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REVIEW

Human diarrhea infections associated with domestic animal husbandry: a systematic review and meta-analysis

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Domestic animal husbandry, a common practice globally, can lead to zoonotic transmission of enteric pathogens. However, this risk has received little attention to date. This systematic review and meta-analysis examines the evidence for an association between domestic exposure to food-producing animals and cases of human diarrhea and specific enteric infections. We performed a systematic review of available literature to examine domestic livestock and poultry as risk factors for diarrhea and applied pre-determined quality criteria. Where possible, we carried out meta-analysis of specific animal–pathogen pairs. We found consistent evidence of a positive association between exposure to domestic food-producing animals and diarrheal illness across a range of animal exposures and enteric pathogens. Out of 29 studies included in the review, 20 (69.0%) reported a positive association between domestic animal exposure and diarrhea. Domestic exposure to poultry revealed a substantial association with human campylobacteriosis (OR 2.73, 95% CI 1.90–3.93). Our results suggest that domestic poultry and livestock exposures are associated with diarrheal illness in humans. Failure to ascertain the microbial cause of disease may mask this effect. Exposure to domestic animals should be considered a risk factor for human diarrheal illness and additional studies may identify potential mitigation strategies to address this risk.

Keywords: Animal husbandry, Diarrhea, Domestic animals, Hygiene, Systematic review

Introduction

Globally, diarrheal diseases kill approximately 1.45 million people per year, and account for 17.4% of infant and 11.9% of early childhood deaths worldwide.[1] Diarrheal diseases are also among the leading causes of malnutrition in children under 2 years of age who live in resource-poor settings.[2] Among the 2.49 billion disability-adjusted life-years (DALYs) in 2010, 3.6% were attributed to diarrhea across all age groups.[3]

Zoonotic transmission of infectious diseases is considered to be a key driver in the current emergence and re-emergence of novel diseases,[4–6] and contact between animals and humans can also increase the occurrence of pathogens already in common circulation via zoonotic transmission pathways. Diarrheal diseases are caused by the transmission of bacterial, parasitic, or viral enteric organisms to humans through the contamination of water or food sources by feces. Environmental contamination from human feces is the predominant risk factor for human diarrhea,[7,8] but zoonotic sources can also be responsible for transmission of diarrheal disease pathogens to humans. Animal feces can contribute to human diarrhea incidence by introducing new zoonotic pathogens that cause diarrheal illness or by increasing transmission of pathogens common to both animals and humans. Several animal hosts are known to be reservoirs of specific diarrheal disease pathogens. For example, poultry animals are associated with transmission of *Campylobacter* spp.[9] and *Salmonella* spp.[9,10] to humans, and ruminants have been identified as the primary animal reservoir for human enterohemorrhagic *Escherichia coli* (EHEC) O157:H7 infections.[9]

The presence of domestic livestock and poultry in close proximity to human beings is common throughout the world but particularly prominent in resource-poor countries, where animal husbandry serves as a primary source of income.[11] Environmental, cultural, and economic factors lead households to keep livestock and poultry within close range of human living quarters, where the animals may be allowed to roam freely and sleep within the home.[12] These conditions increase the potential for fecal contamination by animals within the household environment, and subsequent zoonotic transmission of enteric pathogens harbored by these domestic food-producing animals. In particular, animals have been implicated as a source of fecal contamination of soil.[13,14] This is particularly problematic among young children, in whom fecal-oral transmission may be more common during play. Despite evidence of environmental

contamination, little attention has been paid to this potential zoonotic source of diarrheal diseases in humans.

In this systematic review and meta-analysis, we examine the evidence for an association between domestic exposure to food-producing animals and both human diarrheal cases and infection by specific enteric pathogens. We also consider if there is evidence of specific animal husbandry and hygiene behaviors that are linked to infection and whether possible interventions exist to reduce exposure to diarrheal pathogens through animals.

Methods

Search strategy and inclusion criteria

We systematically searched the National Library of Medicine/PubMed, ISI/Web of Science and Embase literature databases at any time through to 30 September 2013. The search terms were: 'Diarrh*' and 'Animal Husbandry or Livestock or Cattle or Pig or Poultry or Swine or Chicken or Cow or Sheep or Goat or Dairy or Zoonosis or Feces' and 'Household or Domestic or Home or Hygiene'. Additional articles were obtained through hand searches of relevant papers and reviews. For details of the search protocol, see Supplementary Box 1.

Papers were screened by reading titles and abstracts and were included if they examined domestic (or household) livestock and poultry as risk factors for diarrhea. The outcome of interest, diarrhea, was defined broadly as any diarrheal case occurring among any household member (all ages). Specific causal enteric pathogens, if identified, were detailed at a later stage of the analysis. Cross-sectional, cohort and case-control studies were all included. Intervention studies lacking baseline data on the relationship between animal exposure and disease were not considered for inclusion in the meta-analysis because they differed in study design and outcomes measured; there were insufficient intervention studies to consider them independently. Papers were excluded if they related only to: animal pathogens or disease or both; zoonotic potential of domestic pets; zoonotic transmission in the context of an industry or large-scale farming; or human diarrheal illness outside of the context of zoonotic transmission.

The search and review were undertaken by two separate reviewers (LZ and NP). In the case of disagreement, a third reviewer (MF) assessed the article in question to determine its relevance. Relevant articles agreed upon by all reviewers were examined in depth. We applied the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines for epidemiologic reporting of observational studies to gather, assess and report information from studies included in the review.[15]

Quality assessment and grading methodology

We applied the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) methodology to assess the quality of evidence and strength of each individual study.[16] Studies were graded on the basis of the diagnostic and exposure ascertainment methods used to determine strengths and limitations. Studies were graded favorably if a laboratory assay was used to determine or confirm a diagnosis. We awarded points to studies that limited the potential for recall bias by determining household animal exposures through home visits vs questionnaires. We deducted points if studies failed to control for confounders or address selection or recall bias. A more detailed description of the grading methodology is given in Supplementary Box 2 and Supplementary Table 1. Each study could earn a maximum of 8 points and a minimum of −2 points. Relevant data were extracted from each study by LDZ and cross-checked by MCF.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were reported from each study when available. If a study provided a relative risk (RR) only, we calculated ORs if sample sizes of diarrhea cases and animal exposures were provided. If data were not available in the published article to calculate ORs, we contacted authors of these papers to acquire the appropriate data. Studies were excluded if they did not report ORs, did not provide sufficient data to calculate an OR from an RR, and the author did not respond to a request for data.

To gain insights into transmission patterns associated with particular pathogens and animal species, we considered the relationships between specific pathogens and animal exposure pairs separately where possible. We stratified all studies by exposure (poultry, swine, ruminants, goats or sheep) and outcome (*Campylobacter*, EHEC, *Cryptosporidium* or *Giardia* infection or diarrhea case with no laboratory confirmation), resulting in 19 strata (Table 1).

If three or more studies fitted within the same exposure and outcome stratum, we carried out an analysis of heterogeneity and obtained pooled OR estimates. This was ultimately performed for one animal–pathogen pair: '*Campylobacter*–poultry'. Within this stratum, we assessed statistical heterogeneity of results between studies through I^2 and Cochran's Q-tests. We also performed a Breslow–Day test to examine heterogeneity of effect size between studies to report alongside our pooled estimates. These tests examine the degree of inconsistency in the results of studies included in meta-analyses.[15,17] We evaluated age of participants, study location and hygiene practices as potential contributors to any observed heterogeneity. The analysis yielded evidence of heterogeneity (I^2=96.91%) in the pooled stratum, so we used the Mantel–Haenszel random effects method for the meta-analysis as this provides a conservative estimate of the combined effect of animal exposure on reported diarrhea.[17,18] All statistics were calculated using Excel 2007 (Microsoft Corp., Redmond, WA, USA) and SAS V.9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Overview of studies included in review

The search criteria yielded 5835 potentially relevant studies after deleting duplicates, of which 5638 were excluded on the basis of title or abstract review or both (Figure 1).[19] Of the remaining 197 potentially relevant articles, only 29 studies included sufficient data for inclusion in the final systematic review and meta-analysis. The others were excluded for one or a combination of the following reasons: 10 intervention studies lacked relevant baseline data, 75 described molecular evidence for pathogen transmission between animals and humans but did not relate it

Table 1. Data points obtained for each pathogen–animal exposure stratum in a review of 23 studies of Human diarrhea infections associated with domestic animal husbandry. Data were distributed among 19 strata overall, and pooled estimates calculated for strata that had three or more studies

Pathogen	Poultry	Swine	Goat/sheep	Ruminant	Animals (unspecified)	Total
Campylobacter spp.	7	1	1	0	1	10
EHEC/STEC	0	0	1	0	2	3
Unspecified protozoa	0	0	0	0	1	1
Cryptosporidium spp.	1	1	3	1	1	7
Giardia intestinalis	1	0	0	1	3	5
Unspecified pathogen	0	1	0	3	2	6
Total	9	3	5	5	10	

EHEC/STEC: Enterohemorrhagic *Escherichia coli*/shiga-like toxin-secreting *E. coli*.

epidemiologically, 16 descriptive studies had insufficient or non-generalizable data, and five were case studies or anecdotal reports, and 42 were literature reviews. In addition, one study described zoonotic transmission of an enteric pathogen beyond the fecal–oral transmission pathway and 15 described individual reports of fecal–oral transmission of viruses or rare infectious agents.

Of the final 29 relevant articles, 23 were included in the systematic review. Two studies were not included because of the use of a non-comparable effect estimate (incidence density ratios)[20,21] or number of diarrheal episodes rather than number of cases reported.[22] Only our 'Poultry exposure / *Campylobacter* spp. infection' stratum included enough studies (n=7) with sufficient data to evaluate through meta-analysis. A summary of the studies included in the final review is shown in Table 2.

Most papers addressed bacterial pathogens (*Campylobacter* spp.: 10 articles; EHEC: three articles); and protozoal pathogens (*Cryptosporidium* spp.: seven articles; *Giardia intestinalis*: five articles). The remaining six articles did not specify a particular pathogen. Studies assessing specific exposures examined the impact of exposure to domestic poultry (nine studies), swine (three studies), goats and sheep (five studies) and ruminants (five studies). Ten studies did not specify a particular animal of interest, but addressed the broader impact of domestic animal exposure overall. The largest number of studies were carried out in Africa (eight in the Sub-Saharan and four in the Middle East/Northern region), and other regions represented included South America (three studies), Asia (two studies) Oceania (three studies), North America (two studies), and Europe (three studies).

All but one of the 23 studies included in our analysis incorporated water, sanitation and hygiene (WASH) indicators in their analysis. Fifteen studies incorporated indicators for clean water access, six included access to a clean toilet or latrine and eight incorporated food preparation hygiene and food consumption. Because each study controlled for different socioeconomic and WASH indicators, unadjusted estimates were used in our analyses.

Study characteristics and integrity

Approximately equal numbers of cross-sectional, case-control, and cohort studies were included (Table 2). Twenty-three studies incorporated diagnostic approaches (serology, microscopy, or DNA-based methods) to confirm the etiologic agent. Twenty-one studies used some form of interview to gather exposure information and nine incorporated household visits. Researchers in four of the studies that incorporated household visits visited sufficiently often to ascertain the timing of disease status and animal exposures. The grade assigned to each category of assessment (diagnostics, exposure ascertainment and study design/data analysis) is listed with each study on Table 2. Studies that incorporated biological diagnostic assays and mitigated the potential for recall bias for exposures and outcomes through household visits were graded more favorably than studies that did not incorporate these measures. Additional details on point assignment are provided in Supplementary Box 2. On our scale of –2 (worst quality) to +8 (best quality), the mean score was 3.5.

Associations between animal exposure and diarrheal illness

Twenty out of 29 studies (69%) included in our overall analysis reported a significant association between domestic animal husbandry and human diarrheal disease (Figure 2). Among studies that specified causal pathogens, 20 out of 21 (95%) reported a significant positive association between animal exposure and diarrhea. Of the eight studies that did not find an association, six studies (75%) specified neither a causal pathogen nor a diarrheal cause.

Three of the studies included in our final qualitative analysis included animal exposure as the primary exposure of interest;[23–25] one of these focused on the risk of animal exposure in relation to various socioeconomic factors.[24] Animal exposure tended to be analyzed alongside various socioeconomic and water and sanitation indicators.

Of the 29 studies that we included in our qualitative synthesis, only 23 included OR estimates or data from which ORs could be calculated. Our pooled random effects analysis for the relationship between poultry exposure and *Campylobacter* infection revealed an OR of 2.73 (95% CI: 1.90–3.93). There was significant heterogeneity in effect size between studies (Breslow–Day χ^2=17.30, p=0.0082). In addition, analysis of heterogeneity of results between the six studies within the 'poultry/

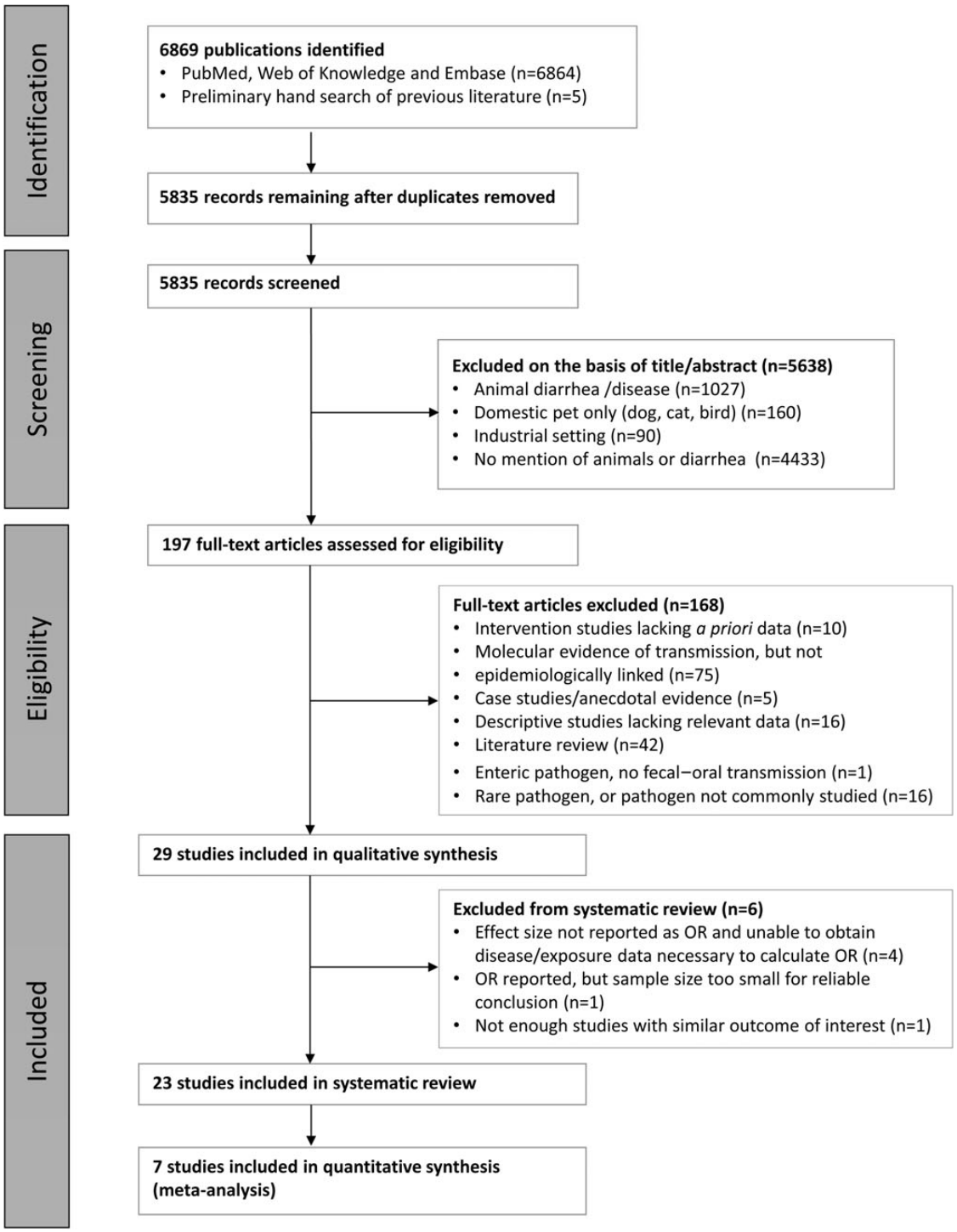

Figure 1. Search procedure for a review of human diarrhea infections associated with domestic animal husbandry. We identified 23 relevant studies with adequate data for inclusion in the systematic review, and seven for inclusion in the meta-analysis.

Campylobacter' stratum yielded an I^2 value of 96.91%, indicating considerable heterogeneity in effect between studies. Despite this, we still performed a meta-analysis as the direction of effect was consistent. It is worth noting that Mantel–Haenszel techniques do not necessarily account for heterogeneity, but that our analysis did describe the average effect of domestic poultry exposure on *Campylobacter* infection found between studies.

While the other animal–pathogen pairs had an insufficient number of studies for quantitative meta-analysis, some trends emerged. Despite having distinct exposure categories

Table 2. Characteristics of 23 studies examining the association between exposure to food-producing animals and diarrhoea

Study	Study design and location	Income class[a]	Quant. review	Pathogen	Population	Subjects (n)	Diagnostic approach (D)	QC	Exposure assessment (E)		Other strengths and limitations (O)	Points	
							Method		Assessment method	Exposure ascertainment		D/E/O	Total
[38]	Cross-sectional study in Accra, Ghana	LMIC	Yes	*Cryptosporidium* spp., various pathogens	Children aged <5 years	227 children	Microscopy and oocyte identification	NS	Interview	NS	NA	1/0/−1	0
[39]	Cross-sectional study in Sana'a City, Yemen	LMIC	Yes	Intestinal protozoa	Outpatients aged 1–80 years with GI complaints at 3 clinical centers	503 patients	Oocyte identification	NS	Questionnaire	NS	Recall bias not addressed	1/0/1	+2
[23]	Cross-sectional study in rural Wisconsin, USA	HIC	Yes	*E. coli* O157:H7	Children aged 1–17 years	215 farm-resident and 396 non-farm resident children	Serology	NS	Population data	NS	Wilcoxon rank-sum used to analyze continuous variable	2/0/1	+3
[20]	Cohort study in Port Moresby, Papau New Guinea	LMIC	No	Not specified	Children aged <5 years	479 children	None	NA	Household visits	Alternate day visits to relate exposure temporally	NA	0/1/4	+5
[40]	Cross-sectional study in Quitafine region, Guinea-Bissau	LIC	Yes	*Cryptosporidium* spp.	Children aged <5 years in 160 households in 8 rural villages	270 children	Oocyst identification	NS	Household visit	NS	NA	1/0/0	+1
[41]	Cohort study in Rahat, Israel	HIC	Yes	*Giardia lamblia*	Infants followed from birth to 18 months	238 infants	Antibody serology	NS	Household visits	Weekly interviews to determine health status	Recall bias is minimized	1/0/5	+6
[42]	Cohort study in Bangui, Central African Republic	LIC	Yes	*Campylobacter* spp.	Children born in a maternity ward, followed for 2 years	111 children	Culture, microscopy	NS	Household visit	Environmental sampling	NA	1/1/0	+2
[43]	Case-control study in Lima, Peru	UMIC	Yes	*Campylobacter jejuni*	Children aged <3 years	104 cases, 104 controls	Culture, microscopy	NS	Interview	NS	NA	1/0/1	+2
[25]	Ismaila province, Egypt	LMIC	No	*Cryptosporidium*, multiple species	Children aged <10 years	165 children	RIDA-QUICK, PCR-RFLP	NS	Household visit	NS	Proportion of children exposed vs unexposed not clear	1/0/4	+5
[22]	Cross-sectional study in Imo State, Nigeria	LMIC	No	NS	Residents in 5 villages	4641 residents in dry season, 5920 in wet season	None	NS	Interview	NS	Not clear whether some residents were enrolled in both seasons	0/0/1	+1
[26]	Cross-sectional study in Hamadan district, Iran	UMIC	No	*Cryptosporidium* spp.	228 participants (all ages)	228 samples	Ziehl–Neelsen oocyst identification	NS	NS	Household visit with animal sampling	Confounding and bias potential not addressed	1/0/0	+1

Continued

Table 2. *Continued*

Study	Study design and location	Income class[a]	Quant. review	Pathogen	Population	Subjects (n)	Diagnostic approach (D)	QC	Exposure assessment (E)		Other strengths and limitations (O)	Points	
							Method		Assessment method	Exposure ascertainment		D/E/O	Total
[24]	Cross-sectional study in Dagoretti, Nairobi, Kenya	LIC	Yes	*Cryptosporidium* spp.	Participants selected for a prior study analyzing risks and benefits of urban dairying	300 dairy households, 100 non-dairy neighboring households	NS	NA	Interview	Environmental sampling	Assessed exposure and risk in context of socioeconomic factors	0/1/4	+5
[44]	Cross-sectional study in Gondar, Ethiopia	LIC	Yes	*Campylobacter* spp.	Diarrheic children aged <5 years who visited teaching hospital	285 total stool samples	Culture, microscopy, dry spot *Campylobacter* test	Yes	Interview	NS	Convenience sample; recall bias not addressed	2/0/1	+3
[27]	Case-control study in Dhaka, Bangladesh	LIC	No	Non-typhoidal *Salmonella*	Medical record review of culture +ve hospital patients	254 cases, 762 controls	Culture and sero-typing	NS	Medical record review	NS	Medical record review may not catch all exposures	1/0/4	+5
[45]	Case-control study in Scotland, UK	HIC	Yes	*E. coli* O157:H7	EHEC cases diagnosed Oct 1996–March 1999 and up to 4 matched controls	183 cases, 545 controls	Laboratory report (no method specified)	NS	Phone and mail questionnaires	NS	Matched controls not found for 36 cases	1/0/4	+5
[32]	Cohort study in Bilbeis, Egypt	LMIC	Yes	NS	Newborns followed for first year	152 infants	Serology/ ELISA	NS	Home visits	NS.	Biweekly home visits to determine diarrhoeal illness	1/0/4	+5
[46]	Cohort study in Bilbeis, Egypt	LMIC	Yes	*Giardia* spp.	Newborns followed for first year	152 infants	Serology/ ELISA	NS	Home visits	NS	Biweekly home visits to determine diarrheal illness	1/0/5	+6
[34]	Cohort study in Bandim II, Bissau, Guinea-Bissau	LIC	Yes	NS	Children aged <4 years in 301 households	648 children	None	N/A	Interviews	Baseline interview	Weekly interviews for disease incidence to avoid recall bias	0/0/5	+5
[33]	Case-control study in 8 villages in Quitafine, Guinea Bissau	LIC	Yes	*Cryptosporidium* spp.	Children aged <4 years in 160 households	125 cases, 125 controls	Microscopy	NS	Interviews	Monthly interviews to determine exposures	Weekly interviews for disease incidence to avoid recall bias	1/1/4	+6
[47]	Cohort study in Pampas de San Juan, Lima, Peru	UMIC	Yes	*Campylobacter* spp.	Families with ≥2 free-roaming chickens and ≥2 children aged <5 years, with ≥1 aged <24 months	423 subjects from 63 families	Culture, microscopy, RAPD, RFLP, serotyping	Yes[b]	Household visit	NS	NA	2/1/2	+5
[48]	Case-control study in England (country-wide)	HIC	Yes	*E. coli* O157:H7	Patients with positive culture at Public Health Laboratory Service labs	369 cases, 511 controls	NS (from laboratory reports)	NS	Mailed questionnaires	NS	Controls were not matched	1/0/2	+3
[49]	Cross-sectional study in Jordan Valley, Jordan	UMIC	Yes	NS	Children aged 0–13 years	197 children	Routine stool analysis	NS	Interviews	Assistants rated cleanliness of home	NA	0/0/1	+1

[50]	Cross-sectional study in Goiania, Goias State, Brazil	UMIC	Yes	*Giardia lamblia*	Children aged 2 weeks–10 years	445	Serology and microscopy	NS	Questionnaire	NS	Convenience sample	1/0/1	+2
[51]	Case-control study throughout Australia	HIC	Yes	*Campylobacter* spp.	All aged ≥5 years	881 cases, 883 controls	Culture	NS	Telephone interview	NS	Potential for recall bias	1/0/2	+3
[52]	Case-control study in Alvsborg County, Sweden	HIC	Yes	*Campylobacter jejuni*, *Campylobacter coli*	County residents with culture-positive campylobacteriosis	101 cases, 198 controls	Microscopy	NS	Phone interview	NS	NA	1/0/2	+3
[53]	Case-control study in Queensland, Australia	HIC	Yes	*Campylobacter jejuni*, *Campylobacter coli*	Children aged 0–35 months	81 cases, 144 controls	Pathology laboratory reports	NS	Questionnaire	NS	Recall bias not addressed for cases	1/1/1	+3
[21]	Cross-sectional study in Khanh Hoa Province, Vietnam	LMIC	No	NS	Children aged <5 years at 2 area hospitals for diarrhea	353 525 individuals, in 75 828 households	None	NA	Census data	NS	NA	0/0/3	+3
[54]	Case-control study in Colorado, USA	HIC	Yes	*Cryptosporidium* spp.	State residents with stool-positive cryptosporidiosis	47 cases, 92 matched controls	Microscopy, PCR for speciation	Yes[b]	Telephone questionnaires	NS	Recall bias not addressed	2/1/2	+5
[55]	Cross-sectional study in Oromia region, Ethiopia	LIC	Yes	*Cryptosporidium* spp., *Giardia duodenalis*	Children in randomly selected households from 2 districts	384 children	Ziehl–Neelsen oocyst identification	Yes[c]	Household visit	Visual inspection	Well-described sampling method	2/0/4	+6

[a] Income classifications based on World Bank 2013 income classifications by country.
[b] Multiple confirmatory assays.
[c] Many quality checks.
HIC: high-income country; LIC: low income country; LMIC: lower middle income country; UMIC: upper middle income country; NS: not specified; QC: quality control; RIDA-QUICK: norovirus test.

Bacterial infections

Reference	No. infected/total: Exposed	Not exposed	Odds ratio (95% CI)
***Campylobacter* spp.**			
Animal not specified			
23	44/67	319/544	2.8 (1.9-4.1)
Poultry			
42[a,c]	20/34	28/77	2.50 (1.08-5.54)
43[a,b]	7/33	8/71	3.20 (CI NS)
44	8/34	10/122	2.87 (1.05-7.84)
47	12/59	22/96	0.86 (0.39-1.90)
51	18/846	5/821	3.6 (1.3-9.7)
52[a]	18/119	3/201	11.83 (3.41-62.03)
53	6/7	81/225	11.80 (1.37-101.75)
Pooled OR	63/252	142/670	2.73 (1.90-3.93)
Swine			
52[a]	7/108	4/202	3.38 (0.84-15.48)
Goat			
42[a,c]	4/5	44/106	5.63 (0.63-27.8)
EHEC/STEC			
Animal not specified			
48	87/149	282/731	2.45 (1.49-4.02)
45	N/A	N/A	4.80 (2.42-9.48)
Sheep			
23	15/21	71/590	2.9 (1.4-6.4)

[a] Unadjusted data reported.
[b] Effect size reported in literature without a confidence interval, but p<0.005.
[c] Effect size in literature reported as RR, but recalculation revealed that RR in literature was, in fact, an OR.

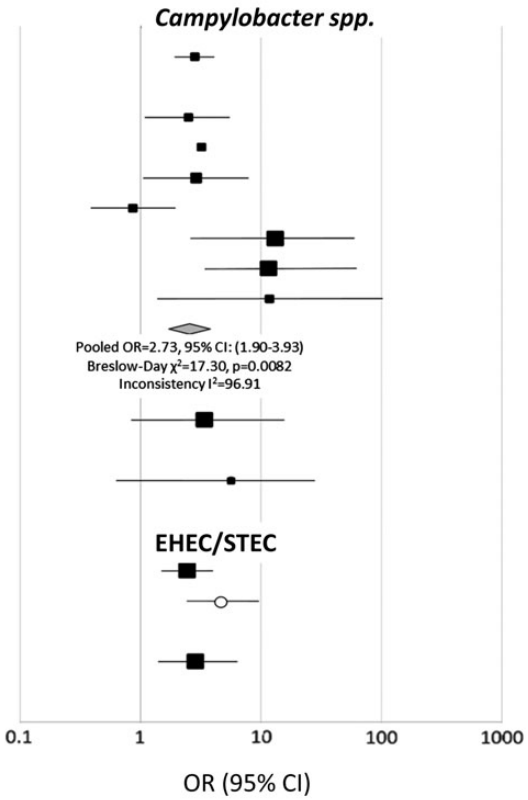

Figure 2. Associations between exposure to domestic food-producing animals and enteric infections with *Campylobacter* spp. and enterohemorrhagic shiga toxin-producing *Escherichia coli* (EHEC/STEC). Data have been separated by specific type of exposure and pathogen of interest. ORs are represented by rectangles of different sizes, according to the grading weight given to each study. Horizontal lines represent 95% CIs. Open circle indicates study for which discrete counts were lacking, but which included ORs. Squares increase in size as study weight ($1/s^2$) increases.

(unspecified animals and sheep), the three studies in the EHEC/STEC disease category all had positive associations with animal exposure (Figure 2). Similarly, four out of five studies examining *Giardia* spp. infection were significantly positively associated with domestic animal exposure (Figure 3). On the other hand, only two out of five studies yielding a significant positive relationship between domestic animal exposure and diarrheal illness attributable to *Cryptosporidium* spp. (Figure 3).

Four out of the six studies deemed ineligible for our quantitative review did not report the effect size as an OR or relevant data from which we could calculate an OR. The results of these studies were therefore not comparable to the other results. One study reported an OR based on two cases and the results were deemed unreliable.[26] Despite these limitations, the results of these studies are worth discussing. In households where animals were present, there was a significant increased risk of diarrheal illness in a cohort study in Papau New Guinea (incidence density ratio [IDR]=1.69, 95% CI: 1.32–2.19).[20] In Egypt, *Cryptosporidium* infections were significantly more likely to be detected in children who had contact with animals in their household (87.3%, 95% CI: 76.4–94.3%) than in children who had no contact (12.7%, 5.7–23.6%).[25] A cross-sectional study in Imo State, Nigeria found a significant protective effect linked with animal exposure (IDR=0.8, 95% CI: 0.7–0.9).[21] In Vietnam, children <5 years old who were hospitalized with diarrhea exhibited no association between animal exposure and diarrheal disease in spatial analysis, even in areas where livestock were most dense (15 747 animals/km^2) (RR: 1.00, 95% CI: 0.84–1.20).[21] Another study in Iran found no significant association between *Cryptosporidium* infection and contact with domestic livestock (OR=0.44, 95% CI: 0.03–7.13); however, this study yielded only two total *Cryptosporidium* cases out of 228 subjects, so these results should be interpreted with care. Finally, a case-control study in Bangladesh found that there was no significant relationship between having animals in the home and non-typhoidal *Salmonella* (NTS) infection (OR=1.03, 95% CI: 0.78–1.37),[27] but as this was the only study that included NTS infection as an outcome, it was not eligible for quantitative synthesis with other studies that focused on bacterial outcomes.

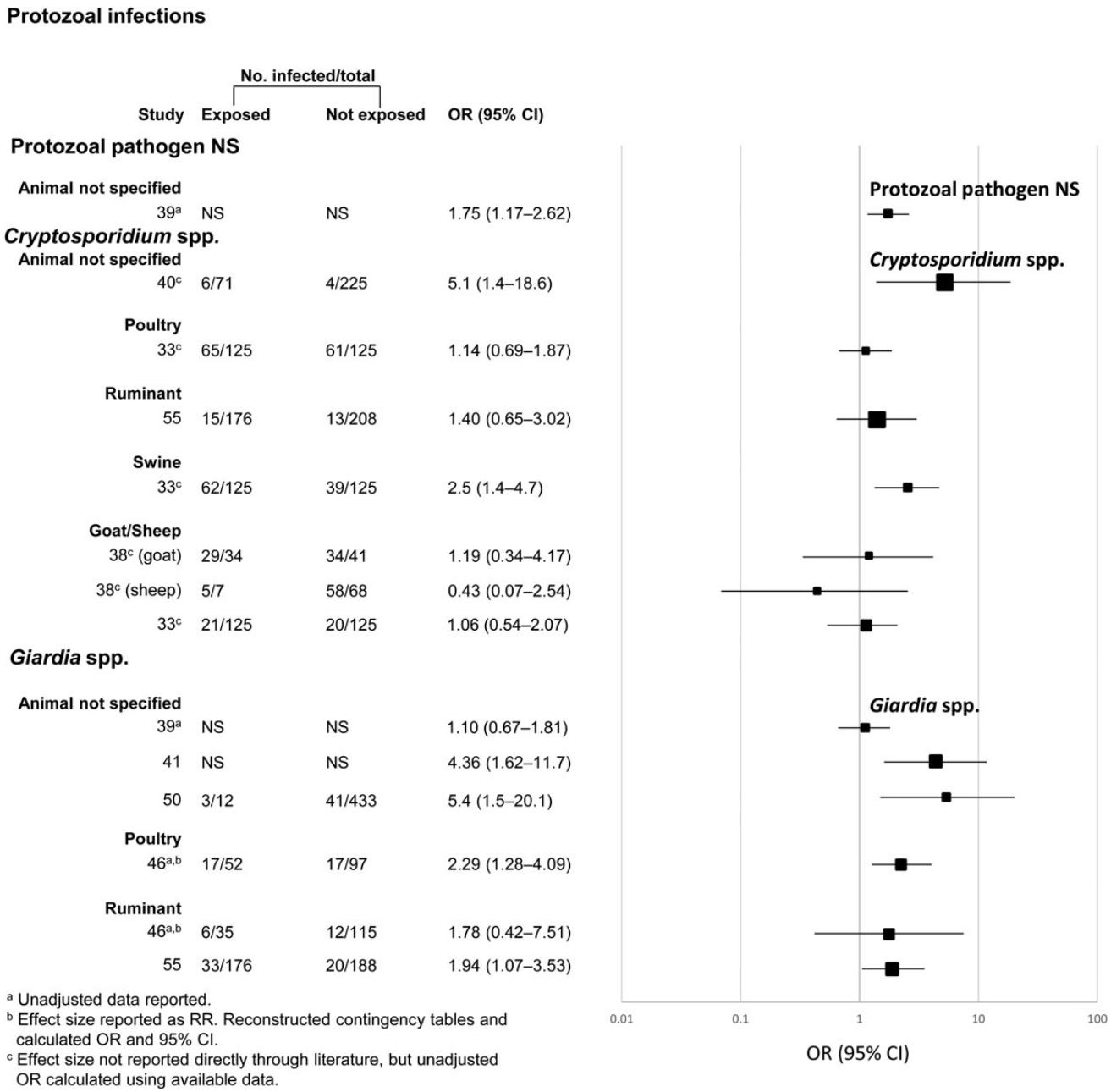

Figure 3. Meta-analysis examining the association between exposure to livestock and infection with *Cryptosporidium* spp. and *Giardia intestinalis*. Data have been separated by specific type of exposure and pathogen of interest. ORs are represented by rectangles of different sizes, according to the grading weight given to each study. Horizontal lines represent 95% CIs. Squares increase in size as study weight ($1/s^2$) increases.

Among the 10 intervention studies identified, the only specific intervention evaluated by more than one study in the literature was corralling of poultry.[12,28–30] One study revealed that children in households with corralled poultry were more likely to have *Campylobacter*-associated diarrhea than those who lived in households with free-roaming poultry (0.57 episodes per year vs 0.27 episodes per year, p=0.006).[29] Another studied revealed that defecation by non-corralled chickens led to increased fecal contamination and increased feces-to-mouth episodes among children under 5 years old.[28] Two other studies examined attitudes to and the social acceptability of poultry corralling, but not the impact of corralling on diarrheal infection.[12,30]

Discussion

This review shows that zoonotic transmission of enteric pathogens in the domestic setting is common, particularly in the context of water contamination by animal excreta. We found consistent evidence of a positive association between domestic

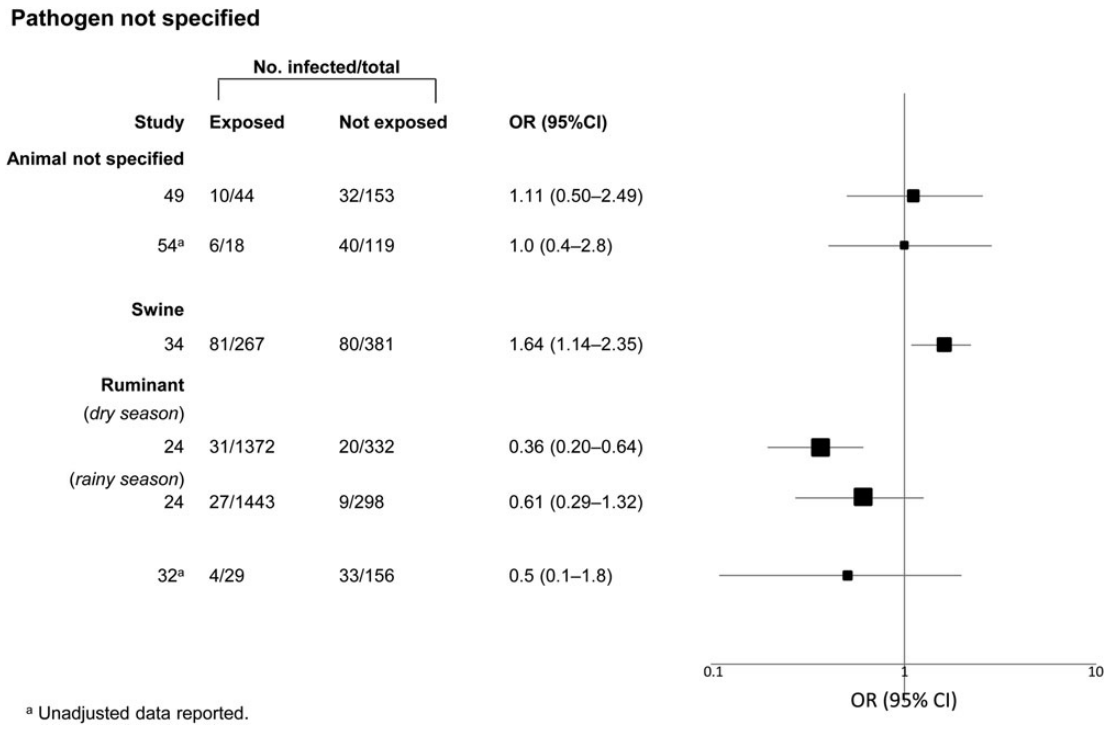

Figure 4. Meta-analysis examining the association between exposure to livestock and diarrheal illness with no specified etiology. Data have been separated by specific type of exposure and pathogen of interest. ORs are represented by rectangles of different sizes, according to the grading weight given to each study. Horizontal lines represent 95% CIs. Squares increase in size as study weight ($1/s^2$) increases.

food-producing animal exposure and diarrheal illness across a range of animal exposures and diarrheal disease pathogens (Figures 2–4). Of the 29 studies included in the full qualitative review, 21 reported a positive association for at least one animal-pathogen pair and only two studies revealed a negative association, or potential protective effect.[22,24] In the one stratum for which we had sufficient studies to carry out a meta-analysis, poultry exposure more than doubled the odds of *Campylobacter* spp. infection. Domestic food-producing animals therefore appear to contribute to enteric pathogen transmission, and zoonotic infection should be considered an important contributor to diarrheal illness. To our knowledge, this is the first systematic review and meta-analysis of the relationship between domestic animal husbandry and diarrheal-related pathogens.

While the overall weight of evidence supported a positive association between domestic food-producing animals and diarrheal disease, we observed heterogeneity in both strength of association and effect size. This could be attributable to factors that differ between the studies, including study design, study location, population sampled, housing and community conditions, hygiene and sanitation, age of the population, nature of the animal exposure and survey methods. The strength of evidence for zoonotic transmission was strongest among studies that elucidated and confirmed a microbial cause of diarrhea through laboratory methods. There were five studies for which no pathogen was specified, and four of these studies found no association between animal exposure and disease. This may indicate the importance of confirming a microbial cause of disease in future studies that examine zoonotic transmission. The limited available data and heterogeneity of effect size between studies, in combination with the strength of the associations observed across studies in the systematic review, highlights the need for more research in this area, especially studies that ascertain the microbial cause of diarrhea.

Our search used three common databases, and was supplemented with hand-searching through the bibliographies of the relevant articles we identified. Despite the strengths of our search methods, this review was limited by the number of relevant articles available. Among the 29 studies included in the qualitative review, only 23 articles could be used for our systematic review, of which only seven studies in the domestic poultry exposure/*Campylobacter* stratum could be subjected to meta-analysis.

In addition to the limited number of articles available for review, we found consistent limitations in the studies we included. On a scale of −2 (worst quality) to +8 (best quality), the mean score for study quality was only 3.5. Most studies used questionnaires or interviews or both to ascertain exposures. Often, questionnaires or interviews were also used to record disease incidence. This practice, while common and relatively simple to implement, may introduce recall and/or interviewer bias.[31] Only in three studies were frequent home visits used to ascertain exposure or disease and thus relate the two temporally;[32–34] this method largely eliminates the risk of recall bias and is recommended for future studies. Several more studies used convenience rather than random sampling, which may contribute to selection bias. The included studies may have been subject to publication bias; however, most of the studies we included assessed animal exposure as an ancillary factor. As animal exposure was the primary or sole exposure of interest in only two[22,24] of these studies, the risk of publication bias was probably minimal.

This review identified several gaps in the available literature on the link between domestic animal husbandry practices and transmission of enteric pathogens. In addition to the 29 relevant articles we found, another 75 articles revealed compelling molecular evidence that identical bacterial and protozoal strains existed in both domestic animals and humans; however, as these data were not epidemiologically linked, they were outside the scope of this review. Molecular epidemiological evidence of transmission, such as that reported in Helmy et al.,[25] would offer additional insights into disease transmission across species.

Our review revealed the need to identify animal husbandry practices that might limit zoonotic transmission. All three studies that evaluated poultry corralling, despite being conducted by different researchers, were performed in and around Lima, Peru, and had inconclusive results. We found no intervention studies that assessed measures to limit exposures to ruminant, goat, sheep and swine feces. There is considerable evidence of the part played by improvements in water, sanitation, and hygiene (WASH) in reducing diarrheal morbidity and mortality, [35–37] and WASH interventions may mitigate pathogen exposure from domestic food-producing animals, but this link has not been adequately explored. No study in this review focused on WASH as a means of limiting disease transmission from animals.

Conclusions

Domestic animal husbandry is critical for the development of communities and economic viability of families, especially in developing countries, and the results of this review should not be taken to suggest cessation of domestic animal husbandry. However, it is important to understand that raising food-producing animals in domestic environments is not without human health risks. More comprehensive research is needed on specific behaviors surrounding animal husbandry that may affect transmission of pathogens between animals and humans; this would facilitate the design and implementation of measures to reduce animal exposure in the domestic environment. Further WASH research should incorporate animals as potential sources of contamination. Clarification of behaviors and community attitudes toward various husbandry practices will help us understand how risk of transmission develops within a household, and how interventions can best be directed. Particularly useful would be reports of observed and self-reported behaviors of humans and animals near the home, presence and state of corralling structures for animals, and individual approaches toward various animal husbandry practices.

Supplementary data

Supplementary data are available at *Transactions Online* (http://trstmh.oxfordjournals.org/).

Authors' contributions: MCF conceived the study; MCF, KL, NPM and LDZ designed the study protocol; LDZ and NPM carried out the literature review; LDZ analyzed and interpreted the data; LDZ wrote the manuscript; MCF and KL critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. MCF and LDZ are the guarantors of the paper.

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