DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

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J Royce
Sapko

DEC 07 2007

NOV 20 2007

The Honorable John D. Dingell
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

Thank you for your letter expressing concerns about the proposed injectible use of cefquinome in cattle. Please excuse the delay of this response.

The Centers for Disease Control and Prevention (CDC) has long recognized antimicrobial resistance as an important public health problem. A key step toward mitigating this problem is the appropriate use of antimicrobial agents in humans and in animals.

We are collecting the records you requested pertaining to CDC's analysis of the use of third- or fourth-generation cephalosporins in food animals. Use of antimicrobial agents in food animals may create a selective pressure for antimicrobial resistance among bacteria (e.g., *Salmonella*) acquired from contaminated food. CDC conducts national surveillance for antimicrobial resistance among these bacteria from humans through the National Antimicrobial Resistance Monitoring System (NARMS). Because of the global nature of antimicrobial resistance and our food supply, CDC frequently consults public health officials and other researchers worldwide. Therefore, a review of our records also includes other scientists' statements on the use of these products in food animals. Shortly, we will provide the records you have requested under separate cover.

Please find enclosed the recommendations that CDC's Division of Foodborne, Bacterial, and Mycotic Diseases presented at the Food and Drug Administration's (FDA) Veterinary Medicine Advisory Committee Meeting on September 25, 2006, and the accompanying slide presentation from that meeting. The slide presentation is also available on FDA's website, which can be found online at www.fda.gov/cvm/VMAC/VMAC0906Pres.htm. You will see that we endorsed the evaluation through Guidance #152 that injectible use of cefquinome for the treatment of respiratory disease in cattle is associated with a "medium" risk of adverse human health consequences. We also cautioned that this risk estimation could increase should fourth-generation cephalosporin use in food animals be judged of critical importance in humans. We also recommended, to help ensure the long-term effectiveness of fourth-generation cephalosporins in humans, that off-label use of cefquinome in animals should be prohibited and that information on the quantity of cefquinome used in cattle should be made available on an ongoing basis.

Thank you for your interest in this important public health topic. I hope this information is helpful. I also will provide this response to Mr. Bart Stupak who cosigned your letter.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

Enclosure

Public Health Service
DEPARTMENT OF HEALTH & HUMAN SERVICES

Centers for Disease Control
And Prevention (CDC)

Recommendations for FDA's Veterinary Medicine Advisory Committee Meeting
September 25, 2006
Division of Foodborne, Bacterial, and Mycotic Diseases (proposed)
Coordinating Center for Infectious Diseases

Background

FDA's Veterinary Medicine Advisory Committee (VMAC) met on September 25, 2006, to discuss the microbial food safety of an antimicrobial drug application currently under review for use in food-producing animals in accordance with FDA/Center for Veterinary Medicine's "Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (Guidance #152). A company has proposed approving cefquinome injections for treating bovine respiratory disease. This is the first proposed use of a fourth generation cephalosporin in food animals in the United States.

CDC Recommendations

CDC provides the following recommendations to the Veterinary Advisory Medicine Committee:

- CDC applauds this application of Guidance #152 and supports the estimation that injectible use of cefquinome for the treatment of respiratory disease in cattle is associated with a "medium" risk of adverse human health consequences. This risk estimation may increase, however, should fourth generation cephalosporins be judged to be of increased clinical importance in humans.

- To ensure the long-term effectiveness of fourth generation cephalosporins in food animals and in humans, cefquinome use in food animals should be limited and controlled by adding fourth generation cephalosporins to the list of drugs prohibited from extra-label use in food animals.

- NARMS does not currently screen *Salmonella* strains isolated from ill persons for resistance to fourth generation cephalosporins. NARMS screening should be expanded to conduct this additional testing. In addition, should resistance to fourth generation cephalosporin be detected in human *Salmonella* strains, the resistance mechanism should be fully characterized. Current resources, however, only allow for continuation of existing NARMS activities.

- To more precisely direct efforts to mitigate emerging resistance to cefquinome should it occur, information on the quantity of cefquinome used in cattle should be made available on an ongoing basis, in a format suitable for public health surveillance purposes.

CDC Data and Perspectives

VMAC, September 25, 2006

Patricia M. Griffin MD
Chief, Enteric Diseases Epidemiology Branch
Division of Foodborne, Bacterial and Mycotic Diseases
National Center for Zoonotic, Vectorborne, and Enteric Diseases
(title is "acting," all organizations "proposed" due to CDC reorganization)

National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS)
Objectives

- Monitor antimicrobial resistance among enteric bacteria from humans, foods, and animals
  - Conduct surveillance in all 50 states
- Focus intervention efforts to decrease the emergence and dissemination of antimicrobial resistance
- Provide a platform for studies
    - Field investigations
    - Studies of resistant mechanisms

Human isolate sampling in CDC NARMS

- Bacteria are isolated in clinical labs and sent to state health department labs for characterization
- Isolates sent to CDC
  - Every 20th *Salmonella*, *Shigella*, and *E. coli* O157
  - All *Salmonella* Typhi, *Listeria*, and *Vibrio*
  - Representative sample of *Campylobacter* from 10 FoodNet sites

What has surveillance shown?

- Increase in muliti-drug resistant (MDR) *Salmonella*
  - e.g., *Salmonella* Typhimurium DT104 and *Salmonella* Newport
  - Spread of genetic material (plasmids containing genes coding for resistance) to multiple serotypes
- Emergence of resistance to antimicrobial agents important in human medicine
  - Third generation cephalosporins – *Salmonella, E coli*
  - Fluoroquinolones – *Campylobacter, Shigella, Salmonella* including Typhi

Salmonella

- A leading cause of foodborne illness in U.S.
  - Estimates: 1.4 million infections, 16,000 hospitalizations, and nearly 600 deaths each year (Mead et al, EID 1999)
  - Accounted for ~13% of foodborne disease outbreaks reported to CDC from 1993-1997 (Olsen et al, MMWR 2000)
- Most infections are self-limited but antibiotics are essential for some serious infections
- Quinolones (e.g., ciprofloxacin) and 3rd generation cephalosporins (e.g., ceftriaxone) are commonly used for treatment of severe salmonellosis
- 3rd generation cephalosporins are the primary treatment for severe illness in children

Resistant *Salmonella* cause more severe infections than susceptible *Salmonella*

- Resistant *Salmonella* strains cause
  - Increased risk of invasive illness and death (Helms et al, JID 2004)
  - Increased risk of bloodstream infection and hospitalization (Varma et al, JID 2005)
  - Increased rate of hospitalization (Varma et al, EID 2005)

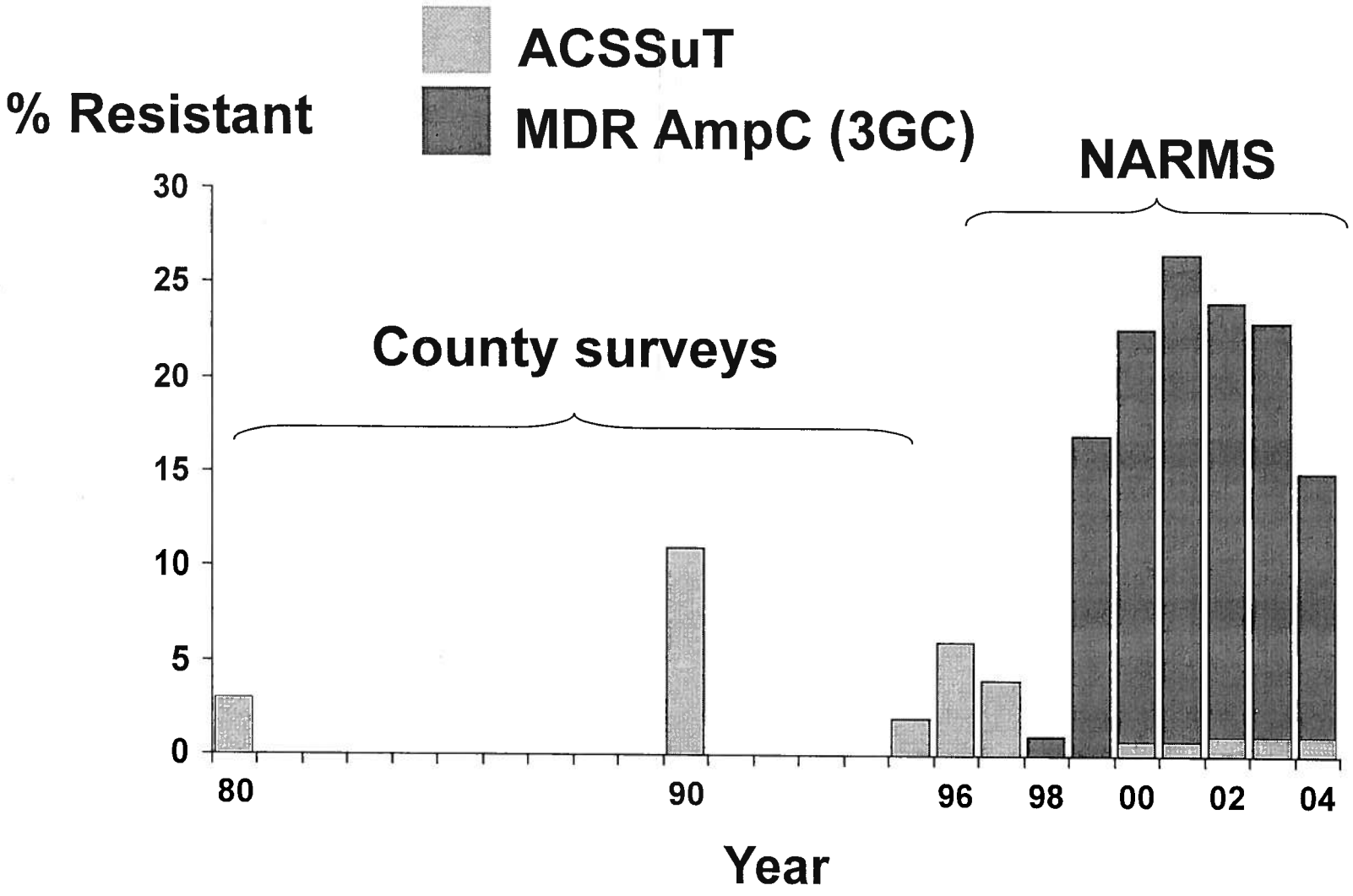
3rd generation cephalosporin (3GC) resistance in *Salmonella*

- 3GC resistance is most commonly caused by a plasmid carrying resistance genes
- Definition of "MDR AmpC resistance": resistant
  - to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline (ACSSuT),
  - *and to* ***3GC*** and amoxicillin-clavulanic acid
- 1998-2001 – 5-fold increase in the proportion of *Salmonella* resistant to 3GC (primarily due to emergence of MDR AmpC *S.* Newport)

Where is 3rd generation cephalosporin (3GC) resistance coming from?

- *Salmonella* with MDR AmpC resistance carry a plasmid with genes coding for the CMY-2 enzyme
  - CMY-2 enzyme mediates resistance to 3GC
- Plasmids that carry genes for the CMY-2 enzymes are spreading to other *Salmonella* serotypes and other bacteria, e.g., *E coli*
- Spread of plasmids may be related to antibiotic pressure from
  - Use of 3GCs
    - Particularly ceftiofur, the only 3GC used in food animals
  - Use of other drugs
    - e.g., giving tetracyline to an animal or person carrying a "MDR AmpC"-resistant *Salmonella* will select for survival of strains that are resistant to both tetracycline and 3GC

Proportion of *Salmonella* Newport resistant to at least ACSSuT



Sporadic *Salmonella* Newport MDR AmpC infections, Massachusetts

- Nov 2000: MA State lab noted 4 *Salmonella* Newport MDR AmpC isolates
  - 2 from ill dairy cows
  - 2 from ill persons --- one was a child who attended a daycare center on a dairy farm

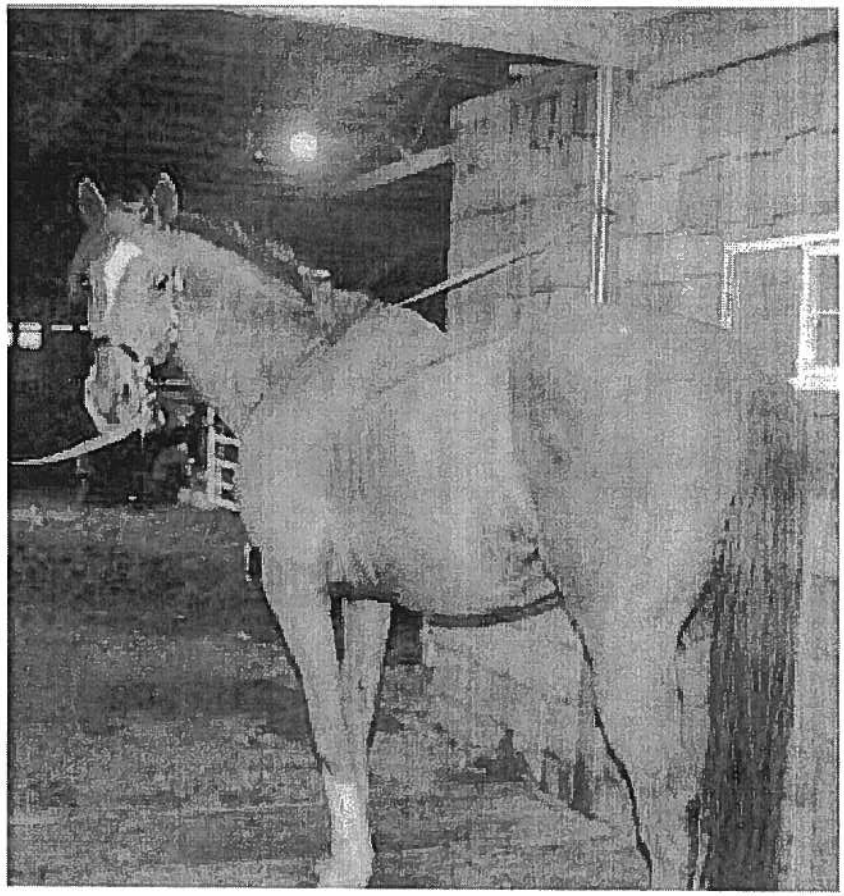
- Risk factors for human illness include contact with cattle and consumption of bovine products (e.g., ground beef, unpasteurized cheese)

Review of cattle isolates, Massachusetts and Vermont 2000-2001

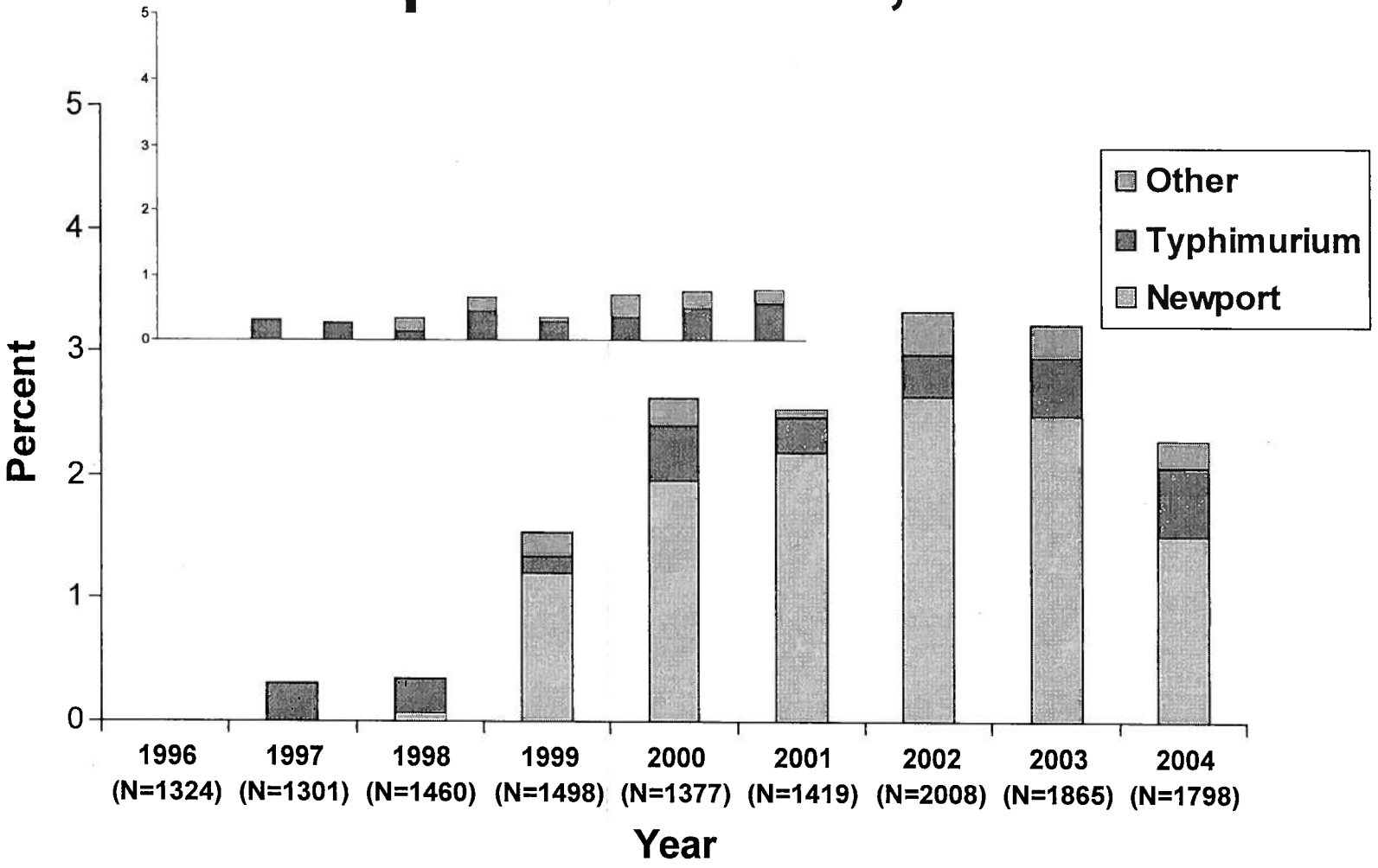
- Detected *S.* Newport MDR AmpC in stools of ill and well dairy cattle
  - Dairy farms with *S.* Newport MDR AmpC often had illness and deaths in cows
  - On one farm, ill persons and milking cows had same strain
- Many cow strains had same PFGE pattern as human strains

Salmonella Newport MDR AmpC in horses

- 2004: *Salmonella* outbreak at New Bolton Center Veterinary Hospital in Pennsylvania
- Cause was *Salmonella* Newport MDR AmpC
- High mortality, closed hospital for 3 months

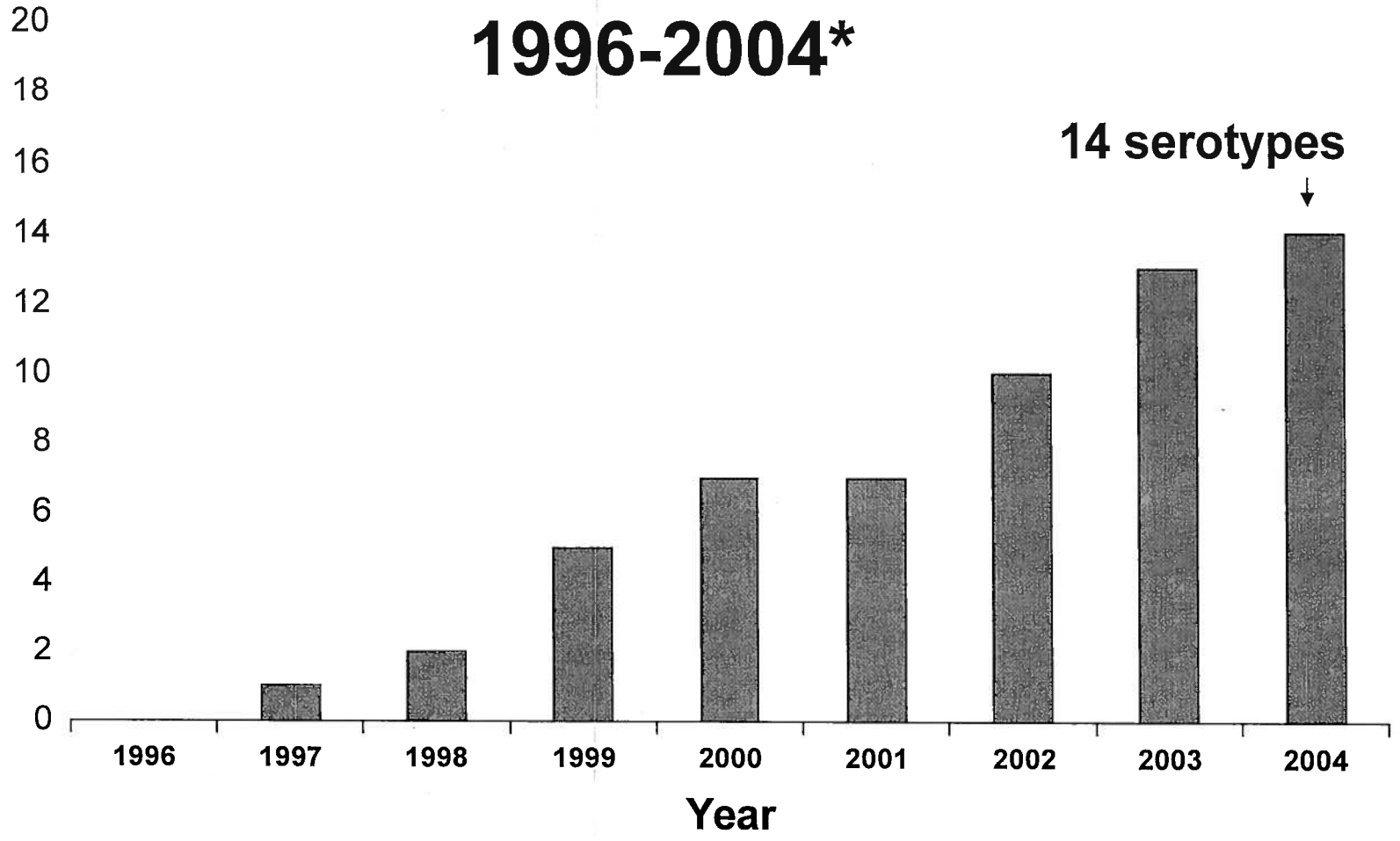


Percentage of all *Salmonella* with MDR-AmpC resistance, 1996-2004*



* 2004 data preliminary, all date excludes *Salmonella* Typhi

Cumulative number of *Salmonella* serotypes with MDR-AmpC resistance, 1996-2004*



* 2004 data preliminary, all date excludes *Salmonella* Typhi

MDR-AmpC resistance jumped to *E. coli* O157:H7

- 2000-2001: 6 *E coli* O157:H7 strains isolated from humans in have the MDR-AmpC plasmid

Fourth generation cephalosporins (4GC) and non-human use

- In February 2005, WHO convened panel of experts to determine critically important antibacterial agents for human medicine for risk management strategies of non-human use
- 4GC were ranked as critically important

4GC are widely used in food animals in Europe

- 4GC are the most common extended spectrum cephalosporin used in Europe
- Very little ceftiofur (3GC) used in Europe
- 4GC resistance has developed in *Salmonella* in Europe
  - resistance is due to the CTX-M gene carried on its own plasmid
  - (resistance not due to cmy-2 gene, present in U.S.)

3GC and 4GC

3GC (ceftiofur) used in food animals in U.S.

Resistance mediated by CMY-2 enzymes encoded on a plasmid

4GC used in food animals in Europe

Resistance mediated by CTX-M enzymes encoded on a plasmid

Resistance will develop to 4GC, how and where?

- Possibilities
  - genes encoding the CMY-2 enzyme in MDR Amp-C *Salmonella* strains may mutate to confer resistance to 4GC
    - this has been done *in vitro*
  - as in Europe, we may find *Salmonella* strains with plasmids carrying the genes for the CTX-M enzyme
- To understand and control emergence, we need to know where and how 4GC are used in food animals

Guidance #152

- CDC strongly supports the continued use of FDA's Guidance #152

- CDC agrees with the sponsor's "medium" risk estimation based on current guidelines
  - risk estimation could increase should 4GC be judged of critical importance in humans

CDC Recommendations

- CDC recommends extra-label prohibition of cefquinome use in food animals
  - Off-label use could lead to emergence and dissemination of resistance from unknown uses

CDC Recommendations (cont.)

- Surveillance is needed to monitor for the emergence and dissemination of 4GC resistance
  - CDC NARMS does not currently screen human *Salmonella* strains for 4GC resistance
    - CDC could add testing plates to monitor for resistance to 4GC
      - Current resources, however, only allow for continuation of existing NARMS activities

CDC Recommendations (cont.)

- Information on quantity of 4GC used, by animal type, should be available on an ongoing basis, in a format suitable for public health surveillance purposes
  - including off-label use

Thank you