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Residential proximity to high-density poultry operations associated with campylobacteriosis and infectious diarrhea

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Abstract

Poultry carry zoonotic bacteria that can cause gastroenteritis in humans. Environmental transmission of pathogens from poultry operations may increase gastrointestinal infection risk in surrounding communities. To evaluate associations between residential proximity to high-density poultry operations and individual-level diarrheal illnesses, we conducted a nested case-control study among 514,488 patients in Pennsylvania (2006–2015). Using electronic health records, we identified cases of five gastrointestinal outcomes: three pathogen-specific infections, including *Escherichia coli* (n = 1425), *Campylobacter* (n = 567), and *Salmonella* (n = 781); infectious diarrhea (n = 781); and non-specific diarrhea (2012–2015; n = 28,201). We estimated an inverse-distance squared activity metric for poultry operations based on farm and patient addresses. Patients in the second and fourth (versus first) quartiles of the poultry operation activity metric had

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increased odds of *Campylobacter* (aOR [CI], Q2: 1.36 [1.01, 1.82]; Q3: 1.38 [0.98, 1.96]; Q4: 1.75 [1.31, 2.33]). Patients in the second, third, and fourth quartiles had increased odds of infectious diarrhea (Q2: 1.76 [1.29, 2.39]; Q3: 1.76 [1.09, 2.85]; Q4: 1.60 (1.12, 2.30]). Stratification revealed stronger relations of fourth quartile and both *Campylobacter* and infectious diarrhea in townships, the most rural community type in the study geography. Increasing extreme rainfall in the week prior to diagnosis strengthened fourth quartile *Campylobacter* associations. The poultry operation activity metric was largely unassociated with *E. coli*, *Salmonella*, and non-specific diarrhea. Findings suggest high-density poultry operations may be associated with campylobacteriosis and infectious diarrhea in nearby communities, highlighting additional public health concerns of industrial agriculture.

INTRODUCTION

Poultry are reservoirs of several zoonotic bacteria that cause acute gastroenteritis in humans, including *Campylobacter*, *Salmonella*, *Escherichia coli*, and *Listeria* (Berghaus et al. 2012; Blaak et al. 2015; Dahshan et al. 2016; Lee et al. 2016; Sahin et al. 2015). Among the most common causes of foodborne illness in the U.S., these pathogens cause significant morbidity and mortality, with serious sequelae such as Guillain-Barré syndrome (*Campylobacter*), reactive arthritis and irritable bowel syndrome (*Campylobacter* and *Salmonella*), end-stage renal disease (*E. coli*), and pre-term labor and fetal infection (*Listeria*) (Humphrey et al. 2007; Scallan et al. 2015). The risk of illness due to foodborne transmission of pathogenic bacteria from poultry meat is well documented (Batz et al. 2012). Environmental transmission of these pathogens from poultry operations to humans presents an additional, though far less-studied risk.

Research has previously linked industrial food animal production (IFAP)—which is characterized by large, homogeneous, and densely packed livestock operations—to increased risk of zoonotic diseases in nearby communities (Casey et al. 2015). In terms of zoonotic bacteria associated with gastroenteritis, a case-control study conducted in counties with high cattle density found that living or working on a dairy farm was positively associated with campylobacteriosis, with strong overlap between human and bovine bacterial isolates (Davis et al. 2013). A study conducted across multiple states that linked *Campylobacter* cases with socioeconomic and environmental data by zip code found that in top poultry and dairy producing regions, campylobacteriosis incidence rates were significantly higher in zip codes with broiler operations or dairy operations compared to zip codes without operations (Rosenberg Goldstein et al. 2016). Other ecological studies using disease surveillance data have reported associations of farm animal density and *Campylobacter*, and the percent of the population living on a farm with risk of *E. coli* infection (Chang et al. 2009; Green et al. 2006). Studies have also found that rural residents living in areas with swine or dairy IFAP experience greater occurrence of diarrhea as measured by interviews with area residents (Arnold 1999; Wing and Wolf 2000), although these studies did not assess specific pathogens and are subject to recall bias.

While studies have shown living or working on a poultry farm and contact with live poultry to be a risk factor for *Campylobacter* and antibiotic-resistant *E. coli* infection (Davis et al.

2013; Price et al. 2007; Studahl and Andersson 2000; Thorsteinsdottir et al. 2010; Wilson 2004), individual-level associations of poultry operations with risk of human infections in surrounding communities are largely unstudied. Environmental contamination from poultry operations has the potential to spread pathogens to nearby communities (Jonsson et al. 2010). Bacterial pathogens colonize animals at an early age and spread quickly through a flock (Blaak et al. 2015; Friese et al. 2013; Hermans et al. 2012; Sahin et al. 2015). From poultry houses, bacteria enter the community environment via aerosolized particles or in dust emitted through ventilation fans, through pests such as flies, and through land-disposal of poultry waste (Blaak et al. 2014; Blaak et al. 2015; Bull et al. 2006; Friese et al. 2013; Graham et al. 2009a; Graham et al. 2009b; Skora et al. 2016). Heavy rainfall can facilitate further transport of pathogens into surface and groundwater and is independently associated with gastrointestinal illness (Gleason and Fagliano 2017; Levy et al. 2016).

Given the limited research related to poultry IFAP and risk of relevant human infections in surrounding communities, the aim of this study was to evaluate associations between residential proximity to poultry operations and individual-level diarrheal illnesses. We conducted a case-control study of the association between residential proximity to poultry operations and five gastrointestinal outcomes. While past research utilized gravity models to analyze zoonotic disease risk in swine and bovine operations (e.g. Casey et al. 2013), to our knowledge this is the first study to use this geospatial method to assess infectious disease risks related to poultry IFAP and to evaluate associations of IFAP with gastrointestinal outcomes. We evaluated three pathogen-specific intestinal infection diagnoses that have been linked to poultry operations: *E. coli, Campylobacter,* and *Salmonella*. In addition, since the majority of patients seeking medical care for diarrhea are not tested for specific pathogens (Scallan et al. 2005), we sought to ascertain the relation of poultry operation proximity to less severe or persistent diarrheal illnesses by evaluating two other diagnoses, specifically infectious and non-specific diarrhea.

METHODS

Study Population

Using electronic health record (EHR) data, we identified child and adult patients with one of five gastrointestinal outcomes from the Geisinger Clinic, an integrated health system in Pennsylvania, USA. Geisinger primary care patients represent the age and sex distribution of the general population in central and northeastern Pennsylvania (J. A. Casey et al. 2016). The study area comprised 38 counties in Pennsylvania, including the health system's primary care market and bordering counties (Figure 1). The latitude and longitude of patients' addresses were geocoded using ArcGIS version 10.1 (Esri, Redlands, CA). For four of our study outcomes, we utilized EHR data from 514,488 patients who had contact with Geisinger from January 2006 to July 2015; for non-specific diarrhea, we limited data to 455,364 patients with contact from January 2012 to July 2015 due to inconsistencies in coding prior to 2012. The Geisinger Institutional Review Board approved the study and waived informed consent.

Case Ascertainment and Control Selection

We identified cases from the five diagnostic groups using Geisinger system diagnostic codes and text descriptions cross-linked to International Classification of Diseases (ICD, 9th and 10th Revision) codes from outpatient, emergency department, and medication records. Indications from medication records were used to identify cases with potential call-in orders for diarrhea not associated with a patient encounter and to enhance incomplete coding from encounters. Diagnoses were identified as follows (ICD-9 codes, ICD-10 codes not documented as they were internally converted to ICD-9 during data extraction): intestinal infection related to *Salmonella* (003.0), *E.coli* (008.0, 008.00, 008.09, 041.4, 041.41, 041.49), or *Campylobacter* (008.43), infectious diarrhea/bacterial enteritis (008.5, 009.2, 009.3, excluding codes with text descriptions indicating travelers' diarrhea), and non-specific diarrhea (787.91, 564.5). We used positive fecal sample laboratory test results to identify *Salmonella* and *Campylobacter* cases in addition to those identified through codes; negative test results received one week before or after a diagnostic code were used to exclude patients as cases. For *Salmonella* and *Campylobacter* cases, 28% and 36% had both a code and positive laboratory test, 25% and 19% had a code only, and 47% and 45% had a laboratory test only, respectively. There were an insufficient number of *Listeria* cases to evaluate. Patients with an inpatient diagnosis for infectious diarrhea and non-specific diarrhea were excluded as potential cases for one year following diagnosis to avoid counting hospital-acquired infections as cases. Given the ambiguity of the non-specific diarrhea ICD-9 code, we used additional exclusion criteria for these cases. Specifically, we did not include cases with text descriptions for "frequent defecation" or "frequent stool," and we excluded cases for one-year after EHR notations for causes of non-infectious diarrhea (e.g., "chemotherapy-induced diarrhea," "antibiotic-associated diarrhea") or if there was a diagnosis for an acute condition associated with diarrhea (i.e., cholera, typhoid, Norwalk virus, receiving chemotherapy). All outcome analyses only included first incident cases. For all outcomes except non-specific diarrhea, 4% or less of cases had repeat diagnoses in subsequent years; 10% of non-specific diarrhea cases had repeat diagnoses, most of which had just one repeat diagnosis.

We randomly selected outpatient controls with no history of diarrhea diagnoses and frequency-matched them to cases by age category (< 1, 1, 2–4, 5–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–99,   100), sex, and year of encounter. If a control had multiple encounters in a year, one encounter was randomly selected for the activity metric assignment date.

Poultry Operation Data

Livestock operations are required to develop a Nutrient Management Plan (NMP) for manure handling if they exceed two animal equivalent units (AEUs, 1000 pounds of live weight on an annualized basis) per acre and have greater than eight AEUs (per Pennsylvania Act 38), or if they exceed 1000 total AEUs (per U.S. Clean Water Act). Operations can also voluntarily develop an NMP. NMPs provide information on livestock operation location and animal type and quantity. We obtained NMPs for poultry operations in the 38-county study area from County Conservation Districts. We located the latitude and longitude of poultry operations using Google Earth with visual confirmation of a poultry house on-site.

The study area contained five types of poultry operation: broilers (chickens raised for meat), layers (egg-laying hens), pullets (young hens produced for breeding operations), turkeys, and ducks. Poultry are reared in large flocks (e.g., approximately 20,000 broilers per flock) within grow-out houses and are produced in cycles throughout the year. Given their predominance in the poultry industry, research on zoonotic pathogens present in poultry operations generally focuses on chickens; however, there is evidence that bacteria such as *E. coli, Campylobacter*, and *Salmonella* are also prevalent in turkeys and ducks (Adzitey et al. 2012a; Adzitey et al. 2012b; Sahin et al. 2015; Siemer et al. 2004).

Poultry Operation Activity Metric Assignment

The poultry operation activity metric was calculated based on previously reported methods (Casey et al. 2013; Rasmussen et al. 2016) and took into account the total number of poultry operations in the study area, the distance between each patient's residence and poultry operations, and the number (in AEUs) of poultry at each operation. We estimated the metric using inverse distance-squared gravity measures (Talen and Anselin 1998) in R version 3.3.1 (R Foundation for Statistical Computing):

$$\text{Activity metric for patient j} = \sum_{i=1}^{n} \frac{a_i}{d_{ij}^2}$$

where n was the number of operations in the 38-county region, a_i was AEUs of poultry at operation i, and d_{ij}^2 was the squared-distance (m^2) between operation i and patient j. The activity metric was not normally distributed and was highly skewed, so was modeled as quartiles, with quartile one representing the lowest activity (and the reference category) and quartile four representing the highest activity.

Covariates

Demographic covariates were obtained from the EHR, including sex, age at diagnosis/encounter, race/ethnicity (non-Hispanic white versus all others), history of Medical Assistance (a proxy for low family socioeconomic status (Schwartz et al. 2014)), and smoking status (former, current, never, missing). Clinical covariates included an indicator (yes vs. no) for an antibiotic order in the EHR (outpatient records for the full study period, inpatient records starting in 2008) in the 30 and 60 days prior to diagnosis/encounter and another indicator for diagnosis with at least one of three gastrointestinal conditions, specifically Crohn's disease (555.x), ulcerative colitis (556.x), and irritable bowel syndrome (564.1). Diagnosis with these gastrointestinal conditions was evaluated because they cause diarrhea and prior research has suggested that conditions resulting in inflammation of the gut may increase vulnerability to gastrointestinal infections (Mann and Saeed 2012). Covariates created using patients' geocoded addresses included continuous distance (meters) between patient residence and the closest Geisinger facility, community type, and community socioeconomic deprivation. We hypothesized that distance to a Geisinger facility might influence care seeking for diarrhea differentially by location of residence. Community type was defined using a mixed definition of place that incorporated minor civil divisions (township, borough, city) and census tracts within cities; townships are the least population

dense and range from rural to suburban, boroughs represent walkable small towns, and cities are the most population dense (Schwartz et al. 2011). Community socioeconomic deprivation, a factor previously associated with hospital admissions for gastrointestinal illness (Olowokure et al. 1999; Pockett et al. 2011), was assigned to communities and was based on a factor analysis of six indicators derived from the 2000 U.S. Census (proportion of population in poverty, unemployed, receiving public assistance, with less than a high school education, not in the labor force, and proportion of households without a car) (Nau et al. 2015). Weather-related covariates included season of diagnosis (defined as winter [December-February], spring [(March-May], summer [June-August], and fall [September-November]), average maximum temperature, total precipitation (mm), and number of extreme precipitation events (precipitation > 90th percentile for the 10-year study period [i.e., > 10.9 mm]) in the week prior to diagnosis/encounter. The week prior was chosen to approximate the incubation period of the assessed pathogens. Temperature and precipitation data came from the weather station closest to each patient's residence and was obtained from the National Climatic Data Center (NOAA 2016).

Statistical Analysis

The goal of the analysis was to evaluate associations between the poultry operation activity metric and the five diagnostic groups representing specific gastrointestinal infections, infectious diarrhea, and non-specific diarrhea. We used logistic regression with robust standard errors clustered by community. Models were adjusted for sex, age, race/ethnicity, Medical Assistance, and smoking status (a risk factor for gastrointestinal disorders (Li et al. 2014)). Several additional covariates were assessed as potential confounders, including season of diagnosis/encounter, distance to closest Geisinger facility, community socioeconomic deprivation, prior antibiotic use, and diagnosis with a gastrointestinal condition (i.e., inflammatory and irritable bowel diagnoses). We repeated regression models for the five gastrointestinal outcomes stratified by community type to assess potential confounding by community type, as prior research in the study area has demonstrated that patients differ on individual-level and place-level variables by community type (J. A. Casey et al. 2016; Nau et al. 2015).

For models with significant associations for the poultry metric with gastrointestinal outcomes, we evaluated effect modification by several variables. We evaluated effect modification variables one at a time by including a cross-product term of the interacting variable with the poultry operation activity metric. Odds ratios and confidence intervals were calculated for poultry operation activity metric/outcome associations in models with statistically significant cross-product terms. Variables evaluated for effect modification included age, given the higher prevalence of diarrhea in young children and older adults (Scallan et al. 2005); Medical Assistance status, because socioeconomic status has been previously associated with gastrointestinal illness (Rose et al. 2016); prior antibiotic use, which can increase the vulnerability of the gut to bacterial infection and diarrhea due to alterations in the gut microbiota (Becattini et al. 2016); season of diagnosis/encounter; average maximum temperature; total precipitation; and extreme precipitation. Season and weather-related variables were evaluated because the incidence of some gastrointestinal illnesses fluctuate by seasonal factors such as temperature (Carlton et al. 2016) and extreme

weather events, including heavy rainfall, have been reported to increase the risk of water-borne diseases like infectious diarrhea (Curriero et al. 2001; Gleason and Fagliano 2017).

Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI) and *P* values. Results were considered significant at *P* < 0.05 (two-tailed). We used Stata version 14.0 (StataCorp, LP, College Station, TX) for data analyses.

RESULTS

Description of Cases, Controls, and Poultry Operations

We identified 28,201 incident cases of non-specific diarrhea between 2012 and 2015, and 781 cases of infectious diarrhea, 1425 cases of *E. coli*-related intestinal infection, 567 cases of *Campylobacter*-related intestinal infection, and 293 cases of *Salmonella* gastroenteritis between 2006 and 2015 (Tables 1a and 1b). Cases overlapped across gastrointestinal outcomes, particularly between non-specific diarrhea and other case types; between 19.8% and 42.0% of the more specific diagnoses were also identified among patients with non-specific diarrhea diagnoses. Reflecting the Geisinger patient population, the majority of patients for all case types were non-Hispanic white and lived in townships. Across case types, a higher proportion of cases than controls had a history of Medical Assistance, and had an antibiotic order in the 30 days prior to diagnosis/encounter. *Campylobacter* and *Salmonella* diagnoses were substantially higher in the summer compared to other seasons.

We collected NMPs for 304 high-density poultry operations, which were located in 16 of the 38 study counties. A comparison with data from the U.S. Agricultural Census (USDA 2017) on the number of broilers, layers, and pullets produced in the study area indicated that the NMP data we collected accounted for roughly 95% of the animals produced. Missing data likely represented smaller poultry operations that were not required to submit an NMP. Broiler operations were most common (Table 2). Operations had a median of 154 poultry AEUs. As AEUs take into account animal weight and number of production days/year, this could translate, for example, to approximately 74,000 broilers raised over the course of six six-week cycles (252 production days) or 49,000 layers in production over a full year.

Association of the Poultry Operation Activity Metric with Case Status

In an unadjusted model, patients with a poultry operation activity metric in the second, third, and fourth quartiles had significantly increased odds of diagnosis with infectious diarrhea compared with patients in the first quartile. Patients in the second and fourth quartiles had significantly increased odds of diagnosis with *Campylobacter* compared with patients in the first quartile (unadjusted results not shown). Adjustment for base covariates (sex, age, race/ethnicity, Medical Assistance, and smoking status) did not substantively change inferences (Figure 2). There were no associations for non-specific diarrhea in an unadjusted model; in an adjusted model, patients with a poultry operation activity metric in the fourth (versus first) quartile had slightly increased odds of diagnosis with non-specific diarrhea, crossing an inferential boundary (*P* < 0.05). We observed no associations for *E. coli*, or *Salmonella* in unadjusted or adjusted models. Although each of the following variables were associated with the outcomes, we found no evidence of confounding by season of diagnosis/encounter,

community socioeconomic deprivation, prior antibiotic use, or inflammatory and irritable bowel diagnoses for any of the five outcomes, therefore these variables were not included in adjusted models. Adjusting for distance to the nearest Geisinger facility slightly increased the strength of the association between the poultry operation activity metric and *Campylobacter*. Since inferences did not change and given the limitations of the variable (i.e., distance between a patient's residence and the closest Geisinger facility, without confirmation that they visited that facility), we opted to exclude this distance measure from the model.

Stratification by Community Type

With the exception of *E. coli*, models stratified by community type revealed significant associations of the poultry operation activity metric and gastrointestinal outcomes by community type (Table 3). In townships, the odds of non-specific diarrhea were significantly higher in the second and fourth (versus first) quartiles of the poultry operation activity metric, the odds of infectious diarrhea were higher in the fourth quartile, and the odds of *Campylobacter* were higher in the third and fourth quartiles. Although statistically non-significant, results for *E. coli* demonstrated an exposure-effect trend. In boroughs, the odds of non-specific diarrhea were significantly higher in the fourth quartile, the odds of infectious diarrhea were significantly higher in the second and third quartiles, and the odds of *Campylobacter* were higher in the second quartile. In cities, the odds of non-specific diarrhea were significantly lower in the second and third quartiles, the odds of *Salmonella* gastroenteritis were lower in the second quartile, and the odds of infectious diarrhea were higher in the second quartile.

Effect Modification Analyses

The number of extreme precipitation events in the week prior to diagnosis/encounter modified the association of poultry operations with *Campylobacter* diarrhea, strengthening the association between the fourth quartile of the poultry operation activity metric and *Campylobacter* as the number of extreme events increased from none to five (Figure 3; global *P* value = 0.004). Medical Assistance status also modified the relation between the poultry operation activity metric and *Campylobacter* diagnosis. Significant associations (aOR [CI], *P* value) were observed for the second, third, and fourth (versus first) quartiles of the poultry operation activity metric among Medical Assistance patients, with an exposure-effect relation (Q2: 2.29 [1.17, 4.48], 0.02; Q3: 2.84 [1.34, 6.05], 0.007; Q4: 3.29 [1.62, 6.65], < 0.001). Among non-Medical Assistance patients, only the fourth (versus first) quartile of the poultry operation activity metric was significantly associated with *Campylobacter* (Q4: 1.52 [1.11, 2.09], 0.01). We found evidence of effect modification by prior antibiotic use for non-specific diarrhea, observing a stronger association for the fourth (versus first) quartile of the poultry operation activity metric among those with an antibiotic order in the 30 days prior to diagnosis/encounter (Q4: 1.22 [1.08, 1.37], 0.002). We found no evidence of effect modification by age, season of diagnosis/encounter, average maximum temperature, or total precipitation for any of the five gastrointestinal outcome models.

DISCUSSION

In this study evaluating patients' residential proximity to high-density poultry operations and diarrheal illnesses we found that patients who lived closer to a greater number or larger operations had a higher odds of diagnosis with campylobacteriosis and infectious diarrhea. The odds of *Campylobacter* increased further with the occurrence of more extreme precipitation events in the week prior to diagnosis. Additionally, proximity to poultry operations was more strongly associated with *Campylobacter* among patients with a history of Medical Assistance, a proxy for low socioeconomic status. We did not find substantive evidence that proximity to poultry operations was related to diagnosis with non-specific diarrhea or intestinal infections related to *E. coli* or *Salmonella*.

Compared to patients in the lowest quartile of the poultry operation activity metric, we observed that patients in the highest quartile had an elevated risk of diagnosis with *Campylobacter*, suggesting that high-density poultry operations may be a risk factor for campylobacteriosis in nearby communities. As one of the most common causes of foodborne illness, *Campylobacter* in poultry has been shown to cause the greatest disease burden among pathogen-food combinations, accounting for cost of illness, lost quality-adjusted life years, and number of illnesses, hospitalizations, and deaths (Batz et al. 2012). Well-adapted to avian hosts, *Campylobacter* is ubiquitous on poultry farms (Sahin et al. 2015). Ecological analyses have observed that in addition to broad population exposure to *Campylobacter*—presumably through a centralized food system endemically infected with the bacteria—rates of campylobacteriosis are higher in rural areas, with significant associations with farm animal density, particularly high chicken density (Green et al. 2006). Jonsson et al (2010) identified clusters of *Campylobacter* simultaneously occurring in humans and broiler flocks, providing additional evidence for potential environmental transmission of *Campylobacter* from poultry operations into nearby communities. By using geocoded patient addresses to evaluate individuals' residential proximities to poultry operations, our findings provide more direct support for such transmission. The observed association could also indicate a common factor related to *Campylobacter* in poultry and humans (Jonsson et al. 2010), as *Campylobacter* is ubiquitous in the environment. Colonization of poultry chicks is believed to occur through horizontal transmission from external reservoirs such as other livestock and free-ranging animals, flies and other pests, contaminated water, and farm equipment (Hermans et al. 2012). Yet poultry flocks also act as a reservoir of *Campylobacter*, likely contributing to the persistence and abundance of bacteria in the environment.

Our primary analysis included all *Campylobacter* cases that occurred in the patient population, and therefore included all routes and sources of transmission, likely weakening observed associations with poultry operations. This was confirmed in analyses stratified by community type, which revealed a stronger, exposure-effect relation of the poultry operation activity metric and *Campylobacter* diagnoses in townships, the most rural community type in the study geography. Stratified models also revealed greater odds of *Campylobacter* for the second quartile of the poultry operation activity metric in boroughs, accounting for the elevated odds ratio observed in the second quartile of the non-stratified model. An individual living in a borough and in the second quartile of the poultry operation activity metric likely

has limited residential exposure to poultry operations, suggesting that there is additional confounding not accounted for in our analysis. Such confounders may be unrelated to poultry operations, such as consuming unpasteurized milk or contaminated water (Carrique-Mas et al. 2005; Green et al. 2006; Jonsson et al. 2010). Although unevaluated in the current study, poultry slaughterhouses comprise another potential source of zoonotic bacteria, and are generally located in urban or peri-urban areas. Slaughterhouses discharge large amounts of wastewater into the environment that can be contaminated with bacteria such as *Salmonella* and *Campylobacter,* risking contamination of surface-water and groundwater in neighboring communities (Gerber et al. 2007).

A novel contribution of this study was the inclusion of temperature and precipitation data from local weather stations, allowing for analysis of the influence of weather-related factors on associations between the poultry operation activity metric and gastrointestinal outcomes. In temperate climates, campylobacteriosis incidence is generally highest in summer, as seen in our study, potentially reflecting the impact of temperature and precipitation on the survival of *Campylobacter*, along with changes in human activities that increase risk of infection (Weisent et al. 2014). We found that as the number of extreme precipitation events in the week prior to *Campylobacter* diagnosis increased from zero to five, the association between the highest quartile of the poultry operation activity metric and campylobacteriosis strengthened. Considering that most people exhibit clinical symptoms within four days of infection (Humphrey et al. 2007), these findings provide further support for the hypothesis that *Campylobacter* diagnoses were related to an environmental exposure and bolster our hypothesis that residential proximity to poultry operations increased risk of campylobacteriosis. Once bacteria enter the external environment, extreme precipitation events can transport pathogens into ground and surface water (Levy et al. 2016), potentially contaminating drinking water and recreational water bodies. Our findings relate to a Maryland study that found a positive association between extreme precipitation events and risk of campylobacteriosis; because this association was only observed in coastal counties that had poultry IFAP, the researchers speculated that runoff from fields applied with poultry waste during extreme precipitation events led to the contamination of water bodies and wells (Soneja et al. 2016). Studies demonstrate the runoff of bacteria from land applied with poultry litter following rainfall events (Soupir et al. 2006), higher prevalence of *Campylobacter* downstream of poultry farms (Vereen et al. 2013), and that bacteria can survive from days to months in manure and water, including through typical poultry litter storage practices (Graham et al. 2009a). It is possible that our poultry operation activity metric inadvertently captured nearby crop field application of poultry litter, since 38% of operations applied litter on crop fields on the home farm and an additional 39% of operations exported at least a portion of the waste to nearby farms. Discharge from wastewater treatment plants comprise another potential source of *Campylobacter* in the environment that increases with heavy rainfall (Rechenburg and Kistemann 2009); thus it is also possible that our findings reflect an underlying association between patients' proximity to waterways downstream of potential discharges, or to septic overflows.

With prior studies demonstrating positive and negative associations, the relationship between socioeconomic status and campylobacteriosis remains unclear (Green et al. 2006; Newman et al. 2015; Rosenberg Goldstein et al. 2016). We found that *Campylobacter* cases were

more likely than controls to have a history of Medical Assistance, a proxy for low socioeconomic status. Additionally, Medical Assistance modified the poultry operation/ *Campylobacter* relation: proximity to poultry operations was more strongly associated with *Campylobacter* diagnosis among patients with a history of Medical Assistance. Our results may be explained by differential healthcare-seeking behavior for gastrointestinal illness by socioeconomic status, as has previously been reported (Scallan et al. 2006; Tam et al. 2003). Alternatively, these findings may indicate the existence of risk factors among patients with low socioeconomic status—such as agricultural employment—that increase their vulnerability to the risk of campylobacteriosis related to poultry operations.

We observed a trend of higher odds of *E. coli* diagnoses among patients in townships with greater proximity to poultry operations, though these results were not statistically significant. We found no association between residential proximity to poultry operations and *Salmonella.* Without bacteria samples from the poultry operations, the surrounding environment, and patient residences, we can only speculate as to why we detected associations for *Campylobacter*, but not *E. coli* or *Salmonella.* It is possible that there was a low prevalence of *E. coli* and *Salmonella* in the poultry operations included in this study. Research assessing the microbiological composition of poultry litter—one indicator of the presence of bacteria in poultry operations—demonstrated that bacterial composition varies by region and other factors (Terzich et al. 2000), and the prevalence of bacteria on poultry farms has been shown to vary with management practices (Berghaus et al. 2012). Considering environmental persistence differs by type of bacteria, it is also possible that environmental conditions hampered transmission of *E. coli* and *Salmonella. Campylobacter*, *E. coli*, and *Salmonella* are able to survive in the open environment, but factors such as the availability of nutrients, soil pH, moisture, and temperature affect bacterial persistence (Blaak et al. 2015; Cook et al. 2014; van Elsas et al. 2011). The complexity and diversity of the natural environment impedes predictions regarding bacterial survival (van Elsas et al. 2011).

Although we observed increased odds of infectious diarrhea for quartiles two, three, and four of the poultry operation activity metric compared to the first quartile, odds of this outcome were highest among patients in the second and third, rather than fourth, quartiles. Models stratified by community type revealed that in townships, the odds of infectious diarrhea were significantly higher for the fourth quartile, providing some support that residential proximity to poultry operations may increase risk for infectious diarrhea. Stratified models also showed that the elevated odds ratios in the second and third quartiles were due to increased odds in boroughs and cities. A closer look at the data revealed that these associations were driven by a high number of cases in just three boroughs and two cities, which we believe indicates a spatial clustering of infectious diarrhea cases picked up by our models but unrelated to poultry operations. Again, this suggests additional confounding that was not accounted for in our analysis. Identifying potential confounders is problematic given the non-specificity of infectious diarrhea as an outcome, which has innumerable causes.

We examined infectious and non-specific diarrhea as outcomes in order to capture gastrointestinal infections whose relatively lower severity or persistence did not warrant

testing for specific pathogens. The lack of specificity for the associated diagnostic codes presents a drawback to the inclusion of these outcomes, because many of these patients likely had diarrheal illnesses unrelated to environmental transmission. This was particularly problematic for non-specific diarrhea, which included diarrheal symptoms whose link to an infectious agent was not characterized. Any associations with poultry IFAP would likely be eclipsed by the abundance of other, more predominant causes of non-specific diarrhea (e.g., medication or chronic illness). Although we did observe significantly higher odds of non-specific diarrhea in the fourth (versus first) quartile of the poultry operation activity metric, and some significant associations in the stratified analysis, the effect sizes were small, as would be expected for this non-specific outcome, in which only a small number of patients within the larger study sample have possible poultry IFAP links.

Interestingly, we observed an interaction with prior antibiotic use for non-specific diarrhea: within the fourth quartile of the poultry operation activity metric, the odds of non-specific diarrhea were significantly higher among patients with an antibiotic order in the 30 days prior to diagnosis/encounter. In evaluating effect modification by prior antibiotic use, we hypothesized that antibiotics may increase the vulnerability of the gut to bacterial infection and diarrhea due to alterations in the gut microbiota (Becattini et al. 2016), including infections originating from poultry operations. Results for non-specific diarrhea provide some support for this hypothesis, but are tempered by the lack of evidence of effect modification by prior antibiotic use for the other outcomes. We lacked data on inpatient antibiotic orders prior to 2008, but this seems unlikely to have affected our findings.

A strength of this study was the use of EHR data to evaluate five diarrheal illnesses; however, although we incorporated fecal culture results in case definitions for *Campylobacter* and *Salmonella,* the use of diagnostic codes limited the specificity of other case definitions. Additionally, considering that the majority of patients with acute gastroenteritis do not seek medical care (Scallan et al. 2006), it is likely that our studied patients represent the more severe or long-lasting diarrheal illnesses in the general population. Such selection bias may have biased our results toward the null, since infections from poultry-related bacteria such as *Campylobacter* are generally self-limiting. Bacterium-specific acquired host immunity may have subjected our findings to misclassification bias (Havelaar et al. 2009). Once infected, acquired immunity against *Campylobacter*, *Salmonella*, and *E. coli* can limit illness duration and severity during subsequent infections with homologous bacterial strains—likely diminishing healthcare seeking—and protect individuals from subsequent illness (Gomes et al. 2016; Griffin and McSorley 2011; Havelaar et al. 2009). As evidenced by research on occupational exposure to *Campylobacter,* acquired immunity is more likely to occur with persistent exposure to bacteria—as would be the case with living near poultry operations—than with exposure to a high-dose or an unfamiliar bacterial type (Havelaar et al. 2009). Thus, without a comprehensive account of study patients' medical history, including all diarrheal episodes, instances of adaptive immunity could have lead to misclassification of cases as controls, biasing estimates toward the null. The small proportion of repeat diagnoses in our study population could be a signal of acquired immunity to persistent bacterial exposure, or may indicate that the trend of not seeking care for diarrheal illness is amplified for subsequent diarrheal episodes.

Another strength of this study included primary collection of NMP data to estimate the poultry operation activity metric. Comparison with U.S. Agricultural Census data suggested that NMP data was quite comprehensive. Missing data likely represented smaller operations and likely would have biased results toward the null. Geospatial analysis allowed us to link IFAP activity to patient residence and demonstrate initial evidence that residential proximity to poultry operations may increase risk for campylobacteriosis and infectious diarrhea. Parallel results in townships in stratified models reinforced these findings, irrespective of the presence of residual spatial confounding, as previously discussed. However, our proximity model is limited in that we cannot determine if the observed associations with *Campylobacter* and infectious diarrhea are, in fact, related to environmental transmission of bacteria from poultry operations rather than another factor captured by the poultry operation activity metric, such as occupational exposure to poultry and other livestock, environmental transmission of bacteria from other types of livestock operations, or obtaining drinking water from a household well (a factor that likely correlates with rural residence) (Carrique-Mas et al. 2005; Green et al. 2006; Potter et al. 2003). Future research with explicit exposure assessment is needed to validate our findings.

We were also unable to evaluate patients' exposure to poultry litter applied to crop fields as fertilizer. Historically, more than 90% of poultry litter was applied to agricultural land, usually within a few miles from where it was produced (Moore Jr. et al. 1995). Although NMPs provide information on crop field application when it is used on-site or directly exported to nearby farms, we found that 49% of NMPs in our study exported poultry litter through the use of a broker, and so lacked sufficient information to identify the crop fields to which litter was applied. According to some brokers, poultry litter is transported up to 50 miles from the source farm, and is used both on crop fields and mushroom farms (personal communication). Brokers are not required to document where they distribute purchased poultry litter or how it is used, further limiting access to information about IFAP and constraining environmental health research related to pathogen transmission via poultry litter application. Finally, while we evaluated high-density livestock operations, zoonotic disease risks are not unique to such operations; for example, chickens raised in free-range systems may be more likely to carry *Campylobacter* than housed animals, potentially due to greater exposure to pathogen reservoirs in the natural environment (Heuer et al. 2001). However, IFAP is the predominant model of poultry production in the U.S., and, increasingly, globally (Casey et al. 2015; Lam et al. 2016), reinforcing the importance of studying IFAP-related disease risks.

CONCLUSION

In one of the first studies to evaluate patients' residential proximity to poultry operations and diarrheal illnesses, we found an association between residing closer to more or larger poultry operations and campylobacteriosis. This association was stronger as the number of extreme precipitation events increased in the week prior to diagnosis, evidence of biologically plausible effect modification that provides further support to a causal inference that *Campylobacter* diagnoses were related to this environmental exposure. We also found that proximity to poultry operations increased risk of infectious diarrhea among patients living in

townships, the most rural community type in the study geography. These findings contribute to growing concern regarding the public health impacts of IFAP.

Acknowledgments

Abbreviations

IFAP   industrial food animal production

NMP   Nutrient Management Plan

AEU   animal equivalent unit

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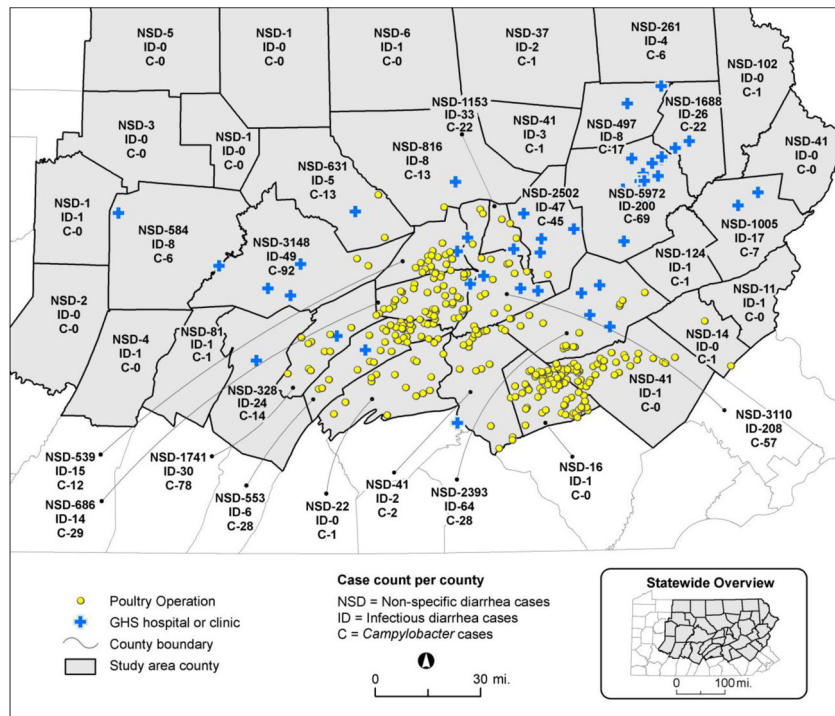
Figure 1.
Map of study area. Numbers within borders of each county indicate the number of cases of non-specific diarrhea, infectious diarrhea, and *Campylobacter*. Yellow circles show locations of poultry operations based on 2015 NMP data. Map created with ArcGIS (10.1, Esri, Redlands, CA).
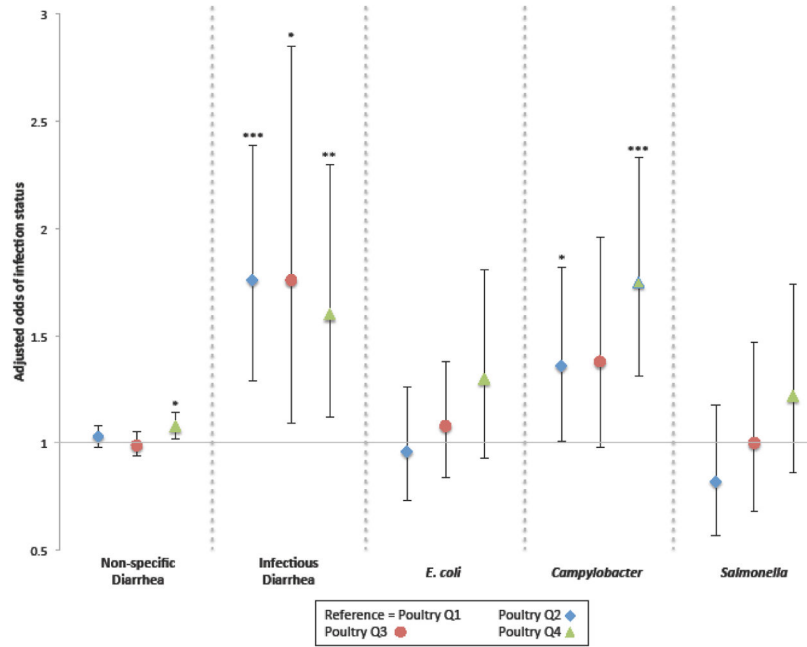
Figure 2.

Adjusted[a] associations of the poultry operation activity metric with diarrheal illness/infection status

[a]Multivariable logistic regression models controlled for age, sex, race/ethnicity, Medical Assistance, and smoking status, as described in *Methods*. Non-specific diarrhea model also adjusted for centered age squared. * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ comparing higher quartiles to first quartile reference group.
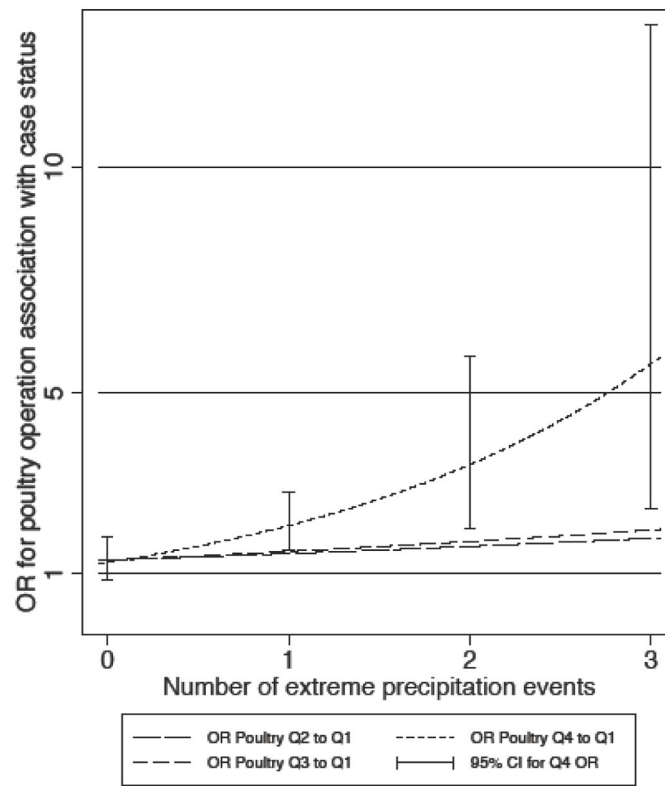
Figure 3.
Plot of odds ratio of *Campylobacter* by poultry operation activity metric quartile (reference = Q1), modified by the number[a] of extreme precipitation events in the week prior to diagnosis.

Abbreviations: OR, odds ratio; CI, confidence interval

[a]Categorized as 0, 1, 2, and 3 or more events since there were few instances of 4 or 5 events

Table 1a

Patient demographic and clinical characteristics for non-specific and infectious diarrhea diagnoses

| Characteristic	No. (%) unless specified			
	Non-specific Diarrhea		Infectious Diarrhea	
	Cases	Controls	Cases	Controls
	n = 28201	n = 84603	n = 781	n = 3901
Male sex	11330 (40.2)	33987 (40.2)	342 (43.8)	1707 (43.8)
Age at diagnosis, median (IQR)	37 (14, 60)	37 (14, 60)	43 (23, 59)	43 (23, 59)
0–4	4433 (15.7)	13299 (15.7)	79 (10.1)	393 (10.1)
5–12	2242 (8.0)	7041 (8.3)	40 (5.1)	216 (5.5)
13–18	1721 (6.1)	5000 (5.9)	36 (4.6)	182 (4.7)
19–44	7815 (27.7)	23285 (27.5)	253 (32.4)	261 (32.3)
45–61	5585 (19.8)	16924 (20)	208 (26.6)	1052 (27.0)
62–74	3658 (13.0)	11039 (13.1)	105 (13.4)	491 (12.6)
75	2747 (9.7)	8015 (9.5)	60 (7.7)	306 (7.8)
Diagnosis/encounter year				
2006	---	---	86 (11.0)	426 (10.9)
2007	---	---	87 (11.1)	432 (11.1)
2008	---	---	97 (12.4)	481 (12.3)
2009	---	---	99 (12.7)	503 (12.9)
2010	---	---	90 (11.5)	454 (11.6)
2011	---	---	92 (11.8)	460 (11.8)
2012	8698 (30.8)	26094 (30.8)	64 (8.2)	316 (8.1)
2013	8307 (29.5)	24921 (29.5)	81 (10.4)	405 (10.4)
2014	7428 (26.3)	22284 (26.3)	65 (8.3)	324 (8.3)
2015	3768 (13.4)	11304 (13.4)	20 (2.6)	100 (2.6)
Race/ethnicity				
Non-Hispanic White	26024 (92.3)	77793 (92.0)	748 (95.8)	3663 (93.9)
Black	764 (2.7)	2469 (2.9)	9 (1.2)	87 (2.2)
Hispanic	1206 (4.3)	3322 (3.9)	17 (2.2)	105 (2.7)

Characteristic	No. (%) unless specified			
	Non-specific Diarrhea		**Infectious Diarrhea**	
	Cases	**Controls**	**Cases**	**Controls**
	n = 28201	*n* = 84603	*n* = 781	*n* = 3901
Other	190 (0.7)	901 (1.1)	6 (0.8)	33 (0.9)
Missing	17 (0.1)	118 (0.1)	1 (0.1)	13 (0.3)
Smoking status				
Current smoker	4396 (15.6)	11064 (13.1)	131 (16.8)	572 (14.7)
Former smoker	6077 (21.6)	15281 (18.1)	179 (22.9)	773 (19.8)
Never smoked	13241 (47.0)	39975 (47.3)	359 (46.0)	1645 (42.2)
Missing	4487 (15.9)	18283 (21.6)	112 (14.3)	911 (23.4)
History of Medical Assistance	7469 (26.5)	15188 (18.0)	142 (18.2)	587 (15.1)
Antibiotic prescription in 30 days prior to diagnosis/ encounter	4133 (14.7)	5830 (6.9)	128 (16.4)	262 (6.7)
Diagnosis/encounter season				
Winter	7638 (27.1)	22471 (26.6)	175 (22.4)	1009 (25.9)
Spring	9062 (32.1)	23697 (28.0)	213 (27.3)	948 (24.3)
Summer	6079 (21.6)	18441 (21.8)	223 (28.6)	901 (23.1)
Fall	5422 (19.2)	19994 (23.6)	170 (21.8)	1043 (26.7)
No. unique counties	38	38	29	35
No. unique communities	851	1046	294	613
Community type				
City	3709 (13.2)	9871 (11.7)	109 (14.0)	372 (9.5)
Borough	8882 (31.5)	25081 (29.7)	251 (32.1)	1115 (28.6)
Township	15459 (54.8)	49293 (58.3)	419 (53.7)	2396 (61.4)
Missing	151 (0.5)	358 (0.4)	2 (0.3)	18 (0.5)
Community socioeconomic deprivation[a], SD units, median (IQR)	−0.4 (−2.56, 2.33)	−0.62 (−2.72, 2.07)	0.17 (−2.42, 3.54)	−0.83 (−2.96, 1.38)

Abbreviations: IQR, interquartile range

[a]Based on six U.S. Census indicators as described in the Methods.

Table 1b

Patient demographic and clinical characteristics for pathogen-specific diagnoses

Characteristic	No. (%) unless specified							
	E. coli		*Campylobacter*		*Salmonella*			
	Cases *n* = 1425	Controls *n* = 7038	Cases *n* = 567	Controls *n* = 2818	Cases *n* = 293	Controls *n* = 1460		
Male sex	338 (23.7)	1677 (23.8)	300 (52.9)	1489 (52.8)	132 (45.1)	658 (45.1)		
Age at diagnosis, median (IQR)	60 (30, 77)	59 (31, 75)	38 (16, 55)	37 (14, 55)	27 (5, 50)	27 (5, 50)		
0–4	112 (7.9)	559 (7.9)	80 (14.1)	398 (14.1)	69 (23.6)	343 (23.5)		
5–12	49 (3.4)	284 (4.0)	46 (8.1)	260 (9.2)	40 (13.7)	166 (11.4)		
13–18	53 (3.7)	258 (3.7)	35 (6.2)	164 (5.8)	11 (3.8)	86 (5.9)		
19–44	275 (19.3)	1377 (19.6)	177 (31.2)	847 (30.1)	77 (26.3)	397 (27.2)		
45–61	257 (18.0)	1250 (17.8)	137 (24.2)	685 (24.3)	54 (18.4)	257 (17.6)		
62–74	268 (18.8)	1484 (21.1)	76 (13.4)	371 (13.2)	28 (9.6)	129 (8.8)		
75	411 (28.8)	1826 (25.9)	16 (2.8)	93 (3.3)	14 (4.8)	82 (5.6)		
Diagnosis/encounter year								
2006	111 (7.8)	534 (7.6)	28 (4.9)	139 (4.9)	34 (11.6)	170 (11.6)		
2007	145 (10.2)	717 (10.2)	23 (4.1)	115 (4.1)	31 (10.6)	155 (10.6)		
2008	131 (9.2)	643 (9.1)	47 (8.3)	235 (8.3)	40 (13.7)	198 (13.6)		
2009	135 (9.5)	667 (9.5)	56 (9.9)	277 (9.8)	30 (10.2)	150 (10.3)		
2010	138 (9.7)	687 (9.8)	54 (9.5)	267 (9.5)	22 (7.5)	108 (7.4)		
2011	121 (8.5)	587 (8.3)	90 (15.9)	445 (15.8)	28 (9.6)	140 (9.6)		
2012	124 (8.7)	614 (8.7)	70 (12.4)	350 (12.4)	30 (10.2)	149 (10.2)		

Characteristic	E. coli Cases n = 1425	E. coli Controls n = 7038	Campylobacter Cases n = 567	Campylobacter Controls n = 2818	Salmonella Cases n = 293	Salmonella Controls n = 1460
No. (%) unless specified						
2013	240 (16.8)	1193 (17.0)	93 (16.4)	462 (16.4)	30 (10.2)	150 (10.3)
2014	190 (13.3)	946 (13.4)	85 (15.0)	423 (15.0)	36 (12.3)	180 (12.3)
2015	90 (6.3)	450 (6.4)	21 (3.7)	105 (3.7)	12 (4.1)	60 (4.1)
Race/ethnicity						
Non-Hispanic White	1326 (93.1)	6664 (94.7)	545 (96.1)	2619 (92.9)	278 (94.9)	1329 (91.0)
Black	32 (2.3)	139 (2.0)	5 (0.9)	70 (2.5)	7 (3.2)	47 (3.2)
Hispanic	54 (3.8)	172 (2.4)	14 (2.5)	91 (3.2)	6 (2.1)	56 (3.8)
Other	11 (0.8)	53 (0.8)	3 (0.5)	31 (1.1)	2 (0.7)	22 (1.5)
Missing	2 (0.1)	10 (0.1)	0 (0.0)	7 (0.3)	0 (0.0)	6 (0.4)
Smoking status						
Current smoker	169 (11.9)	781 (11.1)	67 (11.8)	367 (13.0)	36 (12.3)	183 (12.5)
Former smoker	417 (29.3)	1630 (23.2)	116 (20.5)	495 (17.6)	49 (16.7)	189 (13.0)
Never smoked	632 (44.4)	3413 (48.5)	266 (46.9)	1210 (42.9)	128 (43.7)	545 (37.3)
Missing	207 (14.5)	1214 (17.3)	118 (20.8)	746 (26.5)	80 (27.3)	543 (37.2)
History of Medical Assistance	304 (21.4)	789 (11.2)	122 (21.5)	483 (17.1)	73 (24.9)	293 (20.1)
Antibiotic prescription in 30 days prior to diagnosis/encounter	393 (27.6)	508 (7.2)	153 (27.0)	178 (6.3)	83 (28.3)	84 (5.8)
Diagnosis/encounter season						
Winter	363 (25.5)	1825 (25.9)	86 (15.2)	767 (27.2)	54 (18.4)	351 (24.0)

Characteristic	No. (%) unless specified								
	E. coli		*Campylobacter*		*Salmonella*				
	Cases	Controls	Cases	Controls	Cases	Controls			
	n = 1425	*n* = 7038	*n* = 567	*n* = 2818	*n* = 293	*n* = 1460			
Spring	367 (25.8)	1821 (25.9)	102 (18.0)	680 (24.1)	70 (23.9)	352 (24.1)			
Summer	347 (24.4)	1594 (22.7)	231 (40.7)	602 (21.4)	127 (43.3)	352 (24.1)			
Fall	348 (24.4)	1798 (25.6)	148 (26.1)	769 (27.3)	42 (14.3)	405 (27.7)			
No. unique counties	29	35	26	31	23	32			
No. unique communities	378	675	280	556	185	464			
Community type									
City	196 (13.8)	679 (9.7)	38 (6.7)	303 (10.8)	26 (8.9)	177 (12.1)			
Borough	460 (32.3)	2104 (29.9)	147 (25.9)	846 (30.0)	89 (30.4)	429 (29.4)			
Township	763 (53.5)	4215 (59.9)	381 (67.2)	1657 (58.8)	176 (60.1)	846 (58.0)			
Missing	6 (0.4)	40 (0.6)	1 (0.2)	12 (0.4)	2 (0.7)	8 (0.6)			
Community socioeconomic deprivation, SD units, median (IQR)	−0.05 (−2.37, 2.33)	−0.72 (−2.78, 1.92)	−1.05 (−2.93, 1.1)	−0.79 (−2.97, 1.69)	−0.59 (−2.97, 1.65)	−0.74 (−2.62, 2.07)			

Abbreviations: IQR, interquartile range

a Based on six U.S. Census indicators as described in the Methods.

Table 2

Summary of operations by poultry type

Poultry operation type	No. operations (%)	No. counties in which operations are present	Mean AEUs	Median AEUs	AEU IQR
Total operations	304 (100)	16	248	154	101, 250
Broiler	160 (53)	13	164	149	106, 213
Layer	73 (24)	13	416	172	93, 337
Turkey	36 (12)	11	396	227	149, 279
Pullet	26 (9)	9	113	74	38, 151
Duck	12 (4)	4	136	110	51, 158

Abbreviations: AEU, animal equivalent unit; IQR, interquartile range

Table 3

Adjusted[a] associations of the poultry operation activity metric with diarrhea outcomes, stratified by community type

Poultry operation activity quantile[b] (range, AEU per kilometer² × 10)	Township		Borough		City	
	AOR (CI)	P	AOR (CI)	P	AOR (CI)	P
	Non-specific Diarrhea					
	n = 64,752		n = 33,963		n = 13,580	
1 (0–0.08)	ref		ref		ref	
2 (0.08–0.15)	1.08 (1.01, 1.16)	0.02	1.05 (0.96, 1.14)	0.33	0.85 (0.77, 0.93)	0.001
3 (0.15–0.58)	1.04 (0.98, 1.11)	0.20	1.06 (0.96, 1.17)	0.23	0.52 (0.41, 0.65)	<0.001
4 (0.58–702.62)	1.10 (1.03, 1.19)	0.01	1.12 (1.01, 1.24)	0.03	0.94 (0.82, 1.07)	0.36
	Infectious Diarrhea					
	n = 2815		n = 1366		n=481	
1 (0–0.08)	ref		ref		ref	
2 (0.08–0.15)	1.51 (0.99, 2.31)	0.06	2.12 (1.14, 3.97)	0.02	1.90 (1.08, 3.34)	0.03
3 (0.15–0.58)	1.57 (0.93, 2.64)	0.09	2.55 (1.11, 5.87)	0.03	0.53 (0.18, 1.62)	0.27
4 (0.58–96.61)	1.71 (1.02, 2.85)	0.04	1.50 (0.89, 2.51)	0.13	1.48 (0.57, 3.83)	0.43
	E. coli					
	n = 4978		n =2564		n = 875	
1 (0–0.08)	ref		ref		ref	
2 (0.08–0.15)	1.11 (0.71, 1.74)	0.65	0.62 (0.38, 1.01)	0.06	1.14 (0.76, 1.70)	0.53
3 (0.15–0.58)	1.28 (0.85, 1.95)	0.24	0.97 (0.66, 1.41)	0.86	0.69 (0.25, 1.92)	0.48
4 (0.58–103.11)	1.61 (0.95, 2.72)	0.08	1.02 (0.62, 1.66)	0.95	1.50 (0.86, 2.60)	0.15
	Campylobacter					

Poultry operation activity quantile[b] (range, AEU per kilometer^2 × 10)	Township		Borough		City	
	AOR (CI)	P	AOR (CI)	P	AOR (CI)	P
	n = 2038		n = 993		n = 341	
1 (0–0.08)	ref		ref		ref	
2 (0.08–0.15)	1.29 (0.87, 1.92)	0.21	1.71 (1.08, 2.73)	0.02	1.19 (0.54, 2.61)	0.67
3 (0.15–0.58)	1.69 (1.15, 2.50)	0.01	0.93 (0.44, 1.99)	0.85	0.60 (0.10, 3.57)	0.57
4 (0.58–70.97)	2.03 (1.40, 2.95)	<0.001	1.30 (0.80, 2.11)	0.29	0.96 (0.32, 2.86)	0.9
Salmonella[c]						
	n = 1022		n = 518		n = 203	
1 (0–0.09)	ref		ref		ref	
2 (0.09–0.42)	0.83 (0.54, 1.27)	0.39	0.96 (0.52, 1.77)	0.89	0.33 (0.13, 0.88)	0.03
3 (0.42–55.17)	1.17 (0.74, 1.83)	0.51	1.39 (0.78, 2.48)	0.27	1.00 (0.32, 3.13)	0.99

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; P, p-value; ref, reference group

[a] Multivariable logistic regression models controlled for age, sex, race/ethnicity, Medical Assistance, and smoking status, as described in *Methods*. Non-specific diarrhea model also adjusted for centered age squared.

[b] Poultry operation activity took into account the number of poultry operations in study area, distance between each patient's residence and poultry operations, and number (in AEUs) of poultry at each operation. Activity increased over each quantile, with the lowest activity in quantile 1 (the reference category), as described in *Methods*.

[c] For *Salmonella*, poultry operation activity quantiles were re-categorized as tertiles due to low cell counts in stratified models