agents (e.g., resistance to ≥3 classes)

Antimicrobial Susceptibility Testing

•Isolates were tested using broth microdilution (Sensititre) to determine minimum inhibitory concentrations (MICs) for the following eight classes of antimicrobial agents:

Aminoglycoside:
 Amikacin*
 Gentamicin
 Kanamycin
 Streptomycin
β-lactam/β-lactamase inhibitor combination:
 Amoxicillin-clavulanic acid
Cephem:
 1st gen. cephalosporin
  -Cephalothin*
 3rd gen. cephalosporin
  -Ceftiofur
  -Ceftriaxone
 Cephamycin
  -Cefoxitin*

Folate pathway inhibitor:
 Sulfonamide*
 Trimethoprim-sulfamethoxazole
Penicillin:
 Ampicillin
Phenicol:
 Chloramphenicol
Quinolone:
 Ciprofloxacin
 Nalidixic acid
Tetracycline:
 Tetracycline

*Not tested all years: amikacin (not tested in 1996), cefoxitin (not tested from 1996-1999), cephalothin (not tested since 2004), sulfamethoxazole, and sulfisoxazole (sulfisoxazole replaced sulfamethoxazole in 2004 to represent sulfonamides).
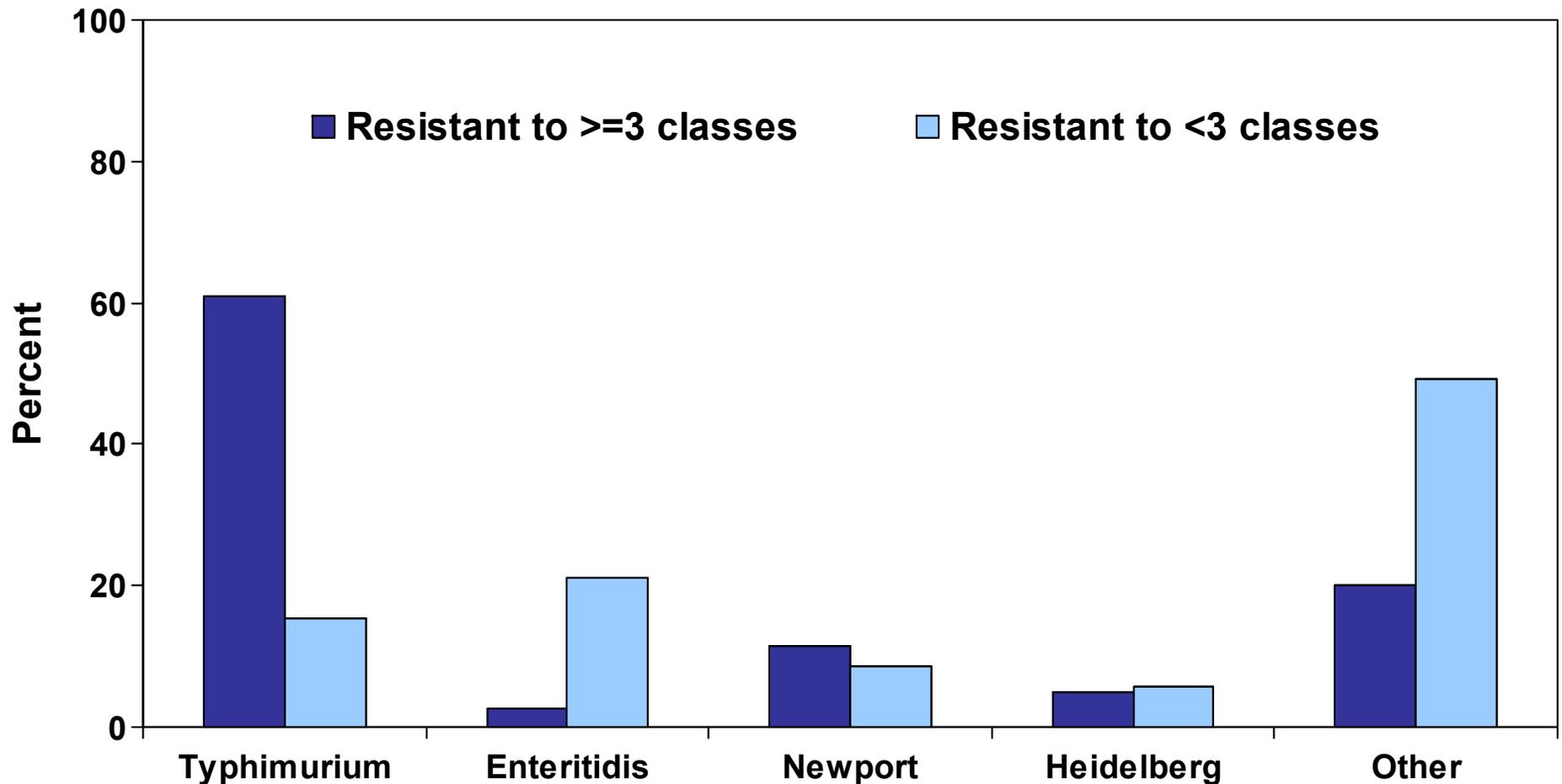
Percentage of resistance to ≥3 classes of antimicrobial agents in non-Typhi *Salmonella*, by year, 1996-2007*
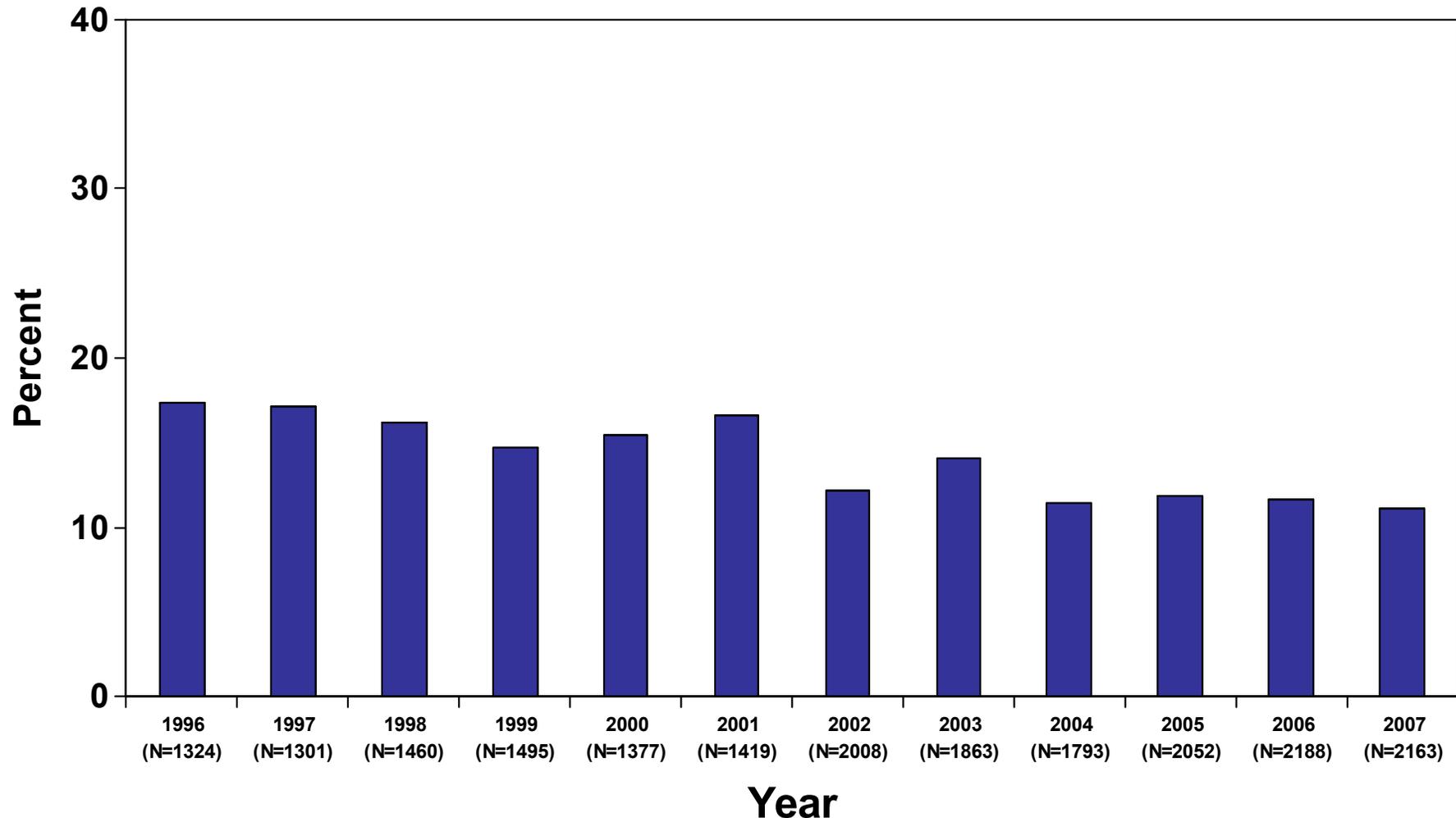
Resistance to ≥3 classes of agents in non-Typhi *Salmonella* declined from 17.4% in 1996 to 11.1% in 2007.

*Preliminary 2007 data

Percentage of serotypes Typhimurium, Enteritidis, Newport, and Heidelberg in non-Typhi *Salmonella*, by number of class resistance, 1996-2007*

Serotypes Typhimurium, Newport, Heidelberg, and Enteritidis were the four most common serotypes and accounted for 54.8% of all non-Typhi *Salmonella* isolates tested from 1996-2007. These four serotypes accounted for 80.0% of isolates resistant to ≥3 classes, a higher proportion compared with 50.8% of isolates resistant to <3 classes (p<0.01). Typhimurium was the most common serotype (21.7%) in all non-Typhi *Salmonella.* It accounted for 61.0% of isolates resistant to ≥3 classes, a higher proportion compared with 15.4% of isolates resistant to <3 classes (p<0.01).

*Preliminary 2007 data

Percentage of resistance to antimicrobial agents in non-Typhi *Salmonella*, by number of class resistance, 1996-2007*

Antimicrobial Class/Agent	Resistant to ≥3 classes N=2,813	Resistant to <3 classes N=17,630
Aminoglycoside		
Amikacin[†]	**0.1**	0.0
Gentamicin	**9.9**	1.0
Kanamycin	**23.6**	0.8
Streptomycin	**86.0**	3.2
β-lactam/β-lactamase inhibitor		
Amoxicillin-clavulanic acid	**23.5**	0.1
Cephem		
Cefoxitin (cephamycin)[†]	**27.1**	<0.1
Ceftiofur (third-gen. ceph.)	**20.7**	0.1
Ceftriaxone (third-gen. ceph.)	**1.5**	<0.1
Cephalothin (first-gen. ceph.)[†]	**21.6**	0.6
Folate pathway inhibitor		
Sulfonamide[†]	**90.8**	3.4
Trimethoprim-sulfamethoxazole	**10.9**	0.5
Penicillin		
Ampicillin	**87.2**	2.4
Phenicol		
Chloramphenicol	**64.0**	<0.1
Quinolone		
Ciprofloxacin	**0.7**	<0.1
Nalidixic acid	**4.6**	1.7
Tetracycline		
Tetracycline	**89.4**	5.3

*Preliminary 2007 data
[†]Amikacin, cefoxitin, and cephalothin were not tested all years; sulfamethoxazole or sulfisoxazole were tested for sulfonamides.

Percentage of ACT, ACSuT, and ACSSuT* in non-Typhi *Salmonella* resistant to ≥3 classes of agents and all non-Typhi *Salmonella*, 1996-2007†
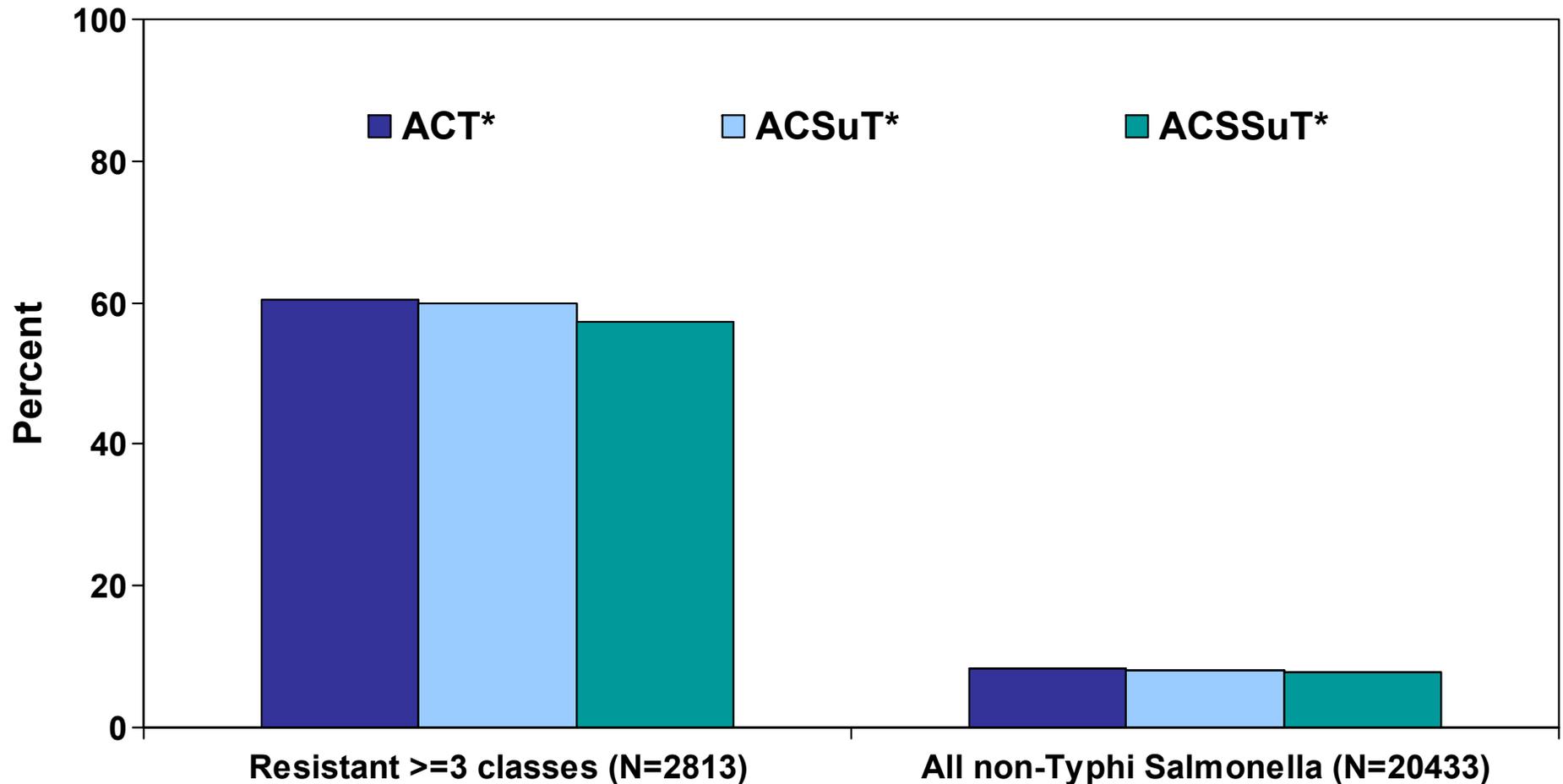
Of 2,813 non-Typhi *Salmonella* isolates resistant to ≥3 classes, 1,702 (60.5%) isolates were resistant to at least ACT, 1,685 (59.9%) to at least ACSuT, and 1,615 (57.4%) to at least ACSSuT. These resistance patterns ranged from 7.9% to 8.3% in all non-Typhi *Salmonella* isolates tested from 1996-2007

*ACSSuT (resistance to at least ampicillin [A], chloramphenicol [C], streptomycin [S], sulfonamide [Su] and tetracycline [T]) represents resistance to ≥5 classes; ACSuT represents resistance to ≥4 classes; ACT represents resistance to ≥3 classes
†Preliminary 2007 data

Resistance to Quinolones and Third-Generation Cephalosporins

- **Of 2,813 non-Typhi *Salmonella* isolates resistant to ≥3 classes, resistance to at least nalidixic acid and ceftiofur was detected in 24 (0.9%) isolates**
  - The 24 isolates resistant to at least nalidixic acid and ceftiofur accounted for all non-Typhi *Salmonella* isolates resistant to these two drugs
    - Additional MDR patterns
      - One (4.2%) of 24 isolates was also resistant to ciprofloxacin and ceftriaxone (0.04% of 2,813 isolates)
      - 14 (58.3%) of 24 isolates were also resistant to at least ampicillin, amoxicillin-clavulanic acid, chloramphenicol, streptomycin, sulfonamide, and tetracycline
    - Additional single drug resistance
      - Resistance to ampicillin (95.8%), amoxicillin-clavulanic acid (83.3%), sulfonamide (83.3%) cefoxitin (75.0%), chloramphenicol (75.0%), streptomycin (75%), tetracycline (70.8%), kanamycin (58.3%), trimethoprim-sulfamethoxazole (25.0%), gentamicin (20.8%), ciprofloxacin (16.7%), ceftriaxone (12.5%)

Key Findings/Conclusions

- From 1996-2007, resistance to ≥3 classes of antimicrobial agents has declined in non-Typhi *Salmonella.*

- *Salmonella* Typhimurium, which is the most common serotype in non-Typhi *Salmonella,* accounts for a higher proportion of isolates resistant to ≥3 classes than isolates resistant to <3 classes.

- ACSSuT, which represents resistance to at least five classes, is a major MDR pattern in non-Typhi *Salmonella* resistant to ≥3 classes.

- Isolates resistant to nalidixic acid and ceftiofur, drugs representative of two clinically important agents (i.e., ciprofloxacin and ceftriaxone), can be detected in non-Typhi *Salmonella* using resistance to ≥3 classes as a cut-off to measure important class resistance.

- These findings support the utility of using resistance to ≥3 classes as an indicator for infections with limited treatment options.

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