

1 **Association between socioeconomic deprivation and incidence of Infectious Intestinal**  
2 **Disease by pathogen and linked transmission route: An ecological analysis in the UK**

3

4 Matylda Buczkowska<sup>1,2</sup>, Saira Butt<sup>1,2</sup>, Claire Jenkins<sup>\*1,2</sup>, Dan Hungerford<sup>2,3,4</sup>, Jeremy  
5 Hawker<sup>2,5</sup>, Neville Q Verlander<sup>6</sup>, Anne-Marie O'Connell<sup>6</sup> and Lisa Byrne<sup>1,2</sup>

6

7 <sup>1</sup> Gastro and Food Safety (One Health) Division, UK Health Security Agency, London, UK

8 <sup>2</sup> National Institute for Health Research Health Protection Research Unit in Gastrointestinal  
9 Infections, University of Liverpool, Liverpool, UK

10 <sup>3</sup> Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool,

11 <sup>4</sup> Field Epidemiology Northwest, Field Service, Health Protection Operations, UK Health  
12 Security Agency, Liverpool, UK

13 <sup>5</sup> UK Field Epidemiology Service, UK Health Security Agency, Birmingham, UK

14 <sup>6</sup> Data & Analytics, UK Health Security Agency, London, UK

15 **\*Author for correspondence:**

16 Claire Jenkins

17 Claire.Jenkins1@ukhsa.gov.uk

18

19

20

This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is unaltered and is properly cited. The written permission of Cambridge University Press must be obtained for commercial re-use or in order to create a derivative work.

21 **Summary**

22 Infectious intestinal disease (IID) studies conducted at different levels of the surveillance  
23 pyramid have found heterogeneity in association of socioeconomic deprivation with illness.  
24 The aim of this study was to analyse the association between socioeconomic deprivation  
25 and incidence of IID by certain gastrointestinal pathogens reported to UKHSA. Data were  
26 extracted from 2015 to 2018 for *Salmonella*, *Campylobacter*, *Shigella*, *Giardia* species, and  
27 norovirus. Rates were calculated per 100,000 person-years by Index of Multiple Deprivation  
28 (IMD) quintile and an ecological analysis, using univariate and multivariable regression  
29 models for each pathogen, was conducted. Incidence of *Campylobacter*, and *Giardia*  
30 species decreased with increasing deprivation. Conversely, the incidence of norovirus, non-  
31 typhoidal *Salmonella*, *Salmonella* typhi/paratyphi, *Shigella* species increased with increasing  
32 deprivation. Multivariable analysis results showed that higher deprivation was significantly  
33 associated with higher odds of higher number of cases for *Shigella flexneri*, norovirus and  
34 *Salmonella* typhi/paratyphi. Infections most associated with deprivation were those  
35 transmitted by person-to-person spread, and least strongly are those transmitted by zoonotic  
36 contamination of the environment. The reduction of person-to-person transmission by  
37 implementing policies targeting over-crowding and poor hygiene, and are likely to be the  
38 most effective solution for reduction of IID inequalities.

39  
40

41 **Key findings**

- 42 • Incidence of *Campylobacter* and *Giardia* species decreased with increasing deprivation
- 43 • Incidence of norovirus, *Salmonella* and *Shigella* species increased with increasing
- 44 deprivation.
- 45 • Infections most associated with deprivation were transmitted person-to-person
- 46 • Infections least associated with deprivation were transmitted by zoonotic transmission
- 47 • Policies targeting over-crowding and poor hygiene most effective in reducing inequalities
- 48
- 49

Accepted Manuscript

50 **Introduction**

51 Infectious intestinal disease (IID), infection of the gastrointestinal tract that causes  
52 gastroenteritis, is estimated to affect 274 people per 1,000 population in the UK per year [1].  
53 While most cases are mild and self-limiting, some pathogens can cause bloody diarrhoea,  
54 septicaemia, meningitis, renal failure, or death [1]. Approximately half of people reporting IID  
55 have missed work or school due to their symptoms, and for particular pathogens, public  
56 health measures require exclusion of individuals in certain risk groups (including children  
57 aged five and under, food handlers and healthcare workers) from childcare, school or  
58 workplace settings [1, 2]. Consequently, the negative impact of IID extends beyond clinical  
59 presentation, potentially affecting the financial and social situations of cases and their  
60 carers'. In 2018, the societal cost of foodborne illness in the UK was estimated to be over 9  
61 billion GBP [3].

62  
63 Additionally, due to the self-limiting nature of most cases of IID, national surveillance  
64 captures only a fraction of cases. For every single case reported to national surveillance,  
65 there is an estimated 147 cases in the community, with approximately 15 cases presenting  
66 to the General Practice [1]. However, the estimates at different levels of the surveillance  
67 pyramid [4] differ widely by pathogen, for example, from five cases in the community for  
68 every *Salmonella* case reported to national surveillance, to 288 cases in the community for  
69 every norovirus case reported to national surveillance [1].

70  
71 Studies conducted at different levels of the surveillance pyramid have found heterogeneity in  
72 association of socioeconomic deprivation with illness [5-8]. In addition, most community or  
73 primary care level studies only examine the combined IID/gastroenteritis clinical syndrome,  
74 rather than the relationship for individual IID pathogens. As the most common transmission  
75 routes (for example, person-person, foodborne, zoonotic, environmental) and  
76 sources/vehicles of infection vary by pathogen, it cannot be assumed that the relationship  
77 between infection and socio-economic factors are the same for each pathogen. In addition,

78 considering the differences in ascertainment at each level of the surveillance pyramid across  
79 pathogens, it is likely that of the proportion of each IID pathogen included in each study  
80 differs. Analyses of datasets comprising cases linked to a microbiologically confirmed IID  
81 would therefore add considerably to the evidence base.

82

83 In this paper, we present the analysis of a large national dataset of laboratory diagnosed IID  
84 from England. The aim of this study was to analyse the association between socioeconomic  
85 deprivation and incidence of IID reported to national surveillance by pathogen. The  
86 objectives were to 1) Compare crude incidence for each gastrointestinal (GI) pathogen by  
87 Index of Multiple Deprivation (IMD) quintile and 2) Analyse the association between IMD  
88 quintile and incidence of each pathogen at neighbourhood level (lower super output area,  
89 LSOA).

90

## 91 **Methods**

### 92 *Data Sources*

93 The Second Generation Surveillance System (SGSS) is UK Health Security Agency's  
94 (UKHSA) primary method for collecting data on positive cases of infections of clinical  
95 significance and antimicrobial resistance from laboratories across England, Northern Ireland  
96 and Wales. Introduced in 2014, it replaced the legacy LabBase2, CoSurv and AmSurv  
97 applications that had previously supported the reporting of laboratory surveillance data to  
98 Public Health England (PHE) and predecessor organisations. The system enables  
99 laboratories to meet their statutory obligation under the Health Protection (Notification)  
100 Regulations to report laboratory confirmed cases of notifiable causative agents to UKHSA  
101 [9].

102 During the reporting period of this study, one hundred and twenty-seven microbiology and  
103 virology NHS and private laboratories across England reported positive test results to SGSS.  
104 Guidance on what, when and how they report is documented in the guide for diagnostic  
105 laboratories [9].

106 Data from the UKHSA SGSS was extracted from 1 January 2015 to 13 December 2018  
107 (inclusive) for *Salmonella*, *Campylobacter*, *Shigella*, *Giardia* species, and norovirus. These  
108 data include demographic characteristics for laboratory confirmed cases of infection in  
109 England. Transmission pathways for each pathogen are included in the Supplementary  
110 Materials [10-15] (Table 1A). A number of other pathogens available in SGSS database  
111 (such as STEC) was excluded. It was because those pathogens have the culture samples  
112 collected and analysed via their own, separate enhanced surveillance systems. It was not  
113 possible to de-duplicate PCR results for the same samples in the reference labs, which is a  
114 process ensuring national surveillance's reliability.

115 Each case was assigned to a LSOA, which are small zones representing neighbourhoods  
116 (~1500 people) based on their residential postcode, using data available from the Office for  
117 National Statistics (ONS) [16]. There are 32,844 LSOAs in England. Socio-demographic  
118 data was obtained from the ONS and included rural/urban classification, region of England,  
119 travel abroad (Yes, No, Unsure), population by year by age (Child, if <20 years old and  
120 Adults, if >=20 years old) and sex (Male and Female), all at the LSOA level [16]. Area level  
121 socioeconomic deprivation was measured through matching individual's LSOA of residence  
122 to the 2019 IMD [17]. The IMD is a composite measure based on seven weighted domains:  
123 income; employment; health; education; barriers to housing and services; crime and living  
124 environment. Mean distance to a general practice (GP) for each LSOA was obtained from  
125 the Public Health England Fingertips website [18]. Individuals whose data was missing from  
126 age, sex or rural/urban classification were excluded from the multivariable logistic regression  
127 analysis.

128

### 129 *Analysis*

130 For the first objective, rates were calculated per 100,000 person-years by IMD quintile, using  
131 the mid-year population estimates by LSOA for 2015, 2016, and 2017, and 2018.

132 *Salmonella* and *Shigella* were disaggregated by species to reflect differing transmission  
133 pathway. 95% confidence intervals (CI) were calculated with the 'PHEindicatormethods'

134 package which used Byar's method [19]. Rate ratios (RR), with 95% CI comparing the most  
135 deprived quintile with the least deprived quintile, were calculated with the 'epitools' package  
136 which used the Wald test. All analyses were done in R version 4.2.1.

137

138 The second objective involved an ecological analysis using the LSOA as the unit of analysis.  
139 Univariate and multivariable ordinal logistic regression models were used, with categorised  
140 count of cases as the outcome and person-years as one of the covariates. In the former  
141 case, IMD quintile was added as a categorical variable, whereas in the latter case sex (Male  
142 and Female), age (Age groups 0-4, 5-9, 10-14, 20-59, 60-69 and  $\geq 70$ ), rurality/urbanicity  
143 and distance to the GP (0-549 metres, 550-1099 metres, 1100-2199 metres and  $\geq 2200$   
144 metres) were also added as categorical variables, together with interaction between  
145 rurality/urbanicity and distance to the GP. The 1<sup>st</sup> IMD quintile represented the least deprived  
146 areas while the 5<sup>th</sup> IMD quintile represented the most deprived areas. The p-values were  
147 obtained by means of the (composite) Wald test and significance level taken to be 5%. Table  
148 1. shows the case categories chosen for each IID for both univariate and multivariable  
149 analysis, based on the distribution of counts for the IID in question. The proportionality of  
150 odds assumption was tested in the univariate and multivariable models, using the gologit2  
151 user-written ado program and method described in the article [20] for that program and  
152 executed in Stata 17.0, in which all inferential analyses were performed. In those cases  
153 where the assumption was not met, a generalised ordinal logistic regression model was  
154 fitted using the above program, where the obtained parameter estimates were then  
155 exponentiated to obtain overall odds ratios (ORs) for those parameters where the  
156 assumption appeared not be violated, and separate ORs for each case category otherwise  
157 [14]. In all cases, their 95% confidence intervals (CIs) were obtained and the measure of  
158 association, together with these CIs, are presented for the IMD quintile in the results section.

159

## 160 **Results**

### 161 *Overview of the epidemiology and microbiological data*

162 There was a total of 314,381 cases reported to SGSS during the 4-year study period, of  
163 which 167,299 (53%) were male and 59,827 (19%) were children (Table 1A.). Distribution of  
164 cases across regions ranged from 6% (n=17,831) in the North East of England to 18%,  
165 (n=56,331), in the South East of England. Most cases (n=249,802, 79%) lived in urban areas  
166 and 4% of cases (n=12,743) reported travelling outside the UK within 7 days of onset of  
167 symptoms (Table 1A.). About two-thirds (n=208,016) of cases were infected with  
168 *Campylobacter* species, 6% with *Giardia* (n=18,114), 6% were infected with *Cryptosporidium*  
169 (n=18,743), 8% with norovirus (n=26,361), 8% with non-typhoidal *Salmonella* (n=26,361),  
170 3% with *Salmonella typhi/paratyphi* (n=8,690), and 3% with *Shigella* (n=8,096). Of the  
171 *Shigella* diagnoses that were speciated (76%), 2,135 cases were infected with *Shigella*  
172 *flexneri* and 3,597 were infected with *Shigella sonnei*. *Cryptosporidium* speciation data were  
173 incomplete on SGSS and these data were excluded from subsequent analysis. The more  
174 deprived quintiles were slightly more represented in the study sample than the two least  
175 deprived quintiles with 68,211 (22%) cases representing the most deprived quintile and  
176 51,858 (16%) cases representing the least deprived quintile. IMD quintile classification was  
177 not conducted for 134 cases (0.04%) due to lack of valid postcodes (Table 2A.). Six hundred  
178 eighty-five individuals had data missing of sex variable, 567 of age variable and 134 of  
179 rural/urban classification variable, which represented approximately 0.2% of the total cases.

180

#### 181 *Comparison of crude incidence for each GI pathogen by IMD quintile*

182 There was a clear trend of decreasing likelihood of (a laboratory report with) all IID  
183 pathogens with increasing deprivation, with each quintile statistically significantly lower than  
184 the preceding quintile. Comparing the lowest and highest quintiles, the rate in the most  
185 deprived quintile was 28% lower than that of the least deprived quintile (RR=0.72; 95% CI:  
186 0.71-0.73) (Table 2., Figure 1A.). Incidence of *Campylobacter* species and *Giardia*  
187 decreased with increasing deprivation, with both pathogens showing a clear trend of each  
188 quintile being lower than the preceding one. The most deprived quintile had a 38% lower  
189 rate of *Campylobacter* (RR=0.62; 95% CI: 0.61 – 0.62), and 39% lower rate of *Giardia*



190 (RR=0.61; 95% CI: 0.58 – 0.64) as compared to the least deprived quintile (Table 2., Figure  
191 1A.). Conversely, the incidence of norovirus, non-typhoidal *Salmonella*, *Salmonella*  
192 *typhi*/*paratyphi*, *Shigella flexneri*, *Shigella sonnei*, and other *Shigella* increased with  
193 increasing deprivation, with all showing a generic trend across the five quintiles. The most  
194 deprived quintile had an 18% higher rate of norovirus (RR=1.18; 95% CI: 1.14 – 1.23), 6%  
195 higher rate of non-typhoidal *Salmonella* (RR=1.06; 95% CI: 1.03 – 1.10), 187% higher rate of  
196 *Salmonella typhi*/*paratyphi* (RR=2.87; 95% CI: 2.41 – 3.42), 152% higher rate of *Shigella*  
197 *flexneri* (RR=2.52; 95% CI: 2.16 – 2.95), 20% higher rate of *Shigella sonnei* (RR=1.20; 95%  
198 CI: 1.08 – 1.34), and 40% higher rate of other *Shigella* (RR=1.40; 95% CI: 1.23 – 1.60) as  
199 compared to the least deprived quintile (Table 2., Figure 1A.).

200

#### 201 *Analysis of the association between IMD quintile and incidence rates of each pathogen*

202 Univariate analysis showed that higher deprivation was significantly associated with higher  
203 odds of higher number of cases for *Shigella sonnei*, other *Shigella*, *Shigella flexneri* and  
204 *Salmonella typhi*/*paratyphi* (Table 3.). Similar trend was also seen for norovirus (Table 4.),  
205 for which quintile 3 and quintile 5 (most deprived) had the highest odds of higher number of  
206 cases. For non-typhoidal *Salmonella*, there was no clear trend with all odds ratios being  
207 close to 1 with the exception of two most deprived quintiles which showed a slightly higher  
208 odds of higher number of cases (Table 4.). Univariate analysis results showed that higher  
209 deprivation was significantly associated with lower odds of higher number of cases for  
210 *Giardia* (Table 4.) and *Campylobacter* (Table 5.).

211

212 Multivariable analysis results showed that higher deprivation was significantly associated  
213 with lower odds of higher number of cases for *Giardia* and *Campylobacter* (Table 6.). There  
214 was a similar trend for *Shigella sonnei* but not all quintiles were significant. Multivariable  
215 analysis showed that higher deprivation was significantly associated with higher odds of  
216 higher number of cases for *Shigella flexneri*, norovirus and *Salmonella typhi*/*paratyphi* (Table

217 6.). For other *Shigella* and non-typhoidal *Salmonella*, there was no clear trend with all odds  
218 ratios being close to 1 and CI including 1 for all or most quintiles (Table 6.).

219

## 220 **Discussion**

221 In this study, which used national surveillance data, we found a heterogeneous relationship  
222 between deprivation and incidence of laboratory confirmed GI infections that varied by  
223 pathogen. Previous studies carried out in the UK and elsewhere reported an association  
224 between a high incidence of GI infections and high levels of deprivation. For example,  
225 nationally representative analysis of 24 million calls to NHS telephone helplines for health  
226 advice in England found that there was a greater risk of GI calls from more disadvantaged  
227 areas compared to less disadvantaged areas [5]. Retrospective, cross-sectional studies from  
228 different countries found a positive link (telephone-based population studies from Australia  
229 and the US) [21, 22], no link (telephone-based population study from Canada) [23] or an  
230 inverse association (postal questionnaire from Australia) [24] between socioeconomic status  
231 and having suffered an episode of GI illness. In contrast, we reported a lower proportion of  
232 notifications of GI infection in cases living in deprived areas. However, the analysis suggests  
233 that this result reflects the high proportion of *Campylobacter* infections in the dataset.

234

235 Overall, pathogens that had common routes of transmission had similar associations with  
236 level of deprivation. For waterborne pathogens such, as *Giardia*, the incidence was lower in  
237 areas of higher deprivation, even after accounting for rural/urban differences. For pathogens  
238 most frequently associated with foodborne transmission, including *Campylobacter* and non-  
239 typhoidal *Salmonella*, the incidence was also lower in areas of higher deprivation, especially  
240 in the multivariable model. For pathogens transmitted by person-to-person contact,  
241 specifically norovirus, *Shigella* species and *Salmonella* typhi/paratyphi, incidence was higher  
242 in more deprived neighbourhoods in the crude analysis and univariate model, although  
243 results varied in the multivariable models. This indicates that for person-to-person  
244 transmission, confounders, such as age and sex, had the biggest impact on the results.

245 Additionally, pathogens such as *Shigella* can, less commonly, be water-borne or food-borne,  
246 particularly in individuals who travelled to developing countries [11]. *Shigella*, *Campylobacter*  
247 and *Giardia* also all share the same transmission pathway: sexual transmission in men who  
248 have sex with men (MSM) [11].

249

250 Our results support the hypothesis that pathogen transmission routes may impact on the  
251 association with IMD. A systematic review on the impact of socioeconomic status on  
252 foodborne illness in high-income countries also found an association between infection with  
253 *Campylobacter* and *Salmonella* species and higher socioeconomic status [25]. Another  
254 systematic review investigating the relationship between socioeconomic status and GI  
255 infections in developed countries found that, in univariate analysis, the increased risk  
256 comparing low and high socioeconomic status groups was significantly higher for pathogens  
257 spread by person-to-person transmission, but lower for environmental pathogens, as  
258 compared to foodborne pathogens, which was similar to our results [26]. The study also  
259 found that the risk of GI infection for lower socioeconomic status (higher deprivation) was on  
260 average significantly higher among studies which analysed hospital cases, compared to  
261 studies that analysed laboratory recorded cases [26]. The review also highlighted that the  
262 relationship between incidence and deprivation was much stronger in children than in adults.  
263 The study by Payment et al., also found that the proportion of GI infections caused by the  
264 different routes of exposure varies significantly across communities due to varying  
265 behavioural and socioeconomic factors [27].

266

267 Previous studies have highlighted overcrowded homes with fewer washing and toilet  
268 facilities per person may be associated with a higher incidence of GI infection in more  
269 deprived areas [28]. We might therefore expect GI pathogens transmitted primarily by close  
270 person-to-person contact to have higher incidence in more deprived areas. Our analyses  
271 supported these findings, showing that a higher proportion of cases living in deprived areas  
272 reported GI infections caused by *Shigella flexneri* species, *Salmonella typhi/paratyphi*, and

273 norovirus. These three pathogen groups do not have significant animal reservoirs, and are  
274 often associated with household transmission, institutional outbreaks and outbreaks among  
275 people living in close communities [10,11]. Outbreaks of *Shigella sonnei* and *Shigella*  
276 *flexneri* have also been detected among MSM in the UK and other developed countries [11].

277

278 Of the zoonotic, foodborne GI pathogens that are rarely associated with person-to-person  
279 transmission, *Campylobacter* and non-typhoidal *Salmonella* were reported less frequently  
280 among cases living in deprived areas. Our results could be influenced by the fact that  
281 individuals who consume fast foods, travellers to low- and middle-income countries as well  
282 as those who live in rural areas and have regular contact with livestock have increased risk  
283 of *Campylobacter* infection [29]. Adams et al. [6] also suggested that lower risk of GI  
284 infection caused by certain foodborne pathogens in individuals living in deprived areas, may  
285 be due to reduced opportunities to eat out and less frequent consumption of high-risk foods,  
286 such as unpasteurised dairy products.

287

288 Zoonotic GI pathogens may be transmitted to humans via multiple routes [12, 14]. Higher  
289 use of recreational contaminated water and international travel has been linked to incidence  
290 in less deprived individuals [14]; at the same time, individuals living in rural areas are more  
291 likely to have contact with animals and the environment, and therefore their risk of infection  
292 is increased despite living in less deprived areas [30].

293

294 Travel outside the UK, especially to countries where specific GI pathogens are endemic,  
295 may increase risk of infection. In the UK, 95% of *Salmonella* typhi/paratyphi cases have a  
296 history of travel to an endemic area and the remaining cases are acquired through contact  
297 with an infected traveller [2]. Adams et al. [6] suggested that individuals in deprived areas  
298 may be less likely to travel abroad, and this risk factor may therefore impact more on  
299 individuals from affluent areas. However, as with foodborne exposures, the assumption that

300 travellers are from the least deprived areas is confounded by the frequency of travel to high-  
301 risk countries to visit family and friends by individuals living in high deprivation areas [2].

302

303 The strength of the study was using nationally representative laboratory data which is the  
304 most comprehensive source of clinical data on individual GI pathogens for England, which  
305 allowed the analysis of specific pathogens and their associated transmission routes.

306 However, the use of national surveillance data results in a dataset that over-represents  
307 pathogens such as *Campylobacter* and under-represents the true burden of norovirus  
308 infection in the community, which limits generalisability at the level of the community. Data  
309 from the Second Study of Infectious Intestinal Disease in the Community (IID2 Study) from  
310 2008-2009 [1] estimated that for every case of *Salmonella* captured by national surveillance,  
311 there were 1.4 GP consultations and approximately 5 community cases; and for cases of  
312 *campylobacteriosis*, there were 1.3 GP consultations and 9.3 community cases. For every  
313 case of norovirus reported to national surveillance, there were 2.3 GP consultations and 288  
314 community cases [1]. Patients reporting IID are otherwise only routinely tested for norovirus  
315 if they are children less than 5 years of age, adults over 60 years, food-handlers, or  
316 immunocompromised patients [1]. For every national surveillance case of *Giardia*, there  
317 were 1.5 GP consultations and approximately 14 community cases [1]. Faecal samples are  
318 not routinely tested for *Giardia* as criteria for testing often includes a history of travel [12].  
319 Ethnicity may interact with deprivation in that ethnic groups with ties to countries where  
320 *Giardia* is endemic may be more likely to travel, and therefore be tested for *Giardia*, than  
321 other ethnic groups.

322

323 Testing patterns by geography and deprivation status were not investigated in this study as  
324 the dataset contained only positive, infected cases. Consequently, the data may reflect  
325 testing bias and differences in access to health services. A systematic review [31] also  
326 showed that patients from patients from lower social classes faced less participatory  
327 consultations which reduced information sharing. Previous studies in the UK also showed

328 lower reporting rates for GI infections among more deprived individuals [32]. Additionally,  
329 laboratory cases generally reflect the most clinically severe cases, and while socioeconomic  
330 deprivation is associated with more severe illness, pathogens such as norovirus usually  
331 causes short-lived symptoms [1]. Consequently, the association of lab-reported incidence of  
332 norovirus with socioeconomic deprivation found in this study may be more likely to reflect  
333 incidence of outbreak-associated norovirus or those in targeted groups. Other potential  
334 confounders, such as ethnicity and travel patterns were not included in the analysis. For  
335 example, there are known ethnic differences in the risk of *Campylobacter* infection in the UK  
336 [13, 33]. Finally, as this was an ecological analysis, conclusions cannot be drawn regarding  
337 individual risk factors and how they can be targeted to reduce inequalities among deprived  
338 groups.

339

340 Our study showed that incidence rates can potentially vary across deprivation quintiles,  
341 depending on the pathogen and its transmission route, based on laboratory data. Our results  
342 were consistent in showing that infections most strongly associated with areas of increasing  
343 deprivation were those transmitted by person-person contact, and that those transmitted by  
344 zoonotic contamination of the environment were least likely to be associated with areas of  
345 deprivation. We therefore suggest the most effective solution for reduction of IID  
346 inequalities is prioritizing reduction of person-to-person infections' spread, especially in  
347 children. Development, introduction and mobilisation of safe and effective vaccines against  
348 GI pathogens which transmit person-to-person and target risk groups, such as children  
349 should be a priority for prevention. As evidenced by the paediatric rotavirus immunisation, GI  
350 vaccine introductions can help to reduce socio-economic inequalities in disease burden  
351 (both health and socio-economic) [34]. Vaccination against *Salmonella typhi* is  
352 recommended for travellers to endemic areas such as parts of Asia (such as India, Pakistan  
353 and Bangladesh) to prevent the infection [35]. There are currently no licensed vaccines for  
354 noroviruses, *Giardia*, *Campylobacter* and *Shigella* although several candidates are under  
355 development [36-40].

356

357 Further research could investigate the relationship between type of symptomatic healthcare  
358 presentation and the number of total laboratory samples from primary care/hospitals and  
359 deprivation. Primary care and hospitals have access to total faecal samples, including  
360 negative samples, which are not reported to SGSS. Self-reporting of GI symptoms and stool  
361 sample testing, for example through a website app, could allow us to understand testing  
362 patterns for GI by socio-demographic and spatial measures [41]. It would be also interesting  
363 to investigate whether ethnicity has an impact on the incidence rates as suggested by other  
364 studies [13, 33].

365

366 The findings of this study suggest that at the level of national laboratory surveillance, the  
367 incidence of pathogens the most strongly associated with increasing deprivation are those  
368 transmitted by person-person spread and least strongly associated are those transmitted by  
369 zoonotic contamination of the environment. Previous studies have shown increased risk of  
370 IID in more deprived regions, particularly in children, at community, primary care and  
371 hospital levels [6]. We therefore suggest that the most effective solution for reduction of IID  
372 inequalities is prioritizing reduction of person-to-person infections' spread, especially in  
373 children.

374

375

376

377

378

379

380

381

382 **Abbreviations**

383 CI: Confidence Interval

384 GI: Gastrointestinal

385 GP: General practice

386 IID: Infectious Intestinal Disease

387 IMD: Index of Multiple Deprivation

388 LSOA: Lower Super Output Area

389 LRT: Likelihood Ratio Test

390 MSM: Men who have sex with men

391 ONS: Office for National Statistics

392 OR: Odds Ratio

393 PHE: Public Health England

394 RR: Rate Ratio

395 SGSS: Second Generation Surveillance System

396 UKHSA: United Kingdom Health Security Agency

397 **Authors' contributions**

398 LB and JH conceptualised and designed the study. LB and CJ were responsible for  
399 supervision. MB and SB were responsible for investigation, validation and formal analysis.  
400 AOC was responsible for data curation. MB and SB were responsible for writing the original  
401 draft. JH was responsible for funding acquisition. NV provided statistical support. MB, SB,  
402 CJ, DH, JH and LB edited the manuscript. All authors read and approved the final  
403 manuscript.



404 **Ethics approval and consent to participate**

405 The UKHSA has approval to handle data obtained through laboratory surveillance under  
406 Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002.  
407 Informed patient consent was not required as UKHSA has the authority to handle patient  
408 data for public health monitoring and infection control under Section 251 of the UK National  
409 Health Service Act 2006.

410 **Consent for publication**

411 Not applicable.

412 **Availability of data and materials**

413 The data that support the findings of this study are available from UKHSA, but restrictions  
414 apply to the availability of these data, which were used under licence for the current study,  
415 and so are not publicly available. Aggregated data are, however, available from the authors  
416 upon reasonable request and with the permission of UKHSA.

417 **Competing interests**

418 The authors declare that they have no competing interests.

419 **Funding**

420 This study is funded by the National Institute for Health and Care Research (NIHR) Health  
421 Protection Research Unit in Gastrointestinal Infections, a partnership between the UK Health  
422 Security Agency, the University of Liverpool and the University of Warwick. The views  
423 expressed are those of the author(s) and not necessarily those of the NIHR, the UK Health  
424 Security Agency or the Department of Health and Social Care.

425 **Acknowledgements**

426 The authors acknowledge the contributions of Theme 1 (People and Places) NIHR Health  
427 Protection Research Unit in Gastrointestinal Infections members.

428 **Keywords**

- 429 • Gastrointestinal Disease
- 430 • Infectious Intestinal Disease
- 431 • Deprivation
- 432 • Incidence
- 433 • Ecological Analysis
- 434 • Transmission Route
- 435 • Inequalities
- 436 • Surveillance
- 437 • Laboratory Data

438

Accepted Manuscript

439 **References**

- 440 1. Tam, CV et al. (2012) The Second study of Infectious Intestinal Disease in the  
441 Community (IID2 Study): Final Report.
- 442 2. Ejidokun, TH et al. (2019) Recommendations for the Public Health Management of  
443 Gastrointestinal Infections 2019: Principles and practice. PHE publications number: GW-  
444 1020.
- 445 3. Daniel, NC et al. (2020) The burden of Foodborne Disease in the UK 2018. Food  
446 Standards Agency.
- 447 4. Lake, IR et al. (2009) Using infectious intestinal disease surveillance data to explore  
448 illness aetiology; a cryptosporidiosis case study. *Health Place* **15**, 333-339. doi:  
449 10.1016/j.healthplace.2008.06.005.
- 450 5. Adams, NL et al. (2019) Social patterning of telephone health-advice for diarrhoea and  
451 vomiting: analysis of 24 million telehealth calls in England. *Journal of Infection* **78**, 95-  
452 100. doi: 10.1016/j.jinf.2018.09.008.
- 453 6. Adams, NL et al. (2018) Socioeconomic status and infectious intestinal disease in the  
454 community: a longitudinal study (IID2 study). *European Journal of Public Health* **28**, 134-  
455 138. doi: 10.1093/eurpub/ckx091.
- 456 7. Rose, TC et al. (2017) Socioeconomic status is associated with symptom severity and  
457 sickness absence in people with infectious intestinal disease in the UK. *BMC Infectious*  
458 *Diseases* **17**, 447 doi.org/10.1186/s12879-017-2551-1.
- 459 8. Tam, CC et al. (2012) IID2 Study Executive Committee. Longitudinal study of infectious  
460 intestinal disease in the UK (IID2 study): incidence in the community and presenting to  
461 general practice. *Gut* **61**, 69-77. doi: 10.1136/gut.2011.238386.
- 462 9. Public Health England (2020) Laboratory reporting to Public Health England: A guide for  
463 diagnostic laboratories.

- 464 10. de Wit, MA et al. (2003) Risk factors for norovirus, Sapporo-like virus, and group A  
465 rotavirus gastroenteritis. *Emerging Infectious Disease* **9**, 1563-1570. doi:  
466 10.3201/eid0912.020076.
- 467 11. Serafino Wani, RL et al. (2015) Invasive Shigellosis in MSM. *International journal of STD*  
468 *& AIDS* **27** (10). Pp. 917-919. ISSN 0956-4624 DOI:  
469 <https://doi.org/10.1177/0956462415610275>
- 470 12. Dunn, N and Juergens, AL (2022) Giardiasis. In: StatPearls [Internet]. Treasure Island  
471 (FL): StatPearls Publishing [Updated 2022 May 8; cited 2022 June 8]. Available from:  
472 <https://www.ncbi.nlm.nih.gov/books/NBK513239/>
- 473 13. Gillespie, IA et al. (2008) Demographic determinants for Campylobacter infection in  
474 England and Wales: implications for future epidemiological studies. *Epidemiology &*  
475 *Infection* **136**, 1717-1725. doi: 10.1017/S0950268808000319.
- 476 14. Janssen, B and Snowden, J (2022) Cryptosporidiosis. In: StatPearls [Internet]. Treasure  
477 Island (FL): StatPearls Publishing [Updated 2021 Nov 30; cited 2022 June 8]. Available  
478 from: <https://www.ncbi.nlm.nih.gov/books/NBK448085/>
- 479 15. Ajmera, A and Shabbir, N (2022) Salmonella. In: StatPearls [Internet]. Treasure Island  
480 (FL): StatPearls Publishing; [Updated 2022 Aug 8]. Available from:  
481 <https://www.ncbi.nlm.nih.gov/books/NBK555892/>
- 482 16. Office of National Statistics [Internet]. [Cited 2022 Jun 08]. Available from:  
483 <https://www.ons.gov.uk/>
- 484 17. English Indices of Deprivation - Postcode Lookup 2019 [Internet]. [Cited 2022 Jun 08].  
485 Available from: <https://imd-by-postcode.opendatacommunities.org/imd/2019>
- 486 18. Wider Determinants of Health - Built and Natural Environment Resources Page  
487 [Internet]. [cited 2022 Jun 08]. Available from: [https://fingertips.phe.org.uk/profile/wider-](https://fingertips.phe.org.uk/profile/wider-determinants/supporting-information/built-and-natural-environment)  
488 [determinants/supporting-information/built-and-natural-environment](https://fingertips.phe.org.uk/profile/wider-determinants/supporting-information/built-and-natural-environment)
- 489 19. Breslow, NE and Day, NE (1987) Statistical methods in cancer research. Volume II. The  
490 design and analysis of cohort studies. *International Agency for Research on Cancer*  
491 *Scientific Publications* **82**, 1-406. PMID: 3329634.

- 492 20. Williams, R (2006) Generalized Ordered Logit/ Partial Proportional Odds Models for  
493 Ordinal Dependent Variables. *The Stata Journal* **6**, 58-82.
- 494 21. Hall, GV et al. (2006) Frequency of infectious gastrointestinal illness in Australia, 2002:  
495 regional, seasonal and demographic variation. *Epidemiology & Infection* **134**, 111-118.  
496 doi: 10.1017/S0950268805004656
- 497 22. Herikstad, H et al. (2002) A population-based estimate of the burden of diarrhoeal illness  
498 in the United States: FoodNet, 1996-7. *Epidemiology & Infection* **129**, 9-17. doi:  
499 10.1017/s0950268801006628.
- 500 23. Majowicz, SE et al. (2004) Magnitude and distribution of acute, self-reported  
501 gastrointestinal illness in a Canadian community. *Epidemiology & Infection* **132**, 607-617.  
502 doi: 10.1017/s0950268804002353.
- 503 24. Bytzer, P et al. (2001) Low socioeconomic class is a risk factor for upper and lower  
504 gastrointestinal symptoms: a population-based study in 15 000 Australian adults. *Gut*  
505 **200149**, 66-72. doi: 10.1136/gut.49.1.66.
- 506 25. Newman, KL et al. (2015) The impact of socioeconomic status on foodborne illness in  
507 high-income countries: a systematic review. *Epidemiology & Infection* **143**, 2473-2485.  
508 doi: 10.1017/S0950268814003847.
- 509 26. Adams, NL et al. (2018) Relationship between socioeconomic status and gastrointestinal  
510 infections in developed countries: A systematic review and meta-analysis. *PLoS One* **13**,  
511 e0191633. doi: 10.1371/journal.pone.0191633.
- 512 27. Payment, P (2001) Transmission of gastrointestinal diseases: hygiene as the final  
513 barrier. *American Journal of Infection Control* **29**, 218-221. doi:  
514 10.1067/mic.2001.115683.
- 515 28. WHO Housing and Health Guidelines. Geneva: World Health Organization [Internet].  
516 2018 March, Household crowding [Cited 2022 June 8]. Available from:  
517 <https://www.ncbi.nlm.nih.gov/books/NBK535289/>
- 518 29. Bessell, PR et al. (2010) Geographic determinants of reported human *Campylobacter*  
519 infections in Scotland. *BMC Public Health* **10**, 423. doi: 10.1186/1471-2458-10-423.

- 520 30. Leitch, GJ and He, Q (2012) Cryptosporidiosis-an overview. *Journal Biomedical*  
521 *Research* **25**, 1-16. doi: 10.1016/S1674-8301(11)60001-8.
- 522 31. Willems, S et al. (2005) Socio-economic status of the patient and doctor-patient  
523 communication: does it make a difference? *Patient Education Council* **56**,139-146. doi:  
524 10.1016/j.pec.2004.02.011.
- 525 32. Olowokure, B et al. (1999) Deprivation and hospital admission for infectious intestinal  
526 diseases. *Lancet* **353**, 807-808. doi: 10.1016/S0140-6736(99)00611-X.
- 527 33. Manaseki, S et al. (2004) Ethnic inequalities in campylobacter infection in Birmingham,  
528 UK: descriptive study of notified cases. *Journal of Epidemiology & Community Health* **58**,  
529 278-279. doi: 10.1136/jech.2003.012294.
- 530 34. Hungerford, D et al. (2018) Rotavirus vaccine impact and socioeconomic deprivation: an  
531 interrupted time-series analysis of gastrointestinal disease outcomes across primary and  
532 secondary care in the UK. *BMC Medicine* **16**, 10. doi: 10.1186/s12916-017-0989-z.
- 533 35. Sulieman, S (2022) Travel Vaccination Update. *Delaware Journal Public Health* **8**, 40-41.  
534 doi: 10.32481/djph.2022.03.007.
- 535 36. Debbink, K et al. (2014) The state of norovirus vaccines. *Clinical Infectious Disease*  
536 **58**,1746-1752. doi: 10.1093/cid/ciu120.
- 537 37. Haserick, JR et al. (2017) Cryptosporidium parvum vaccine candidates are incompletely  
538 modified with O-linked-N-acetylgalactosamine or contain N-terminal N-myristate and S-  
539 palmitate. *PLoS One* **12**, e0182395. doi: 10.1371/journal.pone.0182395.
- 540 38. Davids, BJ et al. (2019) Identification of Conserved Candidate Vaccine Antigens in the  
541 Surface Proteome of Giardia lamblia. *Infection & Immunity* **87**, e00219-19. doi:  
542 10.1128/IAI.00219-19.
- 543 39. Poly F, et al. (2019) Update on Campylobacter vaccine development. *Human Vaccines &*  
544 *Immunotherapeutics* **15**, 1389-1400. doi: 10.1080/21645515.2018.1528410.
- 545 40. Böhles, N et al. (2014) Vaccines against human diarrheal pathogens: current status and  
546 perspectives. *Human Vaccines & Immunotherapeutics* **10**, 1522-35. doi:  
547 10.4161/hv.29241.

548 41. Davies, R et al. (2022) Public acceptability of a technology-mediated stool sample  
549 collection platform to inform community-based surveillance of infectious intestinal  
550 disease: a pilot study. *BMC Public Health* **22**, 958. doi: 10.1186/s12889-022-13307-5.

Accepted Manuscript

## Tables

Table 1. Categories for the count of cases for each pathogen for univariate and multivariable analysis.

Pathogen	Categories for the count of cases	
	Univariate analysis	Multivariable analysis
<i>Campylobacter</i>	0-5, 6-10, $\geq 11$	0, 1, $\geq 2$
<i>Giardia</i>	0, 1, 2, $\geq 3$	0, 1, $\geq 2$
Norovirus	0, 1, 2, $\geq 3$	0, 1, $\geq 2$
Non-typhoidal <i>Salmonella</i>	0, 1, 2, $\geq 3$	0, 1, $\geq 2$
<i>Salmonella</i> typhi/paratyphi	0, 1, $\geq 2$	0, 1, $\geq 2$
<i>Shigella flexneri</i>	0, 1, $\geq 2$	0, 1, $\geq 2$
<i>Shigella sonnei</i>	0, 1, $\geq 2$	0, 1, $\geq 2$
Other <i>Shigella</i>	0, 1, $\geq 2$	0, 1, $\geq 2$



**Table 2. Incidence rate of each pathogen by IMD quintile and RR by each pathogen comparing the most deprived quintile (5) to the least deprived quintile (1).**

	Rate per 100,000 person-years (95% CI)					RR (95% CI)
	IMD quintile					5:1
	1 (least deprived)	2	3	4	5 (most deprived)	
All pathogens	159.47 (158.28 - 160.68)	156.40 (155.23 - 157.58)	150.82 (149.68 - 151.96)	128.69 (127.65 - 129.74)	115.10 (114.12 - 116.10)	0.72 (0.71 - 0.73)
<i>Giardia</i>	9.86 (9.57 - 10.17)	9.18 (8.90 - 9.47)	9.10 (8.83 - 9.39)	6.84 (6.60 - 7.08)	6.00 (5.77 - 6.23)	0.61 (0.58 - 0.64)
<i>Campylobacter</i>	111.98 (110.98 - 112.98)	107.47 (106.50 - 108.45)	100.25 (99.32 - 101.18)	82.04 (81.21 - 82.88)	68.98 (68.21 - 69.75)	0.62 (0.61 - 0.62)
Non-typhoidal <i>Salmonella</i>	14.51 (14.15 - 14.88)	14.67 (14.32 - 15.04)	15.31 (14.95 - 15.68)	15.39 (15.04 - 15.76)	15.45 (15.09 - 15.82)	1.06 (1.03 - 1.10)
Norovirus	10.62 (10.31 - 10.93)	11.97 (11.65 - 12.30)	12.41 (12.08 - 12.74)	11.83 (11.52 - 12.15)	12.58 (12.26 - 12.91)	1.18 (1.14 - 1.23)
<i>Shigella sonnei</i>	1.37 (1.27 - 1.49)	1.66 (1.54 - 1.78)	1.72 (1.60 - 1.84)	1.70 (1.59 - 1.83)	1.65 (1.53 - 1.77)	1.20 (1.08 - 1.34)
<i>Other Shigella</i>	0.87 (0.78 - 0.96)	0.82 (0.74 - 0.91)	1.16 (1.06 - 1.26)	1.19 (1.09 - 1.29)	1.21 (1.11 - 1.32)	1.40 (1.23 - 1.60)
<i>Shigella flexneri</i>	0.51 (0.45 - 0.59)	0.69 (0.61 - 0.77)	0.98 (0.89 - 1.07)	1.30 (1.20 - 1.41)	1.30 (1.20 - 1.41)	2.52 (2.16 - 2.95)
<i>Salmonella</i> typhi/paratyphi	0.39 (0.34 - 0.46)	0.37 (0.32 - 0.43)	0.66 (0.58 - 0.74)	0.98 (0.89 - 1.08)	1.13 (1.03 - 1.23)	2.87 (2.41 - 3.42)

**Table 3. Univariate logistic regression for pathogens with case categories 0, 1, >=2.**

Pathogen	IMD quintile	OR (>=1 cases compared to 0 cases) (95% CI)	OR (>=2 cases compared to <= 1 cases case) (95% CI)	OR (Proportional odds assumption met) (95% CI)	p-value
<i>Shigella sonnei</i>	1 (least deprived)	1.00	1.00		0.0061
	2	1.09 (0.96-1.24)	1.50 (1.08-2.09)		
	3	0.99 (0.87-1.13)	1.47 (1.06-2.05)		
	4	1.05 (0.93-1.19)	1.84 (1.34-2.52)		
	5 (most deprived)	1.06 (0.94-1.21)	1.85 (1.35-2.54)		
<i>Other Shigella</i>	1	1.00	1.00	1.00	<0.001
	2			0.89 (0.76-1.05)	
	3			0.97 (0.83-1.14)	
	4	1.18 (1.01-1.38)	1.68 (1.26-2.24)		
	5	1.23 (1.05-1.43)	1.99 (1.51-2.63)		
<i>Salmonella typhi/paratyphi</i>	1			1.00	<0.001
	2			0.89 (0.69-1.14)	
	3			1.47 (1.18-1.83)	
	4			2.21 (1.80-2.71)	
	5			2.49 (2.03-3.05)	
<i>Shigella flexneri</i>	1			1.00	<0.001
	2			1.24 (1.02-1.50)	
	3			1.59 (1.33-1.92)	
	4			2.34 (1.97-2.78)	
	5			2.46 (2.08-2.93)	

**Table 4. Univariate logistic regression for pathogens with case categories 0, 1, 2, >=3.**

Pathogen	IMD quintile	OR (>=1 cases compared to 0 cases) (95% CI)	OR (>=2 cases compared to =< 1 cases case) (95% CI)	OR (>=3 cases compared to =< 2 cases case) (95% CI)	OR (Proportional odds assumption met) (95% CI)	p-value
<i>Giardia</i>	1 (least deprived)	1.00	1.00	1.00	1.00	<0.001
	2				0.88 (0.82-0.94)	
	3				0.83 (0.77-0.89)	
	4	0.69 (0.64-0.74)	0.63 (0.58-0.70)	0.55 (0.48-0.63)		
	5 (most deprived)	0.60 (0.56-0.65)	0.53 (0.48-0.59)	0.45 (0.39-0.52)		
Non-typhoidal <i>Salmonella</i>	1				1.00	0.0042
	2				1.00 (0.93-1.06)	
	3				1.00 (0.94-1.07)	
	4				1.07 (1.00-1.14)	
	5				1.09 (1.03-1.17)	
Norovirus	1				1.00	<0.001
	2				1.18 (1.10-1.27)	
	3				1.22 (1.14-1.31)	
	4				1.15 (1.07-1.23)	
	5				1.29 (1.20-1.38)	

**Table 5. Univariate logistic regression for pathogens with case categories 0-5, 6-10, >=11.**

Pathogen	IMD quintile	OR (≥6 cases compared to ≤5 cases) (95% CI)	OR (≥11 cases compared to ≤10 cases case) (95% CI)	OR (Proportional odds assumption met) (95% CI)	p-value
<i>Campylobacter</i>	1 (least deprived)	1.00	1.00	1.00	<0.001
	2			0.86 (0.81-0.92)	
	3	0.67 (0.62-0.72)	0.74 (0.68-0.81)		
	4			0.40 (0.38-0.43)	
	5 (most deprived)	0.25 (0.23-0.27)	0.17 (0.15-0.20)		

Accepted Manuscript

**Table 6. Multivariable analysis results for all pathogens.**

Pathogen	IMD quintile	OR <sup>1</sup> (≥1 cases compared to 0 cases) (95% CI)	OR (≥2 cases compared to < 1 cases case) (95% CI)	OR (Proportional odds assumption met) (95% CI)	p-value <sup>2</sup>
<i>Campylobacter</i>	1 (least deprived)	1.00	1.00	1.00	<0.001***
	2			0.93 (0.91-0.95)	
	3	0.86 (0.84-0.88)	0.83 (0.81-0.86)		
	4	0.73 (0.71-0.75)	0.68 (0.66-0.70)		
	5 (most deprived)	0.66 (0.64-0.68)	0.55 (0.53-0.57)		
<i>Giardia</i>	1	1.00	1.00	1.00	<0.001***
	2			0.89 (0.84-0.93)	
	3			0.82 (0.78-0.87)	
	4	0.69 (0.66-0.73)	0.59 (0.53-0.66)		
	5	0.63 (0.59-0.67)	0.56 (0.50-0.63)		
<i>Shigella sonnei</i>	1			1.00	<0.001***
	2			1.07 (0.96-1.21)	
	3			0.92 (0.82-1.04)	
	4			0.85 (0.75-0.95)	
	5			0.84 (0.75-0.95)	
<i>Other Shigella</i>	1			1.00	0.2581
	2			0.85 (0.73-0.99)	
	3			0.89 (0.77-1.03)	
	4			0.93 (0.81-1.08)	
	5			0.95 (0.82-1.10)	
Non-typhoidal <i>Salmonella</i>	1	1.00	1.00	1.00	0.008**
	2	0.98 (0.94-1.02)	1.06 (0.98-1.15)		
	3			0.99 (0.95-1.03)	
	4	1.00 (0.96-1.04)	1.07 (0.99-1.15)		
	5			1.04 (1.00-1.09)	
<i>Shigella flexneri</i>	1	1.00	1.00	1.00	<0.001***
	2			1.13 (0.94-1.37)	
	3			1.38 (1.15-1.65)	
	4			1.60 (1.35-1.90)	
	5	1.67 (1.41-1.98)	0.94 (0.65-1.38)		
Norovirus	1	1.00	1.00		<0.001***
	2	1.13 (1.07-1.18)	1.27 (1.14-1.40)		
	3	1.15 (1.10-1.21)	1.30 (1.17-1.44)		
	4	1.16 (1.10-1.22)	1.29 (1.16-1.43)		
	5	1.35 (1.28-1.42)	1.48 (1.33-1.64)		
<i>Salmonella typhi/paratyphi</i>	1			1.00	<0.001***
	2			0.87 (0.69-1.11)	
	3			1.35 (1.09-1.68)	
	4			1.66 (1.35-2.04)	
	5			1.79 (1.47-2.20)	

1. Multivariable analysis adjusted for categorical sex, age, rurality/urbanicity, distance to the GP and interaction between rurality/urbanicity and distance to the GP  
2.\* p<0.05 \*\*p<0.01 \*\*\*p<0.001