

1 A Spatial Analysis of Giardiasis and Cryptosporidiosis in Relation
2 to Public Water Supply Distribution in North West England

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6 Colour figures in print not required

7 Keywords: Cryptosporidiosis, gastrointestinal disease, giardiasis, Public health, surveillance, Spa-
8 tial analysis

9 Abstract

10 Giardia and Cryptosporidium are both waterborne parasites and leading causes of gastroenteritis.
11 Although specimens from diarrhoeic patients are routinely examined for Cryptosporidium, they
12 are often not examined for Giardia so many cases go undiagnosed. Since 2002, all faecal specimens
13 in Central Lancashire have been tested for infection with Giardia and Cryptosporidium. The aim
14 of this paper is to gain insight into the factors contributing to giardiasis and cryptosporidiosis,
15 including evidence of transmission via drinking water. Our analysis found age to be an important
16 factor for both conditions with a higher risk for young children and a second peak in risk of
17 giardiasis in adults. There was a significantly higher risk of giardiasis for males and a higher risk of
18 cryptosporidiosis for females. The geographical location was significant, showing an increased risk
19 in the north. For one of the water treatment works studied, residence in an area with increased
20 supply was a significant predictor for cryptosporidiosis but not giardiasis.

21 Introduction

22 Giardiasis and cryptosporidiosis are parasitic diseases caused by the protozoa *Giardia duodenalis*
23 (also called *Giardia lamblia* or *Giardia intestinalis*) and Cryptosporidium respectively. They are
24 leading causes of human gastroenteritis worldwide. Both are waterborne parasites with similar
25 reservoirs and transmission routes. The principal risk factors for infection are foreign travel, con-
26 tact with fresh water, countryside activities or person-to-person transmission (Kabore et al., 2010;
27 Hunter et al., 2004). The protozoa are transmitted via human or animal faeces that has found its
28 way into drinking water or food (Sopwith et al., 2005). Zoonotic transmission of Cryptosporid-
29 ium is well established (Chalmers and Giles, 2010) and giardiasis has been associated with farm
30 animal contact (Warburton et al., 1994). Waterborne outbreaks of giardiasis can occur (Nygård
31 et al., 2006) and giardiasis has been associated with consumption of mains tap water in South West
32 England (Stuart et al., 2003) and North West England (Minetti et al., 2015).

33 Giardiasis and cryptosporidiosis are both neglected conditions, due to a widely held view that
34 they are predominately travel-acquired conditions (Minetti et al., 2015; Savioli et al., 2006). There
35 are around 3,000 cases of giardiasis and between 3,000 and 5,000 cases of cryptosporidiosis annually
36 in the UK (Public Health England, 2011a,b), although the true number is likely to be higher as
37 many cases are undiagnosed. The Second Infectious Intestinal Disease study (IID2) estimated that
38 there were 52,434 (95% CI: 15,022 to 183,020) cases of giardiasis and 43,834 (95% CI: 11,393 to
39 168,655) cases of cryptosporidiosis in the UK from April 2008 to August 2009 (Tam et al., 2012).
40 Even the lower bounds of the IID2 estimates suggest that these conditions are largely unreported.
41 Under-reporting occurs for a number of reasons: many people do not present to their GP when they
42 experience symptoms and if they do, a faecal specimen is not always requested. Although faecal

43 specimens are routinely examined for *Cryptosporidium*, laboratories often apply selective criteria
44 to *Giardia*. Criteria vary but usually include travel abroad hence indigenous cases of giardiasis are
45 often undiagnosed.

46 Since 2002, all faecal specimens in Central Lancashire from patients presenting with diarrhoea
47 have been tested for infection with *Giardia* and *Cryptosporidium*. In 2002, the laboratory in
48 Preston introduced an Enzyme Immunoassay (EIA) test, which is more sensitive than the standard
49 test involving light microscopy of specimens. This has been associated with a trebling of diagnosed
50 *Giardia* infections and an increased proportion of cases, especially in young/middle aged adults
51 (Ellam et al., 2008). Since 2002, all specimens in Central Lancashire have been assessed by this
52 laboratory, which gives a better impression of the true incidence of giardiasis and cryptosporidiosis.

53 Nearly all households in Central Lancashire receive a public water supply treated to remove both
54 parasites; less than 1% of the population have a private water supply (Figure 2 of Drinking Water
55 Inspectorate (2014)). Prior to 2000 removal of *Cryptosporidium* was incomplete and waterborne
56 outbreaks occurred (Sopwith et al., 2005; Smith et al., 2006). Water sources include rivers and
57 reservoirs with a complex treatment and distribution system that ultimately supplies water to
58 households in defined water zones.

59 The source of many cases of cryptosporidiosis and giardiasis in the UK is unknown. The aim of
60 this paper therefore, is to gain insight into the factors contributing to, and the etiology of, giardiasis
61 and cryptosporidiosis in Central Lancashire. This includes any potential relationship with water
62 source, through an examination of the spatial distribution of cases in relation to the public water
63 supply.

64 **Methods**

65 **Data**

66 The study region is Central Lancashire, North West England, an administrative district consisting
67 of the Local Authorities (LAs) Chorley, South Ribble and Preston (Figure 1). The region has a
68 total population of 333,949 and is ethnically predominantly white (93%) with 5% Asian or Asian
69 British (Table 1). The main industries of employment are: wholesale and retail trade; repair of
70 motor vehicles; manufacturing; health and social work; real estate, renting and business activities,
71 with only 1% of the population employed in agriculture (Table 2) (Office for National Statistics ;
72 General Register Office for Scotland ; Northern Ireland Statistics and Research Agency, 2005).

73 Information on giardiasis cases and cryptosporidiosis cases in 2003 to 2011 was obtained from
74 surveillance data held by the Cumbria and Lancashire Health Protection Unit. For each case, the
75 age, sex and postcode of the patient was recorded. Other individual level data, such as foreign
76 travel, were unavailable.



Figure 1: Location of the study region(blue shaded area) within North West England . Red lines show the borders of the local authorities.

Source: Ministry of Housing, Communities & Local Government (2016); Map data: Geobasis-DE/BKG, Google

77 Controls were a random sample of all people registered with a GP in the study region. GP
 78 registrations were available for each year 2006 to 2011. From each year, four times the number of
 79 cases occurring in that year were randomly selected as controls. For the years 2003 to 2005, four
 80 times the number of cases occurring in each year were selected randomly from the GP registrations
 81 from 2006. Consequently we used separate control sets for giardiasis and cryptosporidiosis. As
 82 with the cases, the age, sex and postcode of each control was recorded.

83 The postcode for both cases and controls was linked to the Lower Super Output Area (LSOA -
 84 a unit of geography containing an average of 1500 people), and the English Indices of Deprivation
 85 2007 (Department for Communities and Local Government, 2007) was used as an index of multiple
 86 deprivation (IMD) for each LSOA. This was included as deprivation is associated with poor health

87 (Pickett and Pearl, 2001; Haan et al., 1987; Sooman and Macintyre, 1995; Sloggett and Joshi, 1994;
88 Eames et al., 1993; Sloggett and Joshi, 1998). The IMD is a single summary measure based on seven
89 domains of deprivation: Income Deprivation; Employment Deprivation; Health Deprivation and
90 Disability; Education, Skills and Training Deprivation; Barriers to Housing and Services; Crime;
91 and Living Environment Deprivation.

92 Countryside activities are one of the principal risk factors for both giardiasis and cryptosporid-
93 iosis. As individual level information on behaviour was not available, the urban/rural classification
94 was used as a proxy for countryside exposures. The urban/rural classification for each postcode
95 was also established using census data. There are eight classifications, UR 1-8 (Office for National
96 Statistics, 2001b). Classifications UR 1-4 refer to areas where the wider surrounding area is sparsely
97 populated. Classifications UR 5-8 refer to areas where the wider surrounding area is less sparsely
98 populated. The study area only has classifications UR 5-8: Urban (population over 10,000) (UR
99 5); Town and Fringe (UR 6); Village (UR 7); Hamlet and Isolated Dwellings (UR 8).

100 Data on the water zones in the study region and the water treatment works that supply them
101 were obtained from the water company operating in the North West of England: United Utilities.
102 The water sources were either rivers or reservoirs with a number of water treatment works and
103 service reservoirs in the distribution chain. The smallest unit of defined water supply was the
104 water zone. A water zone (WZ) is a geographical area, the boundaries of which can change over
105 time. Each water zone may receive its water from one or more water treatment works (WTW)
106 in various percentages. These percentages can also change over time. Each case and control was
107 assigned to the relevant water zone based on their postcode and year. From this, the percentage
108 of water supply from each water treatment works was found for each case and control.

109 **Statistical analysis**

110 We fit a generalized additive model using a binomial distribution with case/control indicator Y_i
111 (cases = 1, controls = 0) for the i th individual as the response variable and adjust for age (A_i), sex
112 (M, F), where G_{iM} indicates male, the interaction between age and sex, IMD (D_i), urban/rural
113 indicator where U_{il} ($l = 5, 6, 7, 8$) indicates membership of the l th urban/rural category, percentage
114 of water supply from the j th water treatment works (W_{ij}) and geographical location (E_i, N_i).

115 Age is known to have a non-linear relationship with both giardiasis and cryptosporidiosis and
116 consequently was modelled using a cubic spline with knots at ages $c = 18, 40$ and 60 . See Durrleman
117 and Simon (1989) for more details on cubic splines. IMD and percentage of water received from each
118 of the main water treatment works were included as linear terms. A main water treatment works is
119 one which supplies a mean of greater than 1% of the total of an individual's supply. Geographical
120 location was included using a penalised regression spline, providing a fitted surface showing any
121 areas with an excess of cases after adjusting for the other factors.

	Frequency	%
Age		
0-4	18998	6
5-9	21452	6
10-14	22976	7
15-19	22000	7
20-24	20138	6
25-29	21974	7
30-44	75075	22
45-59	65394	20
60-74	43415	13
75+	22527	7
Sex		
Males	163709	49
Females	170240	51
Ethnicity		
White	310974	93
Mixed	2972	< 1
Asian or asian British	16701	5
Black or Black British	1629	< 1
Chinese	1198	< 1
Other	447	< 1
Missing	28	< 1

Table 1: Study region demographics

122 This model was applied separately to giardiasis and to cryptosporidiosis.

$$Y_i \sim \text{Bernoulli}(\mu_i)$$

$$\begin{aligned} \text{logit}(\mu_i) = & \alpha + \beta_0 G_{iM} + \beta_1 A_i + \beta_2 A_i^2 + \beta_3 A_i^3 + \sum_{k=1}^3 \gamma_k A_k^* + \left[\beta_4 A_i + \beta_5 A_i^2 + \beta_6 A_i^3 + \sum_{k=1}^3 \delta_k A_k^* \right] G_{iM} \\ & + \beta_7 D_i + \sum_{l=6}^8 \epsilon_l U_{il} + \sum_{j=1}^6 \zeta_j W_{ij} + s(E_i, N_i) \end{aligned}$$

123

$$A_k^* = \begin{cases} 0 & A < c_k \\ (A_i - c_k)^3 & A > c_k \end{cases} \quad (1)$$

Occupation	Frequency	%
Wholesale and retail trade, repair of motor vehicles	29454	19
Manufacturing	27016	17
Health and social work	17782	11
Real estate, renting and business activities	16478	11
Public administration and defence	12462	8
Education	12200	8
Construction	10396	7
Transport, storage and communication	9305	6
Hotels and catering	7126	5
Financial intermediation	4706	3
Agriculture, hunting and forestry	2265	1
Electricity, gas and water supply	963	1
Mining and quarrying	119	< 1
Fishing	22	< 1
Other	6425	4

Table 2: Industry of occupation for individuals in the study region

124 Inference

125 The model building process used forward selection: variables were added one-by-one starting with
126 the most significant. A likelihood ratio (LR) test was conducted between the models with and
127 without the variable being tested. If the LR test indicated the model was improved with the added
128 variable, it was retained in the model. Interactions between age, sex and IMD were also tested.
129 Once the final model was selected, the fitted values were fixed as an offset and a non-parametric
130 smooth for geographical location was added to model residual spatial variation. P-values for UR,
131 age and WTW were calculated using a LR between models including all levels of the factor, or
132 related variables, compared to none.

133 Results

134 Descriptive Statistics

135 There were 723 giardiasis cases and 488 cryptosporidiosis cases during the study period (Table
136 3). We selected 2892 controls for giardiasis and 1952 controls for cryptosporidiosis, Approximately
137 50% of controls were male for both conditions. 58% of giardiasis cases were male compared to
138 46% of cryptosporidiosis cases. Our study population varied by urban rural status. 81% and

139 84% of giardiasis cases and controls respectively and 84% and 85% of cryptosporidiosis cases and
 140 controls respectively were classified as UR 5 (Urban, population over 10,000). In contrast, a greater
 141 percentage of cases for both conditions was classified as UR 8 (hamlet and isolated dwellings) than
 142 controls: 5% compared to 2% of giardiasis cases and controls respectively and 3% compared to 2%
 143 of cryptosporidiosis cases and controls respectively.

	Giardiasis		Cryptosporidiosis	
	Cases	Controls	Cases	Controls
Total number	723	2892	488	1952
Male n (%)	419 (57.95)	1460 (50.48)	226 (46.31)	996 (51.02)
UR5 n (%)	589 (81.47)	2439 (84.34)	408 (83.61)	1663 (85.19)
UR6 n (%)	58 (8.02)	267 (9.23)	39 (7.99)	161 (8.25)
UR7 n (%)	38 (5.26)	122 (4.22)	24 (4.92)	83 (4.25)
UR8 n (%)	38 (5.26)	64 (2.21)	17 (3.48)	45 (2.31)
Age Mean (SD) [range]	38.49 (20.70) [0, 92]	39.27 (22.39) [0, 99]	18.37 (18.29) [0, 82]	38.34 (22.64) [0, 100]
IMD Mean (SD) [range]	20.61 (16.59) [3.20, 75.04]	21.53 (15.90) [3.14, 75.04]	19.53 (14.83) [3.41, 67.54]	21.98 (16.66) [3.14, 75.04]

Table 3: Summary statistics for giardiasis and cryptosporidiosis

144 The mean ages of cases and controls for giardiasis were very similar at 38 (SD 21) and 39 (SD
 145 22) respectively. However, the mean age of cases of cryptosporidiosis was markedly lower at 18 (SD
 146 18) while the mean age of controls (38, SD 23) is similar to that of controls for giardiasis. Mean
 147 IMD was very similar for cases and controls of both conditions.

148 Water in the study region was mainly supplied by just one WTW: WTW6. Cases and controls
 149 in the study received an average of about 80% of their water from WTW6 (Table 4). The remaining
 150 percentage came from eight other WTW. The majority (95%) of individuals in both the giardiasis
 151 and cryptosporidiosis datasets received at least 95% of their water from one WTW. Six water
 152 treatment works (WTW 1-6) met our definition of a main water treatment plant (supplied more
 153 than 1% of the case or control’s water) and were included in the analysis.

154 Fitted Models

155 There was a significant age-sex interaction for cryptosporidiosis (p-value 0.008). Figure 2b shows
 156 a non-linear relationship between age and odds of cryptosporidiosis. Though the relationship is
 157 different for males and females, both show higher numbers of cases in young children, and a steady
 158 decline with age. The odds of cryptosporidiosis is higher for adult females than males, except
 159 perhaps at around age 50, and is similar for both genders in children. The age-sex interaction was
 160 not significant for giardiasis (p-value 0.337). Sex was also not significant (p-value 0.099) but was
 161 significant in a model without the age-sex interaction (p-value 0.002). Age had a significant non-

WTW Code	Giardiasis % Supply			Cryptosporidiosis % Supply		
	All	Cases	Controls	All	Cases	Controls
WTW7	0.03	0.14	0.00	0.00	0.00	0.00
WTW8	0.11	0.00	0.14	0.04	0.00	0.05
WTW9	0.12	0.20	0.10	0.17	0.39	0.11
WTW1	1.41	1.57	1.36	1.65	1.19	1.77
WTW2	2.28	3.48	1.98	2.49	4.01	2.11
WTW3	3.84	2.75	4.11	3.84	4.30	3.72
WTW4	4.38	7.68	3.56	4.18	6.37	3.63
WTW5	6.65	7.62	6.41	6.11	5.45	6.28
WTW6	81.19	76.56	82.35	81.52	78.29	82.32

Table 4: Water treatment works codes and the mean percentage of total water they supply.

162 linear relationship with giardiasis (p-value < 0.001), but the pattern is different to that observed
163 for cryptosporidiosis (Figure 2a). As with cryptosporidiosis, the odds of giardiasis is highest in ages
164 0-5, but there is another peak in adults at around ages 30-50. The odds of giardiasis is highest for
165 males at all ages except among young children.

166 The effect of deprivation as measured by IMD was not significant for giardiasis (LR p-value 0.904
167 (Table 5)) but was significant for cryptosporidiosis (LR p-value 0.003), indicating a lower odds of
168 contracting cryptosporidium in more deprived areas. The urban/rural indicator was significant for
169 giardiasis (LR p-value 0.027), showing higher odds in rural areas compared to urban areas. The
170 urban/rural indicator was not significant for cryptosporidiosis (LR p-value 0.624).

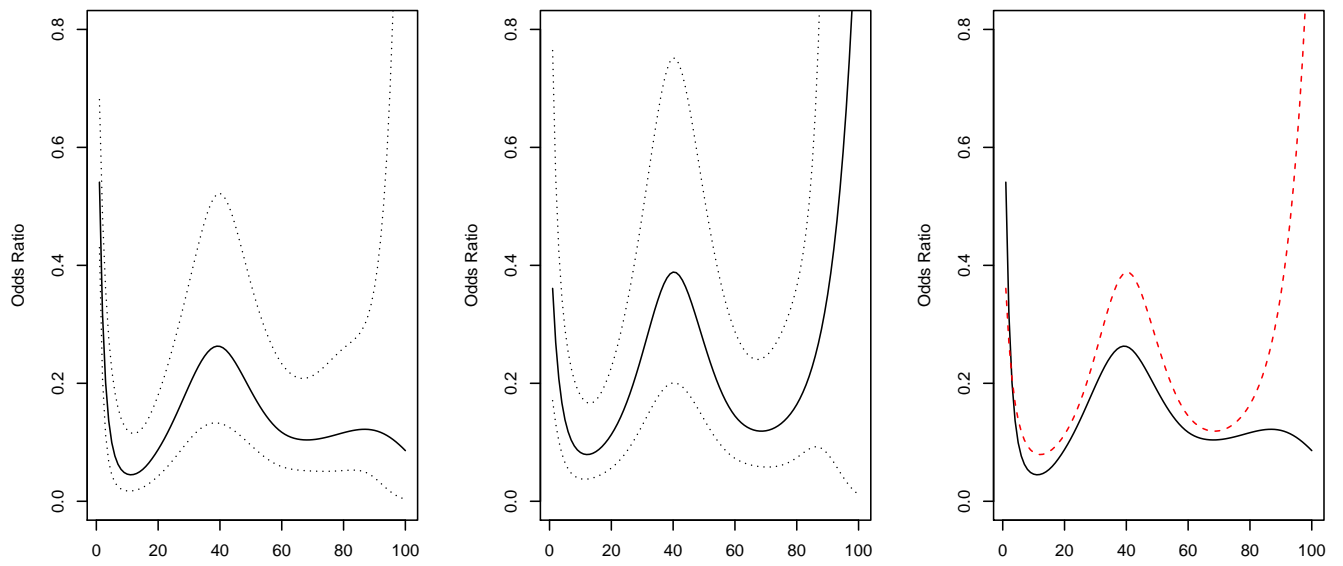
	Cryptosporidium		Giardia	
	Odds Ratio	P-value	Odds Ratio	P-value
IMD	0.989	0.003	1.000	0.904
UR6	1.064		0.957	
UR7	1.334		1.154	
UR8	1.294	0.624	2.012	0.027

Table 5: Fitted odds ratios. Odds ratios for UR 6-8 are comparisons with UR 5. P-values for Urban/rural indicator refer to the significance of including all levels of the factors compared to none.

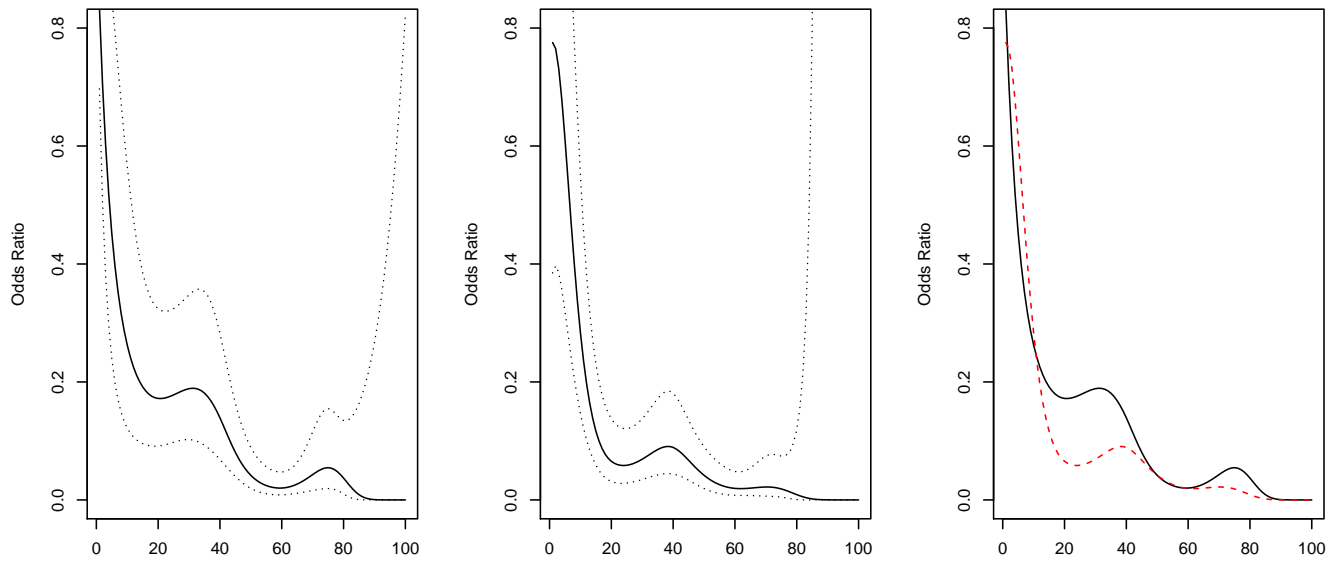
171 The smooth term for geographical location was highly significant (p-value 0.001) for giardiasis.
172 The fitted surface for the region (Figure 3, left) shows an increase in the log-odds of giardiasis in

173 the north of the region. The smooth term was also significant for cryptosporidiosis (p-value 0.004),
174 and again shows an increase in the log-odds of cryptosporidiosis in the north of the region (Figure
175 3, right).

176 The inclusion of water treatment works was significant for cryptosporidiosis (LR p-value <
177 0.001) and for giardiasis (LR p-value < 0.001). There is an indication that there may be something
178 different about WTW2 as its odds ratio is distinct from the others for cryptosporidiosis (Figure 4).
179 An analysis of the contrast between the odds ratio for WTW2 and the average of the odds ratios
180 for the other WTW does not indicate a significant difference for giardiasis (estimate 0.003 [-0.015,
181 0.020]) but does indicate a significant difference for cryptosporidiosis (estimate 0.041 [0.012, 0.071]).



(a) Giardiasis



(b) Cryptosporidiosis

Figure 2: Effect of age on the odds ratio (solid line) of giardiasis (a) and cryptosporidiosis (b), for females (left) and males (centre), with ± 2 standard errors (dotted lines). A direct comparison of males (red, dashed line) and females (black, solid line) is shown on the right.

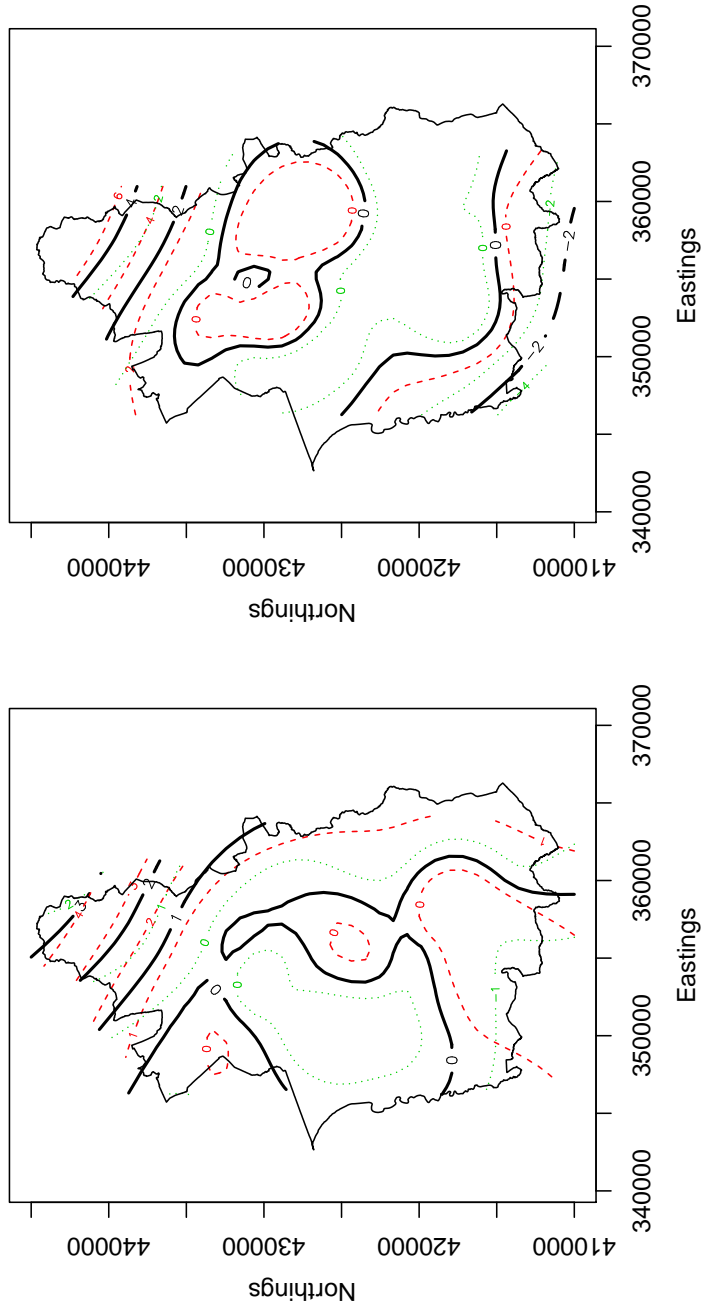


Figure 3: Residual spatial variation (solid line) in the log-odds of giardiasis (left) and cryptosporidiosis (right) after adjusting for other variables with +1SE (green dotted lines) and -1SE (red dashed lines).

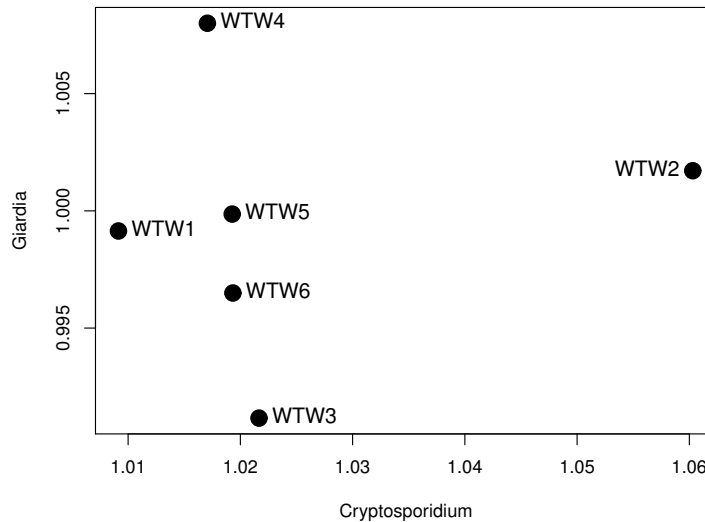


Figure 4: Odds ratios for each WTW for cryptosporidiosis plotted against odds ratios for giardiasis. There is an indication of a difference in odds ratio for cryptosporidiosis for WTW2 compared to the others. Labels give the codes for the WTW.

182 Discussion

183 Our analysis has found age to be an important factor for both cryptosporidiosis and giardiasis, with
 184 a higher risk of both conditions for young children and a second peak in risk of giardiasis in adults.
 185 Sex was also found to be significant with a higher risk of giardiasis for males and a higher risk of
 186 cryptosporidiosis for females. IMD was significant for cryptosporidiosis but not giardiasis, while
 187 the urban/rural indicator was significant for giardiasis but not cryptosporidiosis. The geographical
 188 location was significant for both giardiasis and cryptosporidiosis, showing an increased risk in
 189 the north for both. Water treatment works (WTW) was also significant for both giardiasis and
 190 cryptosporidiosis and WTW2 was significantly different to other WTW for cryptosporidiosis.

191 Since 2002, all specimens sent to the Preston laboratory have been tested for giardiasis and
 192 cryptosporidiosis using the sensitive Enzyme Immunoassay (EIA) test. This gives a more complete
 193 record of cases in our study region, and allows us to gain a better understanding of the true incidence
 194 of these two conditions. Despite the increased completeness of our data, there will still be some
 195 under-reporting of cases. People do not always present to their GP when they have symptoms
 196 and GPs do not always request specimens from them when they do present. It seems particularly
 197 likely that there is under-reporting in males, as males are less likely than females to present to their
 198 GP for any illness (Rowlands and Moser, 2002). However, we see no reason why the likelihood of

199 presenting to the GP should vary spatially. In a separate paper (Reeve et al., 2014) we investigated
200 the variation in specimen requests from GP practices and though there were differences in the rate
201 of specimen requests between GP practices, there was no spatial correlation between the rates. The
202 under-reporting of cases should therefore not materially affect our conclusions about the spatial
203 distribution of giardiasis and cryptosporidiosis in the North West of England.

204 Asymptomatic cases will also contribute to the under-estimation of the prevalence of giardiasis
205 and cryptosporidiosis in the study region. In a community-wide survey, Lopez et al. (1980) found
206 that 76% of infections of *Giardia* were asymptomatic but there was no significant secondary, person-
207 to-person spread. We do not expect that the proportion of symptomatic/asymptomatic cases should
208 vary spatially, so lack of information on asymptomatic cases should not affect our conclusions
209 regarding the existence and effect-size for factors that affect relative risk, but we cannot estimate
210 absolute risk.

211 Our results are consistent with other research showing higher rates of both giardiasis and cryp-
212 tosporidiosis in children and in adults aged 30-40 and higher rates of giardiasis in males (Naumova
213 et al., 2000). However, Naumova (Naumova et al., 2000) also found higher rates of cryptosporidiosis
214 in males, whereas we found higher rates for females.

215 Deprivation level was not found to be significantly associated with giardiasis risk. For cryp-
216 tosporidiosis our results showed that lowered deprivation score was a significant predictor of disease.
217 In prior work, increased deprivation is more commonly associated with higher disease risk (Pub-
218 lic Health England, 2017), but our result is in keeping with a study of the risk of giardiasis and
219 cryptosporidiosis in New Zealand, where lower cryptosporidiosis rates were found in areas of higher
220 deprivation (Snel et al., 2009). That paper suggested that the finding may reflect poor access and
221 use of primary health-care services by more deprived populations. While we have no means of test-
222 ing this idea in our population, previous findings have shown that there is an association between
223 deprivation and lack of engagement in primary healthcare, with people who miss GP appointments
224 more likely to be from deprived areas (Ellis et al., 2017). This could result in an over-representation
225 of diagnoses in the less deprived. We tried alternative models including different forms for the IMD
226 summary (for example using quintiles) but results were unaffected.

227 The higher risk for both conditions found in the north of the study region suggests higher
228 exposures in that area. It is a more rural area so contact with farm animals may be higher.
229 However, other rural areas in the study region do not have the same increase in risk. As such,
230 further investigation may be required into what the potential causes of that increased risk may
231 be. One possible explanation is the use of private water supplies. Private water supplies are
232 more common in rural areas and when supplying single households are not subject to the same
233 stringent water quality regulations as public water supplies, therefore they may pose a greater risk.
234 The Drinking Water Inspectorate (2013) report shows that most of the private water supplies in
235 the Chorley and South Ribble Local Authorities are in the east. Unfortunately, information was

236 not provided by the Preston Local Authority, which is situated in the north of the study region.
237 Urban/rural status is adjusted for in the model, but it may be that this indicator does not fully
238 account for the variation in rural areas.

239 The model estimates of the effect of WTW on the risk of giardiasis and cryptosporidiosis are
240 difficult to interpret individually, since an increase in percentage supply from one WTW implies a
241 decrease in percentage supply from another i.e. there is a linear dependency between WTW. The
242 contrast analysis allows us to compare WTW2 to the other WTW and indicates a difference for
243 WTW2 for cryptosporidiosis, but we cannot say why that difference might occur. It is possible that
244 WTW is acting as a proxy for some other spatial exposure, for example travel abroad or use of a
245 private water supply, and it is that exposure which causes a difference in risk, rather than WTW.
246 WTW2 only supplies relatively low percentages of water, predominately to the north of the study
247 region and one water zone in the south-east. It seems likely that the difference observed for WTW2
248 is linked to the issues already mentioned for the higher risk in the North. We also understand that
249 active quality control procedures have identified no deterioration in *Cryptosporidium*-specific water
250 quality in WTW2 over the period covered by this study (United Utilities, personal communication,
251 8th September 2014).

252 It is not possible to include all WTW in the model due to the linear dependency between the
253 WTW. Consequently, we included the ‘main’ WTW, defined as those supplying a mean of at least
254 1% of an individual’s total supply. We tried using other combinations of WTW but the results
255 were not materially changed. This included adding WTW as a factor i.e. ‘1’ for the WTW that
256 supplies the majority of an individual’s water and ‘0’ for all other WTW. This also did not change
257 the results materially. This may be because most individuals receive at least 95% of their water
258 supply from a single WTW during a year.

259 Our exposure assessment would have been strengthened had we had data on tap water con-
260 sumption patterns at home, and of other water and drinks, at an individual level. Our assessment
261 also assumes that individuals were exposed to tap water at home, whereas people are likely to spend
262 time away from home, commonly at work or at school. However, Villanueva et al. (2007) noted that
263 adding tap water consumption at work did not add to an exposure model in terms of explaining
264 variation in the exposure measured. Additionally, we only had limited data for some cases and none
265 of the controls on other important exposures such as travel abroad or nature of work exposures,
266 so we were not able to include them in the model. Further information on these exposures would
267 provide more information on the behaviour of *Giardia* and *Cryptosporidium*. Ethnicity would also
268 be useful information as it is linked to travel abroad.

269 Geographical location is partially confounded with WTW as the delivery of water from a WTW
270 depends on geographical location. It is also partially confounded with IMD and urban/rural indi-
271 cator. This may account for the non-significant result for IMD for giardiasis, and for urban/rural
272 indicator for cryptosporidiosis.

273 There is a difference in risk between males and females for both conditions, though in different
274 directions: males have a higher risk of giardiasis than females, and females have a higher risk of
275 cryptosporidiosis than males. This could be due to different exposures, such as places of work
276 or frequency of nappy changing. Biological differences between genders could also have an effect,
277 such as differences in immune responses (Klein, 2004). The increased risk of giardiasis for males is
278 particularly striking, given the likely under-reporting of cases in males.

279 The increased risk of both conditions for young children could be due to increased exposure or
280 an under-developed immune system. Reporting bias is also likely to have an effect here, as young
281 children are more likely to be presented and tested for infection than older children and adults.
282 The second peak in risk for giardiasis around ages 30-50 could be explained by lifestyle-related
283 exposures such as nappy changing or outdoor activities.

284 Using controls from 2006 for cases from 2003-2005 assumes that there has been no change in
285 population distribution from 2003 to 2006, but allows us to use data from this extended period.
286 We know that the population in the area has not changed radically over the study period: for 80%
287 of Lower Super Output Areas (LSOAs) in the study area, population change has been less than
288 20% (19.69% for 80% of urban LSOAs, 17.40% for 80% of rural LSOAs) and for 80% of LSOAs the
289 change in mean age has been less than 3.75 years (3.70 for 80% of urban LSOAs, 3.84 for 80% of
290 rural LSOAs) between the 2001 and 2011 census (Office for National Statistics, 2001a, 2011). We
291 repeated the analysis using data only from 2006-2011 and the results were not materially changed.

292 Giardiasis and cryptosporidiosis are neglected conditions in the UK, due to an assumed strong
293 association with travel abroad. The source of infection for many indigenous cases is unknown.
294 Consumption of mains tap water is considered an unlikely source of cryptosporidiosis and giardiasis
295 in the study area and study period due to the water treatment process for both parasites which
296 includes either UV inactivation, physical removal by either coagulation and filtration, or membrane
297 filtration. It is important to remember that outbreaks of both giardiasis and cryptosporidiosis have
298 been associated with drinking water supply (Sopwith et al., 2005; Nygård et al., 2006; Stuart et al.,
299 2003; Minetti et al., 2015; Smith et al., 2006), though in England and Wales, there has been a
300 decline in the number of outbreaks associated with public water supplies since 2000 (Smith et al.,
301 2006).

302 Our comparison of the epidemiology and spatial distribution of these two waterborne parasites
303 highlights important differences between them and adds to the knowledge of factors related to these
304 two conditions in North West England.

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312 **Conflict of interest**

313 None.

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