



November 15, 2019

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RE: Fluoroquinolone Resistant *Salmonella*

Dear Dr. Redfield, Dr. Solomon, and Mr. Shea,

The undersigned member and colleague organizations of Keep Antibiotics Working write to express our concerns about the ongoing rise in human *Salmonella* infections resistant to fluoroquinolones and related recent outbreaks caused by fluoroquinolone resistant *Salmonella*. Given that fluoroquinolones are one of just three antibiotics recommended by the Centers for Disease Control and Prevention (CDC) to treat serious *Salmonella* infections, these outbreaks and the overall increase in resistant human isolates are troubling. Resistance to one of the two alternatives to ciprofloxacin, ampicillin, is already high; therefore, increases in fluoroquinolone resistance will mean in many cases that the third mainline treatment ceftriaxone will be the only option.

We would like to know how CDC, the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) are responding to this rise in resistance and to the resistant outbreaks. Specifically, we request information on what efforts have been made to identify the causes of the rise in resistance and what steps have been taken to identify the sources of these outbreaks. More importantly, we would like to understand what specific actions federal agencies are taking to stop further outbreaks and to change the direction of the upward trend in resistance. We strongly urge CDC, FDA and USDA to work together to ensure that people and animals are not further harmed by the spread of ciprofloxacin resistance in agricultural settings.

Fluoroquinolones (e.g. ciprofloxacin) are considered to be critically important by both the FDA¹ and the World Health Organization (WHO)² because of their importance in treating serious human infections and their role in treating infections like *Salmonella* that are likely to be spread to people from animals through food. CDC's "*Salmonella*: [Information for Healthcare Professionals and Laboratories](#)" webpage states that the recommended treatments for serious *Salmonella* infections are fluoroquinolones, third-generation cephalosporins, and ampicillin. Because of the well-recognized risk that the use of fluoroquinolones in food-producing animals can lead to resistant food-borne infections in people, the FDA prohibits the extra-label use of this class of antibiotics³ and in 2005 prohibited the use of this class in poultry.⁴

Until recently, these efforts have helped to keep resistance to fluoroquinolones in *Salmonella* isolates from U.S. animals and retail meat very low. The most recent National Antimicrobial Resistance Monitoring System (NARMS) report states that "ciprofloxacin resistance is uncommon in *Salmonella* isolates from all nonhuman sources".⁵ In fact, according to FDA, the percentage of *Salmonella* isolates with decreased susceptibility to ciprofloxacin (DSC) has remained below 10% since 1996. When looking at the NARMS integrated [data](#), we see very few ciprofloxacin resistant isolates detected in chicken or turkey (no more than 2% since 2004). This is in contrast to countries without these restrictions where fluoroquinolone resistance or reduced susceptibility to fluoroquinolones in animals and food is much higher. In parts of China, Korea, Thailand, Europe, and Brazil meats such as pork, chicken, and turkey have shown rates of fluoroquinolone resistance ranging from 16%-100% depending on the specific fluoroquinolone antibiotic and sample.⁶

¹ FDA. "CVM GFI #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." *FDA website*, October 23, 2003. <https://www.fda.gov/media/69949/download>.

² WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, and World Health Organization. "Critically important antimicrobials for human medicine, 6th revision." (2019). Licence: CC BY-NC-SA 3.0 IGO.

³ FDA. "The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians." *FDA website*, August 15, 2019. <http://www.fda.gov/animal-veterinary/resources-you/ins-and-outs-extra-label-drug-use-animals-resource-veterinarians>.

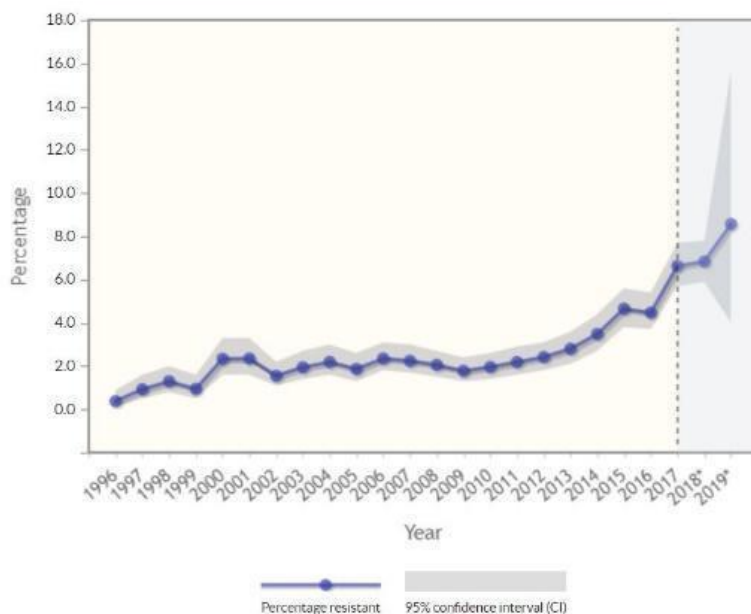
⁴ FDA. "Enrofloxacin for Poultry; Final Decision on Withdrawal of New Animal Drug Application Following Formal Evidentiary Public Hearing; Availability" *Federal Register*, August 1, 2005. <https://www.govinfo.gov/content/pkg/FR-2005-08-01/html/05-15224.htm>.

⁵ FDA. "The National Antimicrobial Resistance Monitoring System: NARMS Integrated Report, 2015" *FDA website*, 2017. <http://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2015-narms-integrated-report>.

⁶ Kim, M.-S. et al. "Prevalence and Antimicrobial Resistance of *Salmonella* Species Isolated from Chicken Meats Produced by Different Integrated Broiler Operations in Korea." *Poultry Science* 91, no. 9 (September 1, 2012): 2370–75. <https://doi.org/10.3382/ps.2012-02357>; Zhang, Lina et al. "Highly Prevalent Multidrug-Resistant *Salmonella* From Chicken and Pork Meat at Retail Markets in Guangdong, China." *Frontiers in Microbiology* 9 (September 10, 2018). <https://doi.org/10.3389/fmicb.2018.02104>; Jiang, Zenghai et al. "Antibiotic Resistance Profiles of *Salmonella* Recovered From Finishing Pigs and Slaughter Facilities in Henan, China." *Frontiers in Microbiology* 10 (2019). <https://doi.org/10.3389/fmicb.2019.01513>; Lertworapreecha, Monthon et al. "Antimicrobial Resistance in *Salmonella* Enterica Isolated From Pork, Chicken, and Vegetables in Southern Thailand," 2012. <https://doi.org/10.5812/jjm.4312>; EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control). "The European Union Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2016." *EFSA*

While reported rates of fluoroquinolone resistance to *Salmonella* in food animals and food have remained low through 2015, resistance in *Salmonella* isolates from sick people has trended upward for over two decades.⁷ Since 1996 resistance has steadily risen from 0.4% in 1996 to 5.8% in 2015. The trend in resistance to the quinolone nalidixic acid is very clear as well. As far back as 2006, experts from CDC published a paper identifying increased resistance to nalidixic acid in non-typhoidal *Salmonella* causing illness in humans.⁸ Since then resistance has continued to climb.

Nalidixic Acid Resistance in Human Non-Typhoidal *Salmonella*, CDC NARMS NOW



Salmonella isolates resistant to ciprofloxacin have been associated with recent outbreaks related to backyard poultry⁹, imported pig ear dog treats¹⁰, and most recently soft cheese and beef¹¹.

Backyard Poultry: Over 1000 people, 275 hospitalizations, and two deaths have been linked to this most recent outbreak. Among isolates associated with the outbreak, resistance or decreased susceptibility has been detected to all three CDC recommended *Salmonella* treatments including fluoroquinolones along with numerous other antibiotics. The CDC investigation notice states,

Journal 16, no. 2 (2018): e05182. <https://doi.org/10.2903/j.efsa.2018.5182>; Banger, Sohan Rodney et al. “Poultry: A Receptacle for Non-Typhoidal Salmonellae and Antimicrobial Resistance.” *Iranian Journal of Microbiology* 11, no. 1 (February 2019): 31–38; Pribul, Bruno R. et al. “Characteristics of Quinolone Resistance in *Salmonella* Spp. Isolates from the Food Chain in Brazil.” *Frontiers in Microbiology* 8 (March 14, 2017). <https://doi.org/10.3389/fmicb.2017.00299>.

⁷ CDC. “NARMS Now.” *CDC website* (2019). <https://wwwn.cdc.gov/narmsnow/>.

⁸ Stevenson, Jennifer E. et al. “Increase in Nalidixic Acid Resistance among Non-Typhi *Salmonella* Enterica Isolates in the United States from 1996 to 2003.” *Antimicrobial Agents and Chemotherapy* 51, no. 1 (January 1, 2007): 195–97. <https://doi.org/10.1128/AAC.00222-06>.

⁹ CDC. “Outbreaks of *Salmonella* Infections Linked to Backyard Poultry | Outbreak of *Salmonella* Infections Linked to Backyard Poultry | May 2019 | *Salmonella* | CDC,” October 22, 2019. <https://www.cdc.gov/salmonella/backyardpoultry-05-19/index.html>.

¹⁰ CDC. “Outbreak of Multidrug-Resistant *Salmonella* Infections Linked to Contact with Pig Ear Pet Treats | Outbreak of *Salmonella* Infections Linked to Pet Treats | July 2019 | *Salmonella* | CDC,” October 30, 2019. <https://www.cdc.gov/salmonella/pet-treats-07-19/index.html>.

¹¹ Plumb, Ian D. “Outbreak of *Salmonella* Newport Infections with Decreased Susceptibility to Azithromycin Linked to Beef Obtained in the United States and Soft Cheese Obtained in Mexico — United States, 2018–2019.” *MMWR. Morbidity and Mortality Weekly Report* 68 (2019). <https://doi.org/10.15585/mmwr.mm6833a1>.

“contact with backyard poultry, such as chicks and ducklings, from multiple hatcheries are the likely source of these outbreaks.” Given the low levels of ciprofloxacin resistance in poultry isolates and the prohibition on the use of this class of drugs in poultry, the detection of ciprofloxacin resistance among these isolates is concerning. This outbreak raises the following questions:

- a) Have CDC, USDA, or FDA identified the hatcheries associated with this outbreak? If not, what steps have been taken and what is keeping the source hatcheries from being identified?
- b) Given the additional risk associated with fluoroquinolone resistance, have the federal agencies identified specific hatcheries related to these resistant isolates and if so has there been an attempt to determine factors such as illegal antibiotic use that may contribute to the resistance?
- c) What authorities do federal agencies have to identify which hatcheries are the source of these outbreaks?
- d) What authorities do federal agencies have to require suppliers of backyard poultry to take steps to reduce the spread of resistant pathogens from their facilities and stop marketing products that consistently lead to human illness?

Pig ears: 143 people have been made ill and 33 hospitalized due to this outbreak linked to imported pig ear dog treats. Like the backyard poultry outbreak, isolates in this outbreak have been found to have decreased susceptibility or resistance to all three of the recommended treatments for *Salmonella* including fluoroquinolones as well as resistance to many other antibiotics. FDA has determined that some of the pig ears were imported from Brazil, Argentina, and Columbia. Reduced fluoroquinolone susceptibility in isolates from pork products from these countries is not unexpected since high levels of fluoroquinolone resistance or reduced susceptibility to fluoroquinolones, as indicated by nalidixic acid resistance, has been detected in *Salmonella* isolates from pigs or pork products in all three countries (Argentina 72.2% nalidixic acid, Brazil 50% ciprofloxacin resistant, Columbia 36% nalidixic acid resistance).¹² On August 22, 2019 FDA updated an existing import alert (Alert 72-03) on pig ears to include suppliers in the three identified countries that have been linked to the existing outbreak.¹³ While we appreciate the strengthened import alert, recalls, and recommendations against using and selling the product, we are concerned that this outbreak indicates a failure in the federal agency response to antibiotic resistance. We would like to know the following:

- a) What are FDA and USDA doing to ensure that imported animal feeds and feed ingredients including pet treats are not introducing resistant pathogens into U.S. animal populations and the food supply?

¹² Viana, Cibeli et al. “Distribution, Diversity, Virulence Genotypes and Antibiotic Resistance for *Salmonella* Isolated from a Brazilian Pork Production Chain.” *International Journal of Food Microbiology* 310 (November 16, 2019): 108310. <https://doi.org/10.1016/j.ijfoodmicro.2019.108310>; Rondón-Barragán, Iang S. et al. “Characterization of *Salmonella* Species from Pork Meat in Tolima, Colombia.” *Revista Colombiana de Ciencias Pecuarias* 28, no. 1 (March 2015): 74–82; Colello, Rocío et al. “Detection and Characterization of *Salmonella* Serotypes in the Production Chain of Two Pig Farms in Buenos Aires Province, Argentina.” *Frontiers in Microbiology* 9 (June 28, 2018). <https://doi.org/10.3389/fmicb.2018.01370>.

¹³ FDA. “FDA Investigates Contaminated Pig Ear Pet Treats Connected to Human *Salmonella* Infections.” *FDA website*, October 30, 2019. <http://www.fda.gov/animal-veterinary/news-events/fda-investigates-contaminated-pig-ear-pet-treats-connected-human-salmonella-infections>.

- b) The high levels of reduced susceptibility to fluoroquinolones in *Salmonella* isolates from pork from the identified countries compared to U.S. pork indicates a failure in the food safety system of those countries. Do USDA and FDA monitor resistance levels globally to identify countries that have high levels of resistance to clinically significant antibiotics and use this information in their monitoring of imported food and feed?
- c) Transferable colistin resistance has been detected in *Salmonella* isolates from animal products in Brazil.¹⁴ Were isolates from this outbreak tested for colistin resistance?
- d) While some pig treats have been recalled and FDA recommends not feeding or selling these products, FDA has not prohibited their sale or import. Why not? Does FDA have the authority to prohibit the sale of these altogether?
- e) What authority does USDA have with respect to animal feed and feed ingredients that may make animals sick or introduce new resistance determinants that may make it more difficult to treat sick animals?
- f) How can the US government work with international bodies such as the Food and Agriculture Organization of the United Nations (FAO) and Codex Alimentarius to reduce the risk of animal and human disease caused by trade in food and feed?

Imported soft cheese and domestically slaughtered beef: 255 people have been made ill and 60 were hospitalized due to this outbreak related to soft cheese imported from Mexico and domestically slaughtered beef. CDC has emphasized that the *Salmonella* Newport strain causing the outbreak shows reduced susceptibility to the macrolide azithromycin, but also notes that many of the isolates are resistant to ampicillin and non-susceptible to fluoroquinolones. Unlike azithromycin, the last two are recommended by CDC as first-line treatments for serious *Salmonella* infections in humans. CDC also notes that the spread of reduced susceptibility to azithromycin may be linked to a 41% increase in sales of macrolides for use in beef between 2016 and 2017. FDA does not break out sales of fluoroquinolone for use in cattle from the overall sales data, but FDA does report that sales of fluoroquinolones for use in food-producing animals increased by 24% between 2016 and 2017. Fluoroquinolones can only legally be used in the U.S. in cattle and swine. Like for azithromycin resistance, fluoroquinolone resistance in this outbreak may be linked to increased use of fluoroquinolones in cattle.

Salmonella isolates from Mexican cattle have high levels of reduced susceptibility to fluoroquinolones as indicated by nalidixic acid resistance (79.2%)¹⁵ compared to isolates from cattle in the U.S. (less than 4%). The questions related to this outbreak are similar to those for the other two.

- a) Have federal agencies attempted to identify the farms from which the outbreak strain originated or identified other farms where the strain is present? If so, have federal agencies worked with the farms to reduce or eliminate the threat?
- b) Have federal agencies attempted to identify whether the movement of cattle between the U.S. and Mexico played a role in this outbreak?

¹⁴ Renata B. et al. “*Salmonella* enterica mcr-1 Positive from Food in Brazil: Detection and Characterization.” *Foodborne Pathogens and Disease* (September 2019). <https://doi.org/10.1089/fpd.2019>.

¹⁵Zaidi, Mussaret B. et al. “Integrated Food Chain Surveillance System for *Salmonella* Spp. in Mexico.” *Emerging Infectious Diseases* 14, no. 3 (March 2008): 429–35. Table 4. <https://doi.org/10.3201/eid1403.071057>.

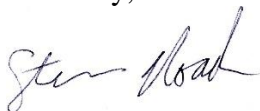
- c) Do federal agencies have a plan to address the risk of antibiotic resistance that results from the cross-border movement of food animals?

While these three outbreaks are troubling in themselves, they accompany a much longer rise in resistance to fluoroquinolones in *Salmonella* isolates from sick people. In the past FDA has taken action to address the threat of fluoroquinolone resistance in foodborne pathogens by putting in place extra-label restrictions and withdrawing approval of the fluoroquinolone class for use in poultry. These outbreaks and the trend in human isolates indicate that more should be done to preserve the efficacy of fluoroquinolones to protect human and animal health. WHO recommends that fluoroquinolones either not be used at all in food animals or only be used in individual animals for disease treatment when other options are not available.¹⁶ FDA in contrast allows fluoroquinolones to be used in cattle and swine to control disease, rather than treat individual animals, and does not require susceptibility testing to support that use.¹⁷ Since FDA does not provide guidance on what is meant by the term “disease control,” it is up to individual veterinarians to decide when use of fluoroquinolone antibiotics is appropriate. We would appreciate responses to the following questions related to the upward trend in resistance to fluoroquinolones in human *Salmonella* isolates.

- a) Do the federal agencies have a plan to address the increase in fluoroquinolone resistance in *Salmonella* causing illness in humans?
- b) Has FDA considered additional steps such as withdrawing control label claims, clarifying when control use of fluoroquinolones is appropriate, or requiring susceptibility testing before use of fluoroquinolones?
- c) Have federal agencies examined whether resistance or reduced susceptibility to fluoroquinolones is increasing in other bacteria present on farms and impacting human and/or animal health?

We appreciate your consideration of this letter and would like to arrange an opportunity for Keep Antibiotics Working and its allies to meet with you to discuss it further.

Sincerely,



Steven Roach

On behalf of the undersigned organizations:

Antibiotic Resistance Action Center (ARAC) at the Milken Institute School of Public Health,
George Washington University
Center for Biological Diversity

¹⁶ World Health Organization. “WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals.” (2017). Licence: CC BY-NC-SA 3.0 IGO.

¹⁷ FDA. “21 Code of Federal Regulations 522.812.”

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=522.812>.

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Consumer Federation of America
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