Animal Antibiotic Use and Public Health

The selected studies below were excerpted from Pew's peer-reviewed 2017 article "Antimicrobial Drug Use in Food-Producing Animals and Associated Human Health Risks: What, and How Strong, Is the Evidence?" in the journal *BMC Veterinary Research*. Each table below represents a wide selection of studies offering some of the most compelling examples of scientific data addressing the three key questions in the above article and Pew's related issue brief, "Antibiotic Use in Food Animals Poses Risk to Public Health." Full citations to the studies listed below can be found in the article.

Table 1

Sample Studies Evaluating the Emergence of Resistance in Pathogens After Food-Producing Animals Were Exposed to Antibiotics

Reference	Species	Bacterium	Antimicrobial drug	Study design	Key findings
1. Controlled trials					
[46]	Broiler chickens	*Campylobacter*	Enrofloxacin Sarafloxacin Ciprofloxacin	2 groups of chickens (25 or 50 each) were infected on Day 16 or 24 of life; half were treated with antibiotics in drinking water from days 30-34. Bacteria from animals receiving antibiotics were monitored for the emergence of resistance and compared with those from untreated animals.	Resistance emerged rapidly in bacteria from treated birds, especially those given enrofloxacin; resistance was retained throughout the study period. Resistance remained low in bacteria from untreated control birds.
[47]	Pigs	*Salmonella* Typhimurium	Aureomycin (standard or subtherapeutic dose)	3 groups of pigs (6 each) were infected; pigs in aureomycin groups were treated via feed for 7 days starting 48 hours after inoculation. Bacteria from animals receiving antibiotics were monitored for the emergence of resistance and compared with those from untreated animals.	Resistance emerged in naturally occurring *E. coli* populations from treated animals, and increased resistance persisted for 2 weeks after treatment. Treated pigs shed higher numbers of *S.* Typhimurium DT104 than did untreated pigs.
[48]	Pigs	*Salmonella* Typhimurium	Aparamycin (various doses) Sulfamethazine and carbadox Gentamicin and neomycin	In 2 trials, 6 groups of pigs (8 each) were infected 2 days after weaning; antibiotics were given in feed and drinking water starting 7 days after infection for 14 days. Bacteria from animals receiving antibiotics were monitored for the emergence of resistance and compared with those from untreated animals.	Resistance of *Salmonella* isolates was not affected by treatment; resistance emerged in native *E. coli* populations and was affected by treatment. Using similar antibiotics in rotation resulted in greater resistance than if dissimilar antibiotics were used.

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Reference	Species	Bacterium	Antimicrobial drug	Study design	Key findings
1. Controlled trials, *continued*					
[49]	Broiler chickens	*Campylobacter*	Fluoroquinolones Enrofloxacin or flumequine in different concentrations	8 groups of chickens (15 each) were infected on Day 19 of life and treated for 4 days via drinking water, beginning 7 days after infection (or for one group on Day 1 of the experiment). Bacteria from animals receiving antibiotics were monitored for the emergence of resistance and compared with those from untreated animals.	Resistance emerged in *Campylobacter* isolates from enrofloxacin-treated birds (isolates from all other groups remained susceptible).
[50]	Beef cattle	*Campylobacter*	Chlortetracycline with or without sulfamethazine Virginiamycin, monensin, or tylosin	30 groups of steers (10 each) received antibiotics via feed for 56 days, starting 18 days after arrival at feedlot. Antibiotics were removed for 91 days, reintroduced for 42 days; animals were monitored for naturally occurring *Campylobacter* infection with or without antibiotic resistance.	Administration of antimicrobial drugs increased the carriage rate for resistant isolates, but results differed by antimicrobial drug and *Campylobacter* species.
[51]	Pigs	*Salmonella* Typhimurium	Oxytetracycline Aparamycin	3 groups of pigs were infected with *S.* Typhimurium; some pigs were from sows treated before farrowing. Bacteria from the pigs were monitored for the emergence of resistance.	Exposure of sows to oxytetracycline via feed was associated with increased resistance in bacterial isolates from pigs.
[52]	Pigs	*Campylobacter*	Enrofloxacin	2 groups of pigs (6 each) were treated with standard therapeutic oral dose for 5 days or not; naturally occurring bacterial populations were compared across groups.	Exposure to enrofloxacin resulted in *Campylobacter* isolates resistant to nalidixic acid and ciprofloxacin (no quinolone resistance detected before antibiotic exposure); resistant isolates detected for up to 35 days.
[53]	Pigs	*Salmonella* Typhimurium	Ceftiofur, aparamycin, or carbadox, followed by oxytetracycline	4 groups of pigs (12 each) were infected and exposed to different antibiotics (given in feed or via injection) starting 2 days after infection.	Frequency of antimicrobial resistance varied—lowest on Day 4 post-inoculation but increased steadily, and was highest on the last day of sampling. Continued increase of select antimicrobial resistance after exposure was discontinued.
2. Observational studies					
[54]	Dairy cattle	*Salmonella*	Various used on conventional farms	Cohort study from 2000-01; 95 farms: 26 organic and 69 conventional, comparing antimicrobial-resistance levels in bacteria.	Results differed by antibiotic; resistance levels were not significantly different for most antimicrobial drugs. Resistance to streptomycin and sulfamethoxazole was greater on conventional farms.
[56]	Broiler chickens, turkeys	*Campylobacter*	Various used on conventional farms	Cross-sectional study; 30 farms: 10 organic, 20 conventional, comparing antimicrobial-resistance levels in bacteria.	Antimicrobial-resistance rates were significantly higher in isolates from conventional farms, with conventional isolates significantly more likely to be multidrug-resistant. Resistance levels varied across antimicrobial drugs.

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Reference	Species	Bacterium	Antimicrobial drug	Study design	Key findings
3. Other studies					
[63]	Bacteria from chicken meat and humans	*Salmonella* Heidelberg, ceftiofur-resistant commensal *E. coli*	Ceftiofur	Correlation study evaluating resistance levels in bacteria collected before, during, and after voluntary discontinuation of ceftiofur use in hatcheries in Quebec, Canada, and studying correlation across provinces and time periods, comparing prevalence of ceftiofur resistance in bacterial isolates from chicken meat and humans.	Statistically significant correlation between prevalence of ceftiofur-resistant *S.* Heidelberg on retail chicken and human infections; in Quebec, levels of ceftiofur use in hatcheries seemed correlated with ceftiofur resistance in chicken *Salmonella* and *E. coli* isolates.
[64]	Pigs	*Enterococcus faecium*	Tylosin; resistance to various antibiotics	Evaluation of prevalence of antimicrobial resistance from pigs receiving antibiotics via feed at 16 farms; 13 farms were examined again 183-287 days later.	Resistance to macrolides, lincosamides, and tetracyclines decreased after tylosin was banned for growth promotion.

Table 2

Sample Studies Evaluating the Emergence of Resistance in Commensals After Food-Producing Animals Were Exposed to Antibiotics

Reference	Species	Bacterium	Antimicrobial drug	Study design	Key findings
1. Controlled trials					
[65]	Cattle	*E. coli*	Chlortetracycline (with or without sulfamethazine) Monensin, tylosin, virginiamycin as growth promoters	6 treatments via feed, 5 pens (10 steers each) per treatment, to observe emergence of antimicrobial resistance after exposure.	Exposure to chlortetracycline and sulfamethazine increased the prevalence of resistance; diet had an important impact on shedding of resistant strains.
[66]	Cattle	*E. coli*	Florfenicol	42 pens (8-10 cows each), 2 per pen enrolled in study to observe emergence of antimicrobial resistance after treatment.	After antimicrobial treatment via injection, antimicrobial resistance increased. Prior treatments were predictive of resistance; animal source and previous management affected results.
[67]	Cattle	Fecal bacteria	Ceftiofur Tetracycline	176 steers; study was performed twice, each time with 88 steers (11 per pen); total of 4 treatment groups to observe antimicrobial resistance after treatment.	Initial and subsequent antimicrobial treatments via injection led to increased frequency of resistance genes.
[68]	Pigs	*Enterococci* *Staphylococcus hyicus*	Tylosin (as growth promoter)	2 trials conducted with 10 pigs (5 per trial) to observe erythromycin-resistance levels in response to exposure.	Prevalence of resistance in *Enterococci* immediately increased 2.4 times in response to tylosin exposure in feed; more gradual resistance in *S. hyicus*, at a rate of 8% per day, 5 times over 20 days.
[130]	Pigs	Aerobic Gram-negative bacteria *Salmonella*	Chlortetracycline	3 farms (12, 2, and 8 barns, respectively), enrolled to observe prevalence of antimicrobial resistance after exposure.	In-feed antimicrobial exposure was associated with increased prevalence of resistance in aerobic Gram-negative bacteria.
2. Observational studies					
[69]	Pigs	Coliform bacteria	Olaquindox	Cohort study of 12 farms in the U.K.; impact of emergence of resistance in coliform bacteria from farms that use olaquindox in feed versus neighboring farms that do not.	Prevalence and level of resistance increased on farms that used it, and to a lesser extent on adjacent farms.
[70]	Pigs	*E. coli*	Various	Cross-sectional study; 34 pig farms in Ontario, Canada; impact of emergence of resistance from farms using antimicrobials during the farrow-to-finish process.	Antimicrobial use increases emergence of resistance.

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Reference	Species	Bacterium	Antimicrobial drug	Study design	Key findings
2. Observational studies					
[71]	Pigs	*E. coli*	Various	Cross-sectional study; 47 farms in Canada; assessing association between antimicrobial use and resistance in pigs.	Antimicrobial use in weaner pigs was associated with resistance more consistently than in other age categories; some evidence for cross-resistance and co-selection.
3. Other studies					
[72]	Pigs, cattle, poultry	*E. coli*	Various	Study examined correlation between antimicrobial use and resistance in 7 countries.	Use of antimicrobial drugs strongly correlated with resistance in *E. coli* at a national level.
[73]	Poultry	*Enterococci* (vancomycin-resistant)	Avoparcin	Correlation study compared resistance prevalence before and after avoparcin ban in Italy.	After avoparcin ban, prevalence of vancomycin-resistant *Enterococci* decreased in poultry meat.

Table 3

Sample Studies Evaluating the Risk of Transmitting Resistant Pathogens to Humans

Reference	Subject	Bacterium	Study design	Key findings
1. Controlled trials: Not applicable because of ethical concerns				
2. Observational studies				
[87]	Human patients	*Salmonella* Newport (MDRAmpC-resistant)	Case-control study of patients in New England from 1999-2001; 34 Newport-MDRAmpC patients, 37 *Salmonella* control patients with susceptible Newport infection, and 94 healthy community controls; observe risk factors for infection.	Association between *S.* Newport-MDRAmpC infection and dairy farm exposure. Bacterial isolates from humans and cattle were indistinguishable or closely related (based on antibiotic-resistance profile and PFGE pattern).
[88]	Human patients	*Salmonella* Newport (MDRAmpC-resistant)	FoodNet case-control study of U.S. patients from 2002-03; 215 case patients; 54 with MDRAmpC-resistant strain and 146 pansusceptible; 1,154 healthy community controls; observe risk factors for infection.	Association of infection with *S.* Newport- MDRAmpC with consumption of uncooked ground beef or home-prepared runny scrambled eggs or omelets during the 5 days before illness onset.
[89]	Human patients	*Salmonella* Newport MDRAmpC	Case-control study of Wisconsin patients from 2003-05; 268 case isolates from Wisconsin and 402 from elsewhere in the U.S. (collected from 2003-04); associations between antimicrobial resistance and reported exposures.	Infections with multidrug-resistant *S.* Newport strains associated with exposures to cattle, farms, and unpasteurized milk.
[90]	Human patients	*Salmonella* Newport (chloramphenicol-resistant)	Case-control study of patients in California from 1985; 45 patients and 89 matched healthy volunteer controls; observing risk factors for infection; epidemic *Salmonella* strain was isolated from hamburger products eaten by cases, as well as where animals were slaughtered, dairies that sent the animals to slaughter, and ill dairy cows.	Infection with resistant *S.* Newport isolates associated with eating ground beef the week before onset and penicillin and tetracycline use the month before onset; chloramphenicol-resistant *Salmonella* from dairy farms was associated with chloramphenicol use on those dairies.
[91]	Human patients	MRSA (nontypable)	National case-control study of Dutch patients from 2003-05; 35 cases, 76 controls to observe risk factors for MRSA infections.	Living in rural areas and contact with pigs and cattle were associated with case patients.
[92]	Veal calf farmers	MRSA ST398	Cross-sectional study of veal calf farmers in the Netherlands from 2007-08 to identify risk factors for carriage; 102 farms randomly selected, 390 farmers (negative for MRSA ST398) filled out questionnaires, nasal swabs taken from farmers and their calves.	Human MRSA ST398 carriage was associated with intensity of animal contact and number of MRSA-positive animals on farm; calves were more likely to be carriers when treated with antibiotics, and good farm hygiene had a protective effect.
[93]	Swine farmers	MRSA ST398	Cross-sectional study of Belgian swine farmers in 2007 to identify risk factors for carriage; 49 randomly selected swine farms, 127 farm personnel and 1,500 pigs were sampled; nasal swabs and wound samples taken from farmers.	MRSA ST398 carriage by farmers was associated with prevalence among pigs on the farm. Other risk factors include having regular contact with pigs, dogs, and horses; and use of protective equipment.

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Reference	Subject	Bacterium	Study design	Key findings
3. Other studies				
[22]	Bacterial isolates	MRSA CC398	Phylogenetic study and population genetic analysis of MRSA CC398 in various countries from 1997-2011; examining the evolution and transmission dynamics, including transmission between species.	Human and animal populations of CC398 are separate, but with multiple transfers back and forth; same data suggest further transmission of animal-associated strains in community settings (e.g., hospitals); different tetracycline-resistance genes showed different evolutionary patterns.
[94]	Human patients	*Salmonella* Typhimurium DT104	Danish study investigating the source of multidrug-resistant infection outbreak in 1998; rare strain isolated from 27 patient cases and 3 pork samples. Pork samples were traced back to herd; resistant infections in humans were more difficult to treat.	A swine herd was the likely source of a human outbreak with MDR *S.* Typhimurium DT104.

Table 4

Sample Studies Evaluating the Risk of Transmitting Resistance Genes to Bacteria That Sicken Humans

Reference	Subject	Bacterium	Study design	Key findings
1. Controlled trials: Not available				
2. Observational studies				
[100]	Poultry workers	*E. coli,* nalidixic acid-resistance	Randomized control trial nested in a case-control study in Nigeria investigating the transmission of *E. coli* from birds to poultry workers. Birds on university and commercial farms were experimentally infected with an *E. coli* strain. Poultry workers in direct contact with infected birds were sampled for colonization, and compared with control workers with or without direct contact, and samples collected from exposed workers before exposure.	After birds were infected, the poultry workers in direct contact with them were colonized; results were similar on the university and commercial farms.
[101]	Poultry farmers	Aerobic bacterial cultures, tetracycline resistance	Randomized control trial combined with a case-control study to examine effects of tetracycline-supplemented feed on bacterial microflora of chicken and contact farmers in the U.S.; case chicken were exposed to tetracycline in feed, controls were not. Emergence of resistance was tested in commensal bacteria. Farm family with chicken contact was tested for resistance and compared with other nearby farm families and medical students.	Antimicrobial resistance emerged in exposed chicken and farm contacts.
[102]	Poultry farmers	Intestinal bacterial flora, tetracycline resistance	Prospective cohort studying resistance in bacterial microflora of chicken, contact farmers, and their neighbors (control) in the U.S.; birds were exposed to tetracycline in feed, emergence of resistance was traced in birds and contact humans, and compared with neighbors.	Antimicrobial resistance emerged under exposure on the farm with prevalence of antimicrobial resistance higher in bacteria from exposed farm families than in neighbors.
[103]	Pig farmers, abattoir workers	*E. coli*	Cross-sectional study from the Netherlands analyzing the prevalence of resistance in pig farmers, abattoir workers, and urban/suburban residents as the control. Fecal *E. coli* from the human groups were tested for resistance to multiple antimicrobial drugs.	Pig farmers had the highest percentage of resistant *E. coli*, urban/suburban residents the lowest.
[104]	Turkey, broiler, and laying-hen farmers; and slaughterers	*E. coli*	Case-control study from the Netherlands on the prevalence and degree of resistance in turkey, broiler, and laying-hen farmers and their respective flocks, as well as poultry slaughterers; comparison across human (and corresponding animal) populations. Humans and birds sampled; antibiotic use on farms recorded; meat samples collected immediately after slaughter.	Prevalence of resistance significantly higher in turkey and broiler samples than laying hens (which correlated with antibiotic use); prevalence of resistance was higher in turkey and broiler farmers and slaughterers than in laying-hen farmers. Isolates from farmers/slaughterers and birds/meat seemed to match, despite variability across farms.

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Reference	Subject	Bacterium	Study design	Key findings
3. Other studies				
[63]	Bacteria from chicken meat and humans	*Salmonella* Heidelberg, ceftiofur-resistant commensal *E. coli*	Correlation study evaluating resistance levels in bacteria collected before, during, and after a voluntary discontinuation of ceftiofur use in hatcheries in Quebec, Canada, and studying correlation across provinces and time periods, comparing prevalence of ceftiofur resistance in bacterial isolates from chicken meat and human cases.	Statistically significant correlation between prevalence of ceftiofur-resistant *S.* Heidelberg on retail chicken and human infections. Levels of ceftiofur use in hatcheries during study period seemed correlated with ceftiofur resistance in chicken *Salmonella* and *E. coli* isolates.

Table 5

Sample Studies Evaluating the Health Impacts Associated With Human Infections Due to Resistant Versus Susceptible Bacteria

Reference	Subject	Bacterium	Study design	Key findings
1. Controlled trials: Not available				
2. Observational studies				
[121]	Patients with *Salmonella* infections	*Salmonella*	U.S. cohort study observing frequency of hospitalization and bloodstream infection in patients infected with *Salmonella* strains from 1996-2001. Two analyses performed; one of *Salmonella* isolates collected through NARMS, the other of patients with NARMS *Salmonella* isolates and corresponding FoodNet interviews.	Resistant isolates more likely associated with bloodstream infections than susceptible isolates; patients with resistant isolates more likely to be hospitalized because of bloodstream infection than those with susceptible isolates; among hospitalized patients, those with resistant isolates had longer stays than those with susceptible isolates.
[122]	Patients with *Salmonella* infections	*Salmonella*	U.S. cohort study from 2006-08 observing clinical outcomes of patients infected with *Salmonella* strains (bloodstream and GI infection).	Bloodstream infections and hospitalizations more likely among patients with resistant than susceptible isolates.
[123]	Patients infected with *Salmonella*	*Salmonella*	U.S. cohort study observing patients infected with *Salmonella* strains from 1989-90; results compared to similar study conducted in 1979-80.	Patients with resistant infections were more likely to be hospitalized than those with susceptible infections; recent antimicrobial treatment as well as age and race were significant predictors of resistance.
[124]	Patients with *Salmonella* infections	*Salmonella* Typhimurium	Canadian cohort study observing patients infected with *Salmonella* strains and their risk of hospitalization from 1999-2000.	Hospitalization more likely in patients infected with resistant than susceptible strains; an estimated 57-72% of hospitalizations were attributable to resistance patterns.
[125]	Patients infected with *Salmonella* Typhimurium	*S.* Typhimurium	Danish matched-cohort study observing death rates of patients infected with *S.* Typhimurium from 1995-99; random controls matched by age, sex, and county of residence; comparison between susceptible and resistant infections; subjects followed for up to 2 years.	Compared with the general population, patients with susceptible *S.* Typhimurium infection were 2.3 times more likely to die; patients with the most resistant strains were 4.8 times more likely to die; patients infected with quinolone-resistant isolates 10.3 times more likely to die.
[126]	Patients with *Campylobacter* infections	*Campylobacter* (quinolone and erythromycin-resistant)	Danish cohort study determining the risk of invasive illness and death associated with 3,471 patients infected with *Campylobacter* isolates.	Patients infected with quinolone-resistant *Campylobacter* strains had a sixfold increased risk of invasive illness or death within 30 days of sample collection, compared with patients infected with susceptible isolates; infections with erythromycin-resistant *Campylobacter* strains associated with greater than fivefold higher risk within 90 days compared to infections with susceptible strains.

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Reference	Subject	Bacterium	Study design	Key findings
[127]	Studies of patients with bloodstream infection due to *Staphylococcus aureus*	*S. aureus*, MRSA	Meta-analysis of cohort studies from multiple countries from 1980-2000; mortality rates of patients infected with methicillin-susceptible and -resistant *S. aureus*.	Increased mortality associated with MRSA infections compared with methicillin-susceptible strains.
3. Other studies				
[128]	Outbreaks of patients infected with *Salmonella*	*Salmonella*	Outbreak analysis of U.S. patients hospitalized due to infection with susceptible or resistant *Salmonella* strains from 1984-2002.	Median proportion hospitalized for each type of outbreak caused by resistant strains was 26%, over 2.5 times higher than median proportion hospitalized for outbreaks caused by pansusceptible strains.