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Industrial Food Animal Production and Community Health

Joan A. Casey[1] · **Brent F. Kim**[2] · **Jesper Larsen**[3] · **Lance B. Price**[4,5] · **Keeve E. Nachman**[6]

Abstract Industrial food animal production (IFAP) is a source of environmental microbial and chemical hazards. A growing body of literature suggests that populations living near these operations and manure-applied crop fields are at elevated risk for several health outcomes. We reviewed the literature published since 2000 and identified four health outcomes consistently and positively associated with living near IFAP: respiratory outcomes, methicillin-resistant *Staphylococcus aureus* (MRSA), Q fever, and stress/mood. We found moderate evidence of an association of IFAP with quality of life and limited evidence of an association with cognitive impairment, *Clostridium difficile*, *Enterococcus*, birth outcomes, and hypertension. Distance-based exposure metrics were used by 17/33 studies reviewed. Future work should investigate exposure through drinking water and must improve exposure assessment with direct environmental sampling, modeling, and high-resolution DNA typing methods. Investigators should not limit study to high-profile pathogens like MRSA but include a broader range of pathogens, as well as other disease outcomes.

Keywords IFAP · CAFOs · Air pollution · Asthma · Zoonotic disease · Odor

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✉ Joan A. Casey
joanacasey@berkeley.edu

Brent F. Kim
bkim40@jhu.edu

Jesper Larsen
jrl@ssi.dk

Lance B. Price
lprice@gwu.edu

Keeve E. Nachman
knachma1@jhu.edu

1 Robert Wood Johnson Foundation Health and Society Scholars Program, UC San Francisco and UC Berkeley, 50 University Hall, Room 583, Berkeley, CA 94720-7360, USA

2 Department of Environmental Health Sciences and Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA

3 Microbiology and Infection Control, Statens Serum Institut, 5 Artillerivej, 2300 Copenhagen S, Denmark

4 George Washington University, 950 New Hampshire Avenue 713, Floor 7, Washington, DC 20052, USA

5 Pathogen Genomics Division, Translational Genomics Research Institute, Flagstaff, AZ, USA

6 Department of Environmental Health Sciences, Center for a Livable Future, and Risk Sciences and Public Policy Institute, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room W7013, Baltimore, MD 21205, USA

Introduction

The 20th century saw unprecedented transformation in the scale and practices associated with food animal agriculture. The resulting industrial model first emerged in US poultry production over the 1930s–1950s [1], with parallel developments in Europe [2]. Industrial food animal production (IFAP) today [2] is characterized by large-scale, highly specialized, densely stocked operations designed to maximize output at minimal cost to producers. In the USA, for example, the majority of swine and laying hens are confined to operations with inventories of over 5000 swine or 100,000 birds [3]. Production relies heavily on inputs, including specially formulated feeds, pharmaceuticals, and synthetic hormones (in cattle), the use of which has been implicated in the presence of environmental, occupational, and/or food-borne hazards [4, 5]. This model has become increasingly globalized, with multinational

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corporations expanding operations in Southeast Asia, Mexico, Eastern Europe, and other parts of the world [1, 6].

Figure 1 illustrates how IFAP can lead to adverse health effects in nearby communities via the generation and spread of microbial and chemical hazards. Studies have identified bacterial pathogens, such as antibiotic-resistant strains of *Staphylococcus* and *Enterococcus*, in and around IFAP operations, including colonizing animals and surfaces [7–10], in manure [11–16], and carried by flies [17, 18] and rats [19] near operations. IFAP is also a source of airborne pathogens [8, 20–22], endotoxins [23], particulate matter (PM) [24], hydrogen sulfide (H_2S), ammonia, odorous chemicals, and other contaminants [23, 25–28], which may be spread from operations to the downwind environment, e.g., via ventilation fans and emissions from decomposing manure [7, 8, 26, 27, 29–32]. IFAP workers are subject to heightened exposures to these hazards and have been shown to exhibit elevated rates of respiratory illness [33, 34], psychological distress [35, 36], and colonization/infection with resistant pathogens [5, 37, 38], the latter potentially transmissible to workers' communities. Spreading IFAP waste on agricultural fields—a common method of disposal—presents further opportunities for microbial [13, 39–43] and chemical [44] contaminants (e.g., nitrates, antibiotic residues, heavy metals, and excreted hormones) to be transported through environmental media, including ground and surface waters. Failed containment and extreme weather events may also lead to the discharge of stored waste into nearby water sources [45]. Taken together, these and other exposure pathways have been implicated in adverse health outcomes among nearby residents.

The breadth of research on the community health effects associated with IFAP has not been the subject of a recent review [46–49]. A 2010 systematic review [49] examined evidence of respiratory, gastrointestinal, and mental health outcomes; however, this review reflects a limited subset of the broader body of research. Furthermore, the review was funded by two major industry groups and may have been subject to bias from competing interests.

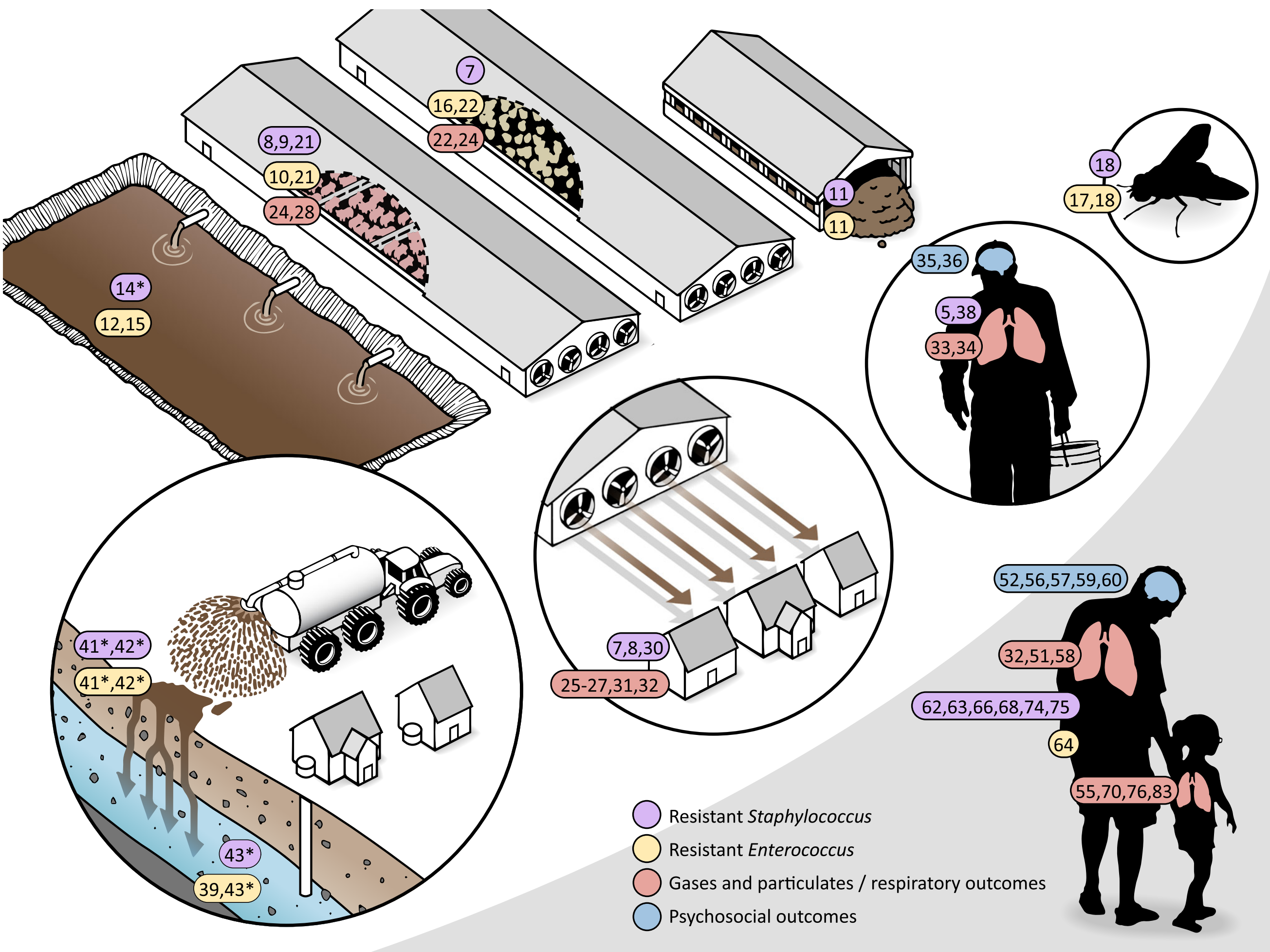

Fig. 1 Studies that document selected hazards associated with IFAP, illustrating potential pathways through the environment, and adverse health outcomes in nearby populations. *Numbers* indicate study citations. *Study investigated the presence of resistance genes, which could be acquired by *S. aureus*, *Enterococcus*, or other pathogens

For this review, we identified studies published after the year 2000 by searching PubMed and Google Scholar using key words related to animal production including IFAP, concentrated animal feeding operation (CAFO), livestock operation, and agriculture and key words related to health outcomes, including health, infection, asthma, stress, and aquatic health. We scanned the reference lists of the identified studies for additional papers missed by our search strategy. We included all studies that addressed health outcomes, either clinical or subclinical, either in humans or in animals. Several related areas of research were excluded or mentioned only briefly because they were beyond the scope of this review: studies of people living or working on a farm, measurement of environmental hazards without an associated health outcome, exposures related to meat consumption, issues of environmental justice, and climate change implications. In this article, we review 33 studies completed since 2000, identified from our search of the scientific literature, that characterize health effects in communities near IFAP. We also discuss methodological challenges, policy implications, and future research directions.

Exposure Assessment

Both infectious and noninfectious disease can occur as a result of a single exposure via a single pathway, but more commonly, diseases are multifactorial and several pathways may act simultaneously (e.g., odor, air pollution, weather, community characteristics, and socioeconomic status) to influence the relationship between IFAP and health outcomes. This systemic causation partially explains why few studies have linked direct environmental measurements to human health outcomes [50•, 51, 52]. Studies have used a variety of tools to assign exposure to study populations: self-report, aggregation to a specified geographical area, distance-based methods, interpolation from sampled points to estimate those not sampled, direct environmental sampling, and microbiologic methods [53] (Fig. 2a).

Self-Report

To evaluate exposures, many studies asked participants to report presence, severity, and/or duration of livestock odor [27, 50•, 51, 52, 54–56]. Four studies, two in Germany [57, 58] and two in the Netherlands [59, 60], asked participants about annoyance due to livestock odor. Few studies used self-reported livestock odor as the only exposure variable [56, 57]; many also incorporated direct measurements or used dispersion modeling to estimate individual-level exposure [27, 50•, 51, 52, 59, 60]. Self-reported odor has the potential to bias estimates away from the null if those experiencing health outcomes are more aware of and report more exposure, a particular issue with retrospective data collection (i.e., recall bias) [61]. Study design can reduce risk of bias. For example, Deiters et al. and Larsen et al. [62, 63•] supplemented self-reported livestock contact with microbiologic analysis of methicillin-resistant *Staphylococcus aureus* (MRSA) strains.

Geographical Aggregation

Five studies aggregated IFAP exposure to the zip code [64, 65], municipality [63•, 66], or county [67] level. Two included population density to account for differences in characteristics of the aggregated units that might influence the outcome [66, 67]. Feingold et al. also assessed spatial variation in risk and clustering of livestock-associated MRSA cases.

Distance-Based Exposure and Interpolation

Likely due to simplicity, interpretability, and data availability, distance-based measures were the most common way to estimate exposure (17/33 studies reviewed). Three types of distance metrics were used: (1) buffers around IFAP with radii varying from 800 to 3200 m [54, 56, 57, 64, 68–71], (2) proximity measures [55, 58, 72, 73], and (3) gravity models (i.e., inverse distance-squared model) [74–77]. Pavilonis et al. [76] also incorporated wind direction in their gravity model [76].

In regions where some air pollution monitors are available, but not at the study subject's exact residence, researchers have estimated exposure using validated [78] local and long-range models [59, 60].

Direct Environmental Sampling

Direct sampling most closely captures human exposure. Researchers in North Carolina set up a central monitoring trailer for 2 weeks in study participants' neighborhoods and continuously measured H_2S, semivolatile PM_{10}, and PM_{10} [27, 50•, 51, 52]. In 2008, Wing et al. reported a significant positive association between H_2S concentration and self-reported odor, adding credence to studies using self-reported odor as an exposure measure [27]. In a comprehensive investigation of a Q fever outbreak that originated at a goat dairy in the Netherlands, Hackert et al. took environmental samples from the barn; blood samples from veterinarians, farmers, and their close contacts; and aerosamples 1000 m from the barn to characterize many phases of exposure [79•].

Microbiologic

Microorganisms sampled from IFAP and the community must be characterized with high-resolution DNA typing methods to determine whether isolates found in people with no livestock exposure are linked to the livestock reservoir. Over the years, several typing methods have been used, including phenotypic

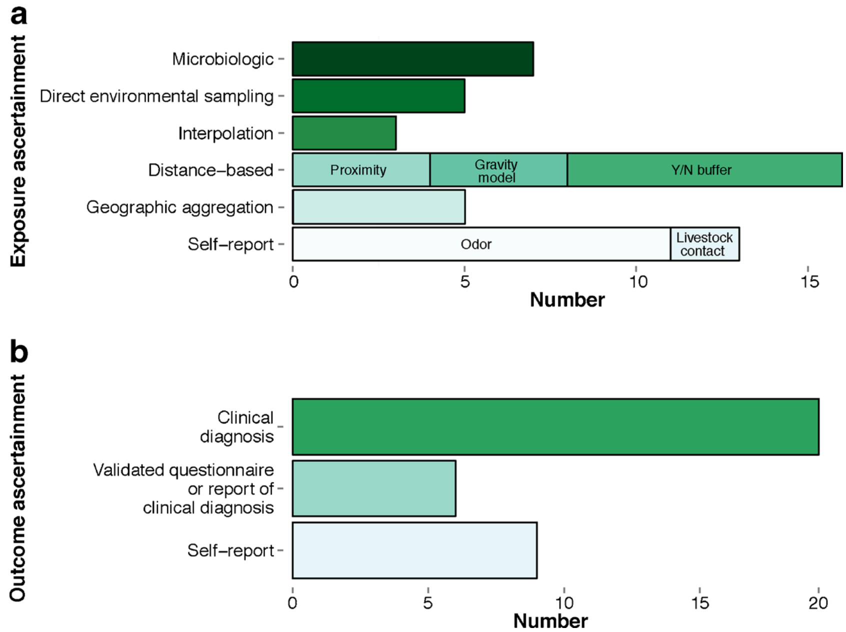

Fig. 2 Methods of exposure assessment and outcome ascertainment in reviewed health outcome research since 2000. **a** Main method of exposure assessment (n=33 studies); all are mutually exclusive except for self-report, which complemented other methods in many studies. **b** Main method of outcome ascertainment (n=33 studies); all are mutually exclusive

characterization, DNA fingerprinting, single-locus and multilocus sequence typing, DNA microarrays, optical mapping, and whole-genome sequence typing (WGST) [80]. The increased use of WGST is bound to improve our understanding of the relationship of microorganisms at the animal-human interface in the coming years. Its discriminatory power has already been shown in a number of retrospective outbreak investigations, but the technology still has to be translated from a research tool into one that is useful in routine surveillance programs and early warning systems.

Outcome Ascertainment

In studies reviewed, outcome ascertainment methods were less variable than exposure assessment. Researchers used just three types: self-reported outcome, self-report of clinical outcome or a validated questionnaire, or a medically documented clinical diagnosis (Fig. 2b). Clinical diagnoses were most common (18/33 reviewed studies) and the only method used for zoonotic pathogen research.

Empirical Work on IFAP and Health Outcomes

Respiratory Outcomes

A small number of studies in a few locations (Iowa [70, 76] and North Carolina [50•, 51, 55] in the USA, as well as northwestern Germany [32, 58] and the Netherlands [77]) have examined relationships between IFAP and the occurrence of respiratory outcomes in nearby residents or schoolchildren. All studies included swine operations, though some also included other animal species (chickens, cows, goats, sheep, and mink).

Assessed respiratory outcomes varied across studies. Most studies used self-reported wheeze/whistle, medication use or prescription, or asthma diagnosis, collected through questionnaires [32, 51, 55, 58, 70, 76]. Fewer studies also used objective clinical measurements of lung function, including forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) or clinical diagnosis codes [32, 51, 58, 77]. A study of children attending schools near IFAP examined functional limitations (in the form of missed school or activity limitations) stemming from asthma symptoms [55].

With some exceptions, the limited available evidence suggests a relationship between exposures to air pollutants from IFAP and respiratory morbidity (Table 1). One strength of this small database includes the notion that using multiple variations of exposure assessment (proximity- or density/gravity-based, objective pollutant measurement, and subjective odor monitoring) yields generally consistent relationships between exposures and outcomes related to asthma (diagnosis, wheeze, and medication use). Another strength is that many of the observed effects (asthma, wheezing, and COPD) are consistent with those seen in hog confinement workers who are more highly exposed [81]. Despite these strengths, some limitations exist, especially in regard to study design; the majority of the studies available are cross sectional. Only one prospective cohort study of respiratory outcomes was identified [51], and while its findings were consistent with other findings, the overall confidence in the relationships would be bolstered with additional prospective studies. In addition, the literature has focused on swine, making it difficult to draw conclusions

Table 1 Summary of health outcomes and proportion of studies reporting an association between living near industrial food animal production and poor health outcomes

Health outcome	Study design	Proportion with greater than or equal to one significant association with IFAP	Weight of evidence	References
Respiratory				
Asthma	Observational/Cross sectional	3/4		[51, 58, 70, 76, 77]
	Longitudinal	1/1		
Wheeze	Observational/Cross sectional	2/4	Mostly consistent evidence of an association, stronger for asthma and lung function	[32, 51, 55, 58, 70]
	Longitudinal	1/1		
Lung function (FEV_1, PEF, and COPD)	Observational/Cross sectional	2/3		[32, 51, 58, 77]
	Longitudinal	1/1		
Allergic rhinitis	Observational/Cross sectional	1/3		[32, 58, 77]
Cognitive impairment	Experimental	0/1	Weak evidence of an association	[69, 87]
	Observational/Cross sectional	1/1		
Stress/Mood	Experimental	0/1	Sufficient evidence of an association	[52, 54, 59, 60, 69, 87, 88]
	Cross sectional	4/4		
	Longitudinal	2/2		
Quality of life and activities of daily living	Ethnography	1/1	Moderate evidence of an association	[27, 56, 57, 59, 71]
	Observational/Cross sectional	4/4		
Zoonotic disease				
MRSA	Observational	6/6	Sufficient evidence of an association	[62, 63•, 66, 68, 74, 75]
C. difficile	Observational/Longitudinal (humans) and Observational (swine)	1/1	Insufficient evidence of an association	[85]
Enterococcus	Observational	1/1	Insufficient evidence of an association	[64]
Q fever	Observational/Cross sectional	1/1	Sufficient evidence of an association	[72, 73, 79•]
	Longitudinal	2/2		
Birth outcomes	Ecologic	1/6	Insufficient evidence of an association	[65, 67]
Blood pressure	Observational/Longitudinal, short term	1/1	Weak evidence of an association	[50•]

about broiler, egg layer, cattle, and dairy operations with regard to respiratory health. Of the few studies that relied upon objective pollutant measurements to characterize exposure, H_2S and fine PM were found to be predictors of reporting chest tightness and wheeze, respectively [51]; a different study relying on interpolated estimates of measured ammonia concentrations did not find significant associations with wheeze [32].

Two other studies painted a blurrier picture of the relationship between IFAP and respiratory outcomes. One study which built upon an earlier investigation that did find significant relationships relied upon interpolated ammonia exposures from area monitors to assign exposure and did not find associations with wheeze or allergic rhinitis but did show a significant increase in allergen sensitization and a significant decrease in FEV_1 [32]. Another study in the Netherlands used electronic health records and multiple methods of farm pollution exposure assessment and found significant inverse relationships with asthma, allergic rhinitis, and COPD [77].

The European GABRIEL Advanced Studies have shown a protective effect against asthma and atopic sensitization for children who grew up on a farm that both raised cows and cultivated feed crops, though associations were less clear for atopy [82]. In contrast, research in Iowa found higher prevalence of asthma among children growing up on a farm raising swine (with an elevated effect for swine farms that use antibiotics), even among those with lower rates of atopy and personal histories of allergies [83]. Many studies of respiratory outcomes in our database did not account for farm contact/residence in assessment of relationships between respiratory outcomes and animal operations.

Zoonotic Diseases in Humans Living in Close Proximity to IFAP

IFAP is an enormous reservoir of zoonotic bacteria (including those resistant to important antimicrobials for human use) such as *Salmonella* spp., *Campylobacter* spp., *Escherichia coli*, and *Enterococcus* spp., *Coxiella burnetii*, *S. aureus* (including MRSA), and *Clostridium difficile*. Although food animals are the primary hosts of these microorganisms, they may also be present in IFAP workers and in the surrounding environment, which could put people living in close proximity at risk for acquisition and infection.

In particular, *C. burnetii*, the cause of Q fever in humans, and MRSA have been increasingly recognized as important pathogens in people living near IFAP. Sheep, goats, and cattle are considered the most common reservoirs of *C. burnetii*, which is excreted in milk, urine, feces, and birth material from infected animals [84]. In the Netherlands, Smit et al. demonstrated a strong association between human Q fever and the number of goats within a 5-km radius of the residential address [73]. In another study of a large single-point source outbreak of Q fever in the Netherlands, Hackert et al. showed that most community cases were scattered downwind from the index farm and that the risk of *C. burnetii* exposure and development of Q fever increased with residential proximity to the index farm [79•]. Most recently, Hermans et al. demonstrated a strong spatiotemporal relationship between residential proximity to goat-manure-applied crop fields and human Q fever in the Netherlands [72]. Taken together, these studies support the conclusion that exposure to a contaminated environment is a primary source of Q fever in community settings.

Several studies from Europe have shown that the distribution of human cases of MRSA strains belonging to clonal complex 398 (MRSA CC398) is concentrated in rural areas where food animals are raised [62, 63•, 66]. Worryingly, a substantial proportion of these people have no direct animal contact, suggesting that MRSA CC398 is spreading from IFAP into surrounding communities [62, 63•, 66]. In Denmark, living in the same municipality as an IFAP worker with MRSA CC398 infection was associated with a 2.5-fold higher risk of developing an MRSA CC398 infection in the general population [63•]. It remains unclear how spread into the community occurs. While MRSA usually spreads through human-to-human contact, it is possible that other modes of transmission play a role, including spread via contaminated environmental media, pests, and fomites. A study from Germany found low numbers of MRSA CC398 in air samples (<15 bacteria/m^3) and on soil surfaces downwind of IFAP operations [8]. It is unknown, however, whether these concentrations are high enough to represent a risk for human acquisition and development of infection. In the USA, living in close proximity to IFAP operations and manure fields has been associated with an increased overall risk of MRSA infection and carriage [68, 74]. Nearby IFAP operations and manure fields were not sampled and MRSA isolates from the patient populations were not available for typing due to the retrospective study designs, thereby hindering molecular tracking of the source. In a prospective study, some MRSA types seemed to predominate in people living in close proximity to IFAP [75], but again, there was no sampling of local IFAP operations. US studies were unable to directly control for livestock contact and therefore did not exclude IFAP workers from the analysis. However, Casey et al. showed that adjusting for the prevalence of livestock workers at the community level did not change the results [74].

Only a few studies have investigated whether other microorganisms can spread from IFAP into the surrounding communities. In the Netherlands, Goorhuis et al. found that the human infections with *C. difficile* ribotype 078 were concentrated in more rural areas where pigs are raised and that isolates from pigs and humans were closely genetically related [85]. Kelesidis and Chow showed that daptomycin-nonsusceptible enterococci cases lived in close proximity to animal and crop operations in Los Angeles County, but this study did not attempt to track the source of these microorganisms [64]. Conversely, Odoi et al. found no link between cattle density or intensity of manure application IFAP and human *Giardia lamblia* infection in Ontario [86].

Few studies have directly measured the transmission of antibiotic-resistant zoonotic pathogens into communities proximal to livestock production. The most robust studies have been conducted on livestock-associated MRSA, and these show strong evidence for transmission to communities near IFAP. Additional studies are needed to assess the risk due to other pathogens resistant to clinically important antibiotics.

Cognitive Impairment, Stress, and Mood

Only two studies evaluated cognitive impairment from exposure to IFAP, providing weak evidence [69, 87]. In an experimental design, Schiffman et al. found no effect of acute (1 h) exposure to swine IFAP air (i.e., air containing elevated levels of H_2S, NH_3, PM, and endotoxin) compared to exposure to 1 h of clean air on attention, memory, or mood [87]. During short-term exposure, volunteers did experience increased headaches, eye irritation, or nausea. Kilburn et al. compared people living <3 km from a hog manure lagoon (n=25) to those living >3 km (n=22), to evaluate chronic exposure to IFAP, and found significantly more neurobehavioral abnormalities in those living <3 km [69]. They also reported worse moods (as measured by the Profile of Mood States, e.g., tension, depression, anger, vigor, fatigue, and confusion) among those living <3 km from manure lagoons. When restricting analysis to those <3 km from a lagoon, shorter distances to a lagoon were not associated with stronger effects, perhaps due to low power, unobserved confounding, or selection bias.

Several studies in the USA have evaluated the effect of exposures to swine IFAP on stress or mood, using cross-sectional [69], experimental [87], and longitudinal designs [52, 54]. Horton et al. used a community-based, longitudinal design among 101 participants living near swine IFAP operations and found self-reported odor, and directly sampled H_2S, and semivolatile PM_{10} were each associated with feelings of stress or annoyance and nervousness or anxiety [52]. In an earlier community-based study, Avery et al. had 15 participants living <1.5 mi from a swine operation take twice-daily salivary samples after rating livestock odor and found evidence that exposure to odor reduced the function of the mucosal immune system (as measured by secretory immunoglobulin A) [54]. Although not directly measured, they hypothesized that this association was mediated by stress caused by odor exposure.

European studies have focused on odor annoyance due to exposure to livestock (i.e., swine, poultry, and cattle) and cross-sectional studies have consistently reported odor annoyance among participants living in areas with high livestock density [58–60, 88], with attenuated affects for those living or working on a farm [57, 59, 60]. Hooiveld et al. also noted that while self-reported symptoms (e.g., respiratory, gastrointestinal, and stress) were associated with higher self-reported odor annoyance, few participants sought health care services to resolve their concerns [88]. This finding highlights the importance of measuring symptoms directly or carefully selecting health outcomes for research that are available in the health care record.

Despite differences in exposure assessment, outcome ascertainment, and study design, six out of seven studies reported at least one significant association between IFAP exposure and cognition, mood, or stress, providing sufficient evidence of an association. Schiffman et al. did not observe any effects of an acute laboratory exposure, suggesting that chronic, unpredictable exposures are more salient [87].

Quality of Life

Three studies in the USA [27, 56, 71] and two in Europe [57, 59] have considered the relationship between odors from IFAP and quality of life. Four of the five studies assessed exposure by proximity to livestock operations and self-reported odor; one used modeled annual ammonia concentration at the household [59]. All studies used self-reported outcomes.

Wing et al. provided early evidence by interviewing 100 individuals in North Carolina who lived near swine or cattle operations and 55 who did not (N=155) [71]. Of all symptoms recorded, the greatest differences between communities were seen on quality of life questions; for example, those living within 2 mi of a swine operation reported being unable to go outside 15.4 times (on average) in the prior 6 months, compared to 2.1 times for those not living near an operation. Radon et al. assessed quality of life with the Short-Form 12 Health Survey (SF-12), a reliable and valid measure of physical and mental health in a variety of contexts. In analyses adjusted for factors like age, sex, schooling, and smoking, they reported a strong association between odor annoyance and reductions in physical and emotional SF-12 scores [57].

Blanes-Vidal et al. found evidence supporting a coping hypothesis: Odor leads to behavioral interference (e.g., disruption of lifestyle or unwanted changes in social behavior), mediated by annoyance perception [59]. In a Danish sample, they reported that modeled ammonia exposure was associated with increased odds of behavioral interference and health risk perception and that odor annoyance mediated 81 and 44 % of the relationships, respectively. Two community-based participatory research projects also found support for this hypothesis where residents living near swine operations commonly changed their activities, including social interactions, physical activities, and sleep, due to odor [27, 56]. Tajik et al. reported that even in the absence of odor, participants felt stress and anxiety regarding the potential impact to daily routines or embarrassment if guests were present when odor occurred [56]. Taken together, these studies provide moderate evidence that exposure to IFAP impacts activities of daily living or quality of life.

Other Studies

Two ecologic studies evaluated the effect of geographically aggregated livestock exposure on indices of infant health and mortality [65, 67]. Sneeringer conducted a time-series analysis using two decades of US, nationwide, county-level data on livestock numbers (i.e., beef, dairy, swine, and poultry) and infant births and deaths [67]. While accounting for county-level confounding variables, she found that a 100,000 head increase in livestock was associated with a 7.3 % increase in county infant mortality rate. No association was seen between livestock count and four birth outcomes: continuous birth weight, low birth weight, 5-min Apgar score, or preterm birth. The author proposed an underlying air pollution mechanism based on several secondary analyses. Similarly, Blake did not find an association between zip code-level counts of dairy cows in the San Joaquin Valley in California and birth weight but found cow density to be associated with higher nitrate levels in well water [65].

We also identified a single study of the relationship between air pollution from animal operations and blood pressure [50•]. Using a case-crossover design, Wing et al. found that, after adjusting for stress, increases in community H_2S measurements, but not PM, were significantly associated with rising systolic blood pressure. This finding provides support for a psychophysiological mechanism where stress from odor triggers physiological response.

Susceptibility/Vulnerability Factors

Certain populations, including the young and old, the immune-compromised, the uninsured, racial and ethnic minorities, and the poor and those living in deprived communities, are at particular risk of health effects from IFAP exposure. These susceptible or vulnerable populations may lack neighborhood resources necessary to buffer or avoid IFAP exposures [89]. Indeed, several studies have suggested that livestock operations are more likely to be sited in communities of color or low socioeconomic status [55, 90–92]. This environmental injustice contributes to health disparities [93].

Aquatic Toxicology Studies

Animals living near IFAP experience similar exposures as humans. Aquatic toxicology studies, which describe effects in high-exposure animals, can inform us about IFAP-associated health risks in both human and animal populations. Several studies have evaluated the effect of steroidal hormones from beef cattle feedlot runoff on aquatic life [94–99]. The body of evidence suggests that androgens, specifically trenbolone acetate used to promote muscle growth in cattle and its metabolites 17α-trenbolone and 17 β-trenbolone, which appear relatively stable in manure [100], bind readily to fish androgen receptors [101] and have been detected in waterways near feedlots [95, 97, 99] and can cause problems in fish.

Leet et al. found that fathead minnows exposed to an IFAP effluent mixture for 45 days were significantly heavier and longer than the controls and further analysis revealed ovaries in the testes of 84 % of exposed males, compared to 0 % of controls [96]. In IFAP ditchwater-exposed wild fish, Leet et al. also observed lower species richness, faster growth, and worse reproductive conditions compared to reference site fish [95]. The authors reported a male-skewed sex ratio in fathead minnows exposed to IFAP ditchwater for their first 6 weeks of life (60.4 ± 3.3 % males in the IFAP-exposed group vs. 48.7 ± 3.9 % males in control group). They did not detect an estrogenic effect (measured by vitelloeginin activity) in fathead minnows during a 7-day in situ exposure, suggesting that androgens might have a greater impact on aquatic life [95]. These ecotoxicological studies could have implications in humans reliant on impacted groundwater.

Methodological Issues in Community Health IFAP Studies

Access to Populations and Health Outcomes

IFAP is usually sited in rural areas, which have lower population densities, more diffuse health care, and a population that may have medical skepticism [102] or indirect involvement in IFAP [103], all of which present potential barriers to their involvement in research. Wing and colleagues in North Carolina have effectively used community-based participatory research [104] to engage community members in academic health research [27, 50•, 51, 52, 54, 56, 71]. In the USA, state and national agencies do not require reporting of most diseases associated with IFAP (with the exception of Q fever), so data acquisition on diseases of interest is challenging. Despite this barrier, most studies utilized a clinically diagnosed outcome (Fig. 2b). Casey et al. used data from the Geisinger Health System, which provides medical care in an area covering 69,000 km^2 to study associations of IFAP and MRSA infection [74, 75]. Databases available in several European countries also enabled studies on individuals dispersed across large geographies.

Exposure Characterization

In comparison to outcome assessment, access to information about IFAP is extremely limited. In the USA, swine and poultry operations are generally vertically integrated, privately owned, and inaccessible to researchers. Unlike in some European countries, almost no information exists about antibiotic type, quantity, or duration of use in US IFAP [105]. Most studies reviewed relied on self-report or distance-based exposure estimates, sometimes paired contemporaneously with self-reported outcomes, potentially biasing results of either or both measurements.

In addition, in the few studies that were able to measure environmental media, samples were restricted to indicator pollutants (e.g., H_2S, PM, or ammonia) or bacteria (e.g., MRSA) [27, 50•, 51, 52]. IFAP exposures are multifactorial, including not only air pollution but also water pollution, odor, and potential impacts on housing values [106] that might have additive, multiplicative, or nonlinear effects on health outcomes.

Establishing Causality

Randomized experiments allow causal inference by allowing us to assume that exposed individuals represent what would have happened to the unexposed if they had been exposed. However, in environmental health, randomizing people to a harmful exposure is not an option. In IFAP research, as in many observational studies [107], it might not be possible to fully account for individual-level characteristics, like income or education, that are also related to health and to living near IFAP (i.e., confounding bias). Additionally, sicker individuals or people with certain health behaviors might be more likely to live near to IFAP (i.e., selection bias).

To investigate how IFAP impacts health, researchers should take advantage of available data, natural experiments [108], and creative sensitivity analyses. Government agencies often collect wind data, which future studies should consider incorporating in distance-based models, since bacteria, antibiotics, and antibiotic-resistant genes are more common downwind from farms [8, 30, 31] and wind can affect the spread of air pollution and odor [25, 31, 109]. In a sensitivity analysis, Casey et al. assessed the odds of an MRSA infection in those living near a manure-applied crop field compared to those living near any crop field and found that risk was only associated with manure-applied crop fields [74]. For acute outcomes, researchers have used cases as their own controls in a short-term longitudinal design to reduce the number of necessary participants and to handle unmeasured confounders [27, 50•, 51, 52, 54, 87]. Long-term longitudinal designs to establish temporality and reduce selection bias are another important step toward causal inference.

Discussion and Future Directions

Some important strides have been made in characterizing the public health burdens placed on communities by IFAP. We found sufficient evidence of an association between living near IFAP and respiratory outcomes, MRSA, Q fever, and stress/mood. To date, much of the existing epidemiologic literature describes investigations that follow on observational, cross-sectional design. While these studies are useful, more prospective studies, especially those that involve primary data collection for both exposures and outcomes, are needed to generate additional, stronger evidence.

In addition, characterization of chemical exposures typically involves measurement of a narrow set of indicator pollutants, while it is well understood that emissions from IFAP operations tend to be complex multipollutant mixtures [81, 110, 111]. More sophisticated approaches that examine the spatiotemporal patterns of mixtures and that may not track well with traditionally used indicator chemicals are needed [112]. Building on improvements in exposure characterization, novel approaches aimed at disentangling the contributions of individual contaminants and multicontaminant synergies within mixtures [113] should be applied in the context of IFAP. These techniques have increasingly been used in the urban context for air pollution research but may also be useful in evaluating exposures to rural mixtures.

Future studies should explicitly investigate community exposure through water pollution. Given the potential for land-applied animal waste to impact groundwater [65, 114–116], and the reliance of rural communities on these sources for drinking water [117], it is prudent to directly consider their potential contributions to morbidity and mortality.

One strength of the existing body of literature is that it includes community-driven studies [50•, 51, 55, 118]; these studies build upon established trust between researchers and communities by meaningfully involving community members to design, conduct, contextualize, and disseminate research [119]. Continued use of this approach holds promise for answering questions relevant to community-identified needs.

In the case of microorganisms, future investigations should not be limited to high-profile antibiotic-resistant pathogens like MRSA but should also include a broader range of potentially infectious microorganisms to quantify the total infectious disease burden borne by people living near IFAP. New studies should include samples from IFAP operations, environmental media, and people with and without direct livestock contact and use high-resolution DNA typing methods to identify the transmission pathways into the community and risk factors for human colonization and infection. In addition, emphasis should be placed upon clinically relevant health outcomes such as infection, rather than colonization, especially for microorganisms where the risk of infection given colonization is not well understood. This knowledge would inform evidence-based intervention strategies to control the spread of these microorganisms into the community.

Conclusions

We reviewed 33 studies of community exposure to IFAP and human health outcomes, 17 published since the last review was conducted in 2010. Residence near IFAP has consistent positive associations with respiratory outcomes, MRSA infection and colonization, Q fever, and stress/mood outcomes. Future research should improve exposure assessment through direct environmental sampling, taking into account pollutant mixtures, and continued efforts at community-based participatory research.

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Compliance with Ethics Guidelines

Conflict of Interest Joan A. Casey, Brent F. Kim, Jesper Larsen, Lance B. Price, and Keeve E. Nachman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This review contains studies by Joan A. Casey and Keeve E. Nachman that used electronic health record data on patients for which IRB approval was received. The review also contains a study by Jesper Larsen and Lance B. Price that used electronic records on humans which was approved by the Danish Data Protection Agency.

This article does not contain any studies with animal subjects performed by any of the authors.

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