Locally acquired Hepatitis E in Cornwall, UK. Geographical clustering, environmental and social factors: a case control study

[1,2]Jeremy G Hunter, [1,2]Richard G Madden, [1,2]Ashleigh M Stone, [1]Nick Osborne, [1]Ben Wheeler, [2]Louisa Vine, [3]Maggie Barlow, [3]James Lewis, [1,4]Richard P Bendall, [5]Nan X Lin, [5]William E Henley, [1]William H Gaze, [1,2]Harry R Dalton

[1]European Centre for Environment & Human Health, Peninsula College of Medicine & Dentistry, Universities of Exeter and Plymouth, Truro UK; [2]Cornwall Gastrointestinal Unit, Royal Cornwall Hospital Truro, Cornwall, UK; [3]Health Protection Agency, St Austell, Cornwall, UK; [4]Clinical Microbiology, Royal Cornwall Hospital Truro, Cornwall, UK; [5]Centre for Health and Environmental Statistics, University of Plymouth, Plymouth, UK.

Corresponding Author

Dr Harry Dalton BSc DPhil (Oxon) FRCP

Cornwall Gastrointestinal Unit

Royal Cornwall Hospital

Truro, UK, TR1 3LJ

email harry.dalton@rcht.cornwall.nhs.uk

Tel: 0044 1872253858. Fax: 0044 1872252794

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ABSTRACT

Background and Aims

HEV is an emerging infection in developed countries, and is considered a porcine zoonosis. In most cases the route of infection is uncertain. A previous study showed that HEV was associated geographically to pig farms and coastal areas. AIM: To study the geographical, environmental and social factors in HEV infection.

Methods:

Cases of HEV and controls were identified from 2047 consecutive patients attending a rapid-access jaundice clinic. For each case/control the following were recorded: distance from home to nearest pig farm, distance from home to coast, rainfall levels during the 8 weeks prior to presentation and socioeconomic status. A further 611 Cornish residents were tested for anti-HEV IgG.

Results:

33 cases and 132 age/sex matched controls were identified. 20/33 HEV cases clustered in the west of Cornwall. (OR= 2.7, 95% CI= 1.1 to 6.5, p= 0.023). There was no difference in seroprevalence between west Cornwall and the remaining study area. There was no difference between cases and controls in distance from the nearest pig farm, socioeconomic status or rainfall during the 8 weeks preceding disease presentation. Cases were more likely to live within 2000m from the coast (OR=2.49, 95% CI= 1.13 to 5.4, p=0.022).

Conclusion:

Cases of HEV cluster in the west of Cornwall. This is not due to increased exposure to HEV at population level as HEV seroprevalence was constant across the study area. Living within 2000m of the coast appears to be a risk factor for contracting HEV. The reason for this is uncertain.

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Key words

Hepatitis E virus (HEV), epidemiology, environment, pigs, socioeconomic status, flooding.

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INTRODUCTION

Hepatitis E infection is the commonest cause of acute viral hepatitis worldwide and is endemic in many developing countries. In the majority of cases it causes a self-limiting hepatitis in young adults, but pregnant females or patients with chronic liver disease have a significant mortality. In this setting hepatitis E virus (HEV) is transmitted oro-faecally, often via infected water supplies, frequently resulting in outbreaks involving thousands of cases [1].

Locally acquired hepatitis E infection is increasingly recognised in developed countries [2,3], where it is considered an emerging infection [3]. In contrast to developing countries where disease incidence is higher in juveniles and young adults of either sex, acute hepatitis E infection causes a self-limiting hepatitis mainly in middle aged and elderly men. Mortality rates of up to 10% have been observed, the deaths largely occurring in patients with pre-existing chronic liver disease [2,3,4]. Chronic hepatitis E infection with associated cirrhosis has also been demonstrated in immunosuppressed individuals, including transplant recipients receiving immunosuppressive therapy [5,6], and patients with haematological malignancies [7] and HIV infection [8].

Waterborne transmission has been implicated in large genotype 1 and 2 outbreaks where the disease is restricted to humans [1]. However, in developed countries hepatitis E genotype 3 is thought to be a porcine zoonosis and has been identified in pig herds worldwide [3]. HEV genotype 3 has also been transmitted by consumption of infected pork products [9,10,11], but in most cases the exact route of transmission remains uncertain [12]. Environmental contamination with HEV is incompletely

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understood, but HEV has been found in pig slurry lagoons, watercourses, and human sewage [13,14]. These observations suggest that environmental factors may be important in the transmission of HEV from pigs to humans, and that waterborne transmission of HEV genotype 3 (as in genotypes 1 and 2) may be a significant route of transmission.

Few data are available regarding geographical and environmental factors relating to hepatitis E infection, but one study suggested that hepatitis E cases appeared to cluster around the coast [15]. The aim of the study was to investigate geographical, environmental, and social factors associated with locally acquired hepatitis E infection, using a case-control approach.

PATIENTS AND METHODS

The setting

Cornwall is a geographically isolated maritime peninsula situated at the extreme southwest tip of mainland Britain (figures 1a and 1b). Cornwall has a surface area of approximately 3500 Km^2 and a population of approximately 530,000 [16]. During the summer months the population is considerably increased by visitors on holiday. The study was based at the Royal Cornwall Hospital in Truro, a teaching hospital of 850 beds. This institution has a catchment population of approximately 400,000 and covers most of Cornwall, except for parts of eastern parts of the county (figure 1c) who seek secondary health care services from the adjacent county. Cornwall is an ideal geographic area to perform epidemiological studies due to its static population, low levels of immigration and geographic isolation. Hepatological studies are of

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particularly of particular interest in this regard due to the existence of the well established rapid access Jaundice Hotline clinic [17].

The Jaundice Hotline

The Jaundice Hotline provides a fast track referral system for patients with jaundice in Cornwall. Our data was prospectively drawn from the 2047 consecutive patients attending this clinic based at the Royal Cornwall Hospital, between 1998-2011. Any patient with jaundice in the community may be referred by their primary care physician for an out-patient assessment at the Jaundice Hotline. Such patients are seen and assessed within 72 hours of referral. A detailed history, including risk factors for viral hepatitis, alcohol consumption and drug history is taken, together with a full clinical examination. All patients undergo abdominal ultrasound examination for evidence of parenchymal liver disease or biliary obstruction. Patients with no biliary obstruction have serological tests to screen for parenchymal liver disease with autoantibodies, immunoglobulins, iron and copper studies and serum alpha-1 antitrypsin concentration. Patients are also tested for acute and chronic viral hepatitis including hepatitis A, B, C, E, *Epstein Barr virus*, and *Cytomegalovirus*.

Cases

The cases were identified by the Clinical Microbiology laboratory at the Royal Cornwall Hospital. Many of the cases presented to the Jaundice Hotline clinic but a minority were identified from hospital inpatients. Details of laboratory testing, clinical features and natural history of cases of locally acquired hepatitis E in Cornwall have been described in detail elsewhere [18]. All PCR positive cases were HEV genotype 3. Cases of hepatitis E were excluded from the current study if they had travelled outside the UK in the 8 weeks prior to presentation. Cases of hepatitis E

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in holiday makers visiting Cornwall were also excluded from the study if they had been resident in Cornwall for less than 2 weeks prior to symptom onset.

Controls

The control population was drawn from patients presenting to the Jaundice Hotline over the same time period, and found not to have hepatitis E infection. Controls were age and sex matched to the cases in a ratio of 4:1. Due to postulated associations [19], control patients were excluded from the study if the cause of their jaundice was viral hepatitis or alcohol related disease. Control subjects were also excluded if they were not normally resident in Cornwall, for example holidaymakers.

Demographic, geographic and environmental data

The home residential location (postcode) for each case and control was recorded. The postcode of all pig-holdings in Cornwall over the study period was obtained from Health Protection Agency records. Rainfall data in Cornwall was obtained from the UK Government's Environment Agency's national Flood Reconnaissance Information System obtained in response to a datashare request. Rainfall data were derived from highly accurate rain gauges within 2km of each of the case and control residences. For each subject the following variables were measured:

- the distance from the place of residence to the nearest pig holding
- the distance from the place of residence to the coast
- amount of local rainfall in each of the 8 weeks prior to presentation
- the district council in which the individual resided

In addition, an index of socioeconomic deprivation, the Index of Multiple Deprivation score was obtained for each postcode. This score combines 37 indicators into seven

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domain indices including income, employment and health deprivation and disability, education, skills and training, barriers to housing and services, living environment and crime [20]. Participants were categorised into socioeconomic status (SES) quintiles for analysis, with the most deprived quintile used as reference.

Seroprevalence data

To determine geographical variations in seroprevalance across the study area, 611 Cornish residents were tested for anti-HEV IgG (Wantai Biological Pharmacy Enterprise, Beijing, China). These individuals were aged ≥ 18 years with no history of liver disease and were identified from in-patients and out-patients attending the Royal Cornwall Hospital, Truro. For each individual tested in this way, the home postcode was recorded.

Statistics

Logistic regression models with adjustment for age, sex, socioeconomic index, and urban or rural living were used to explore differences in the distributions of geographical and environmental factors between cases of hepatitis E infection and the controls. Exposure effects were expressed as odds ratios with 95% confidence intervals. The shape of the relationship between age and anti-HEV IgG seroprevalence in different districts was explored using logistic regression models with linear and quadratic terms for age. Effects of district-level summaries of the geographical and environmental factors on annual incidence of HEV were tested using Poisson regression models with an offset term for the 2010 annual population in each district. All statistical analyses were conducted using the R Foundation software version 2.15.0 (Vienna, Austria) [21].

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The dataset was analysed with and without the two eastern most districts of Cornwall, as part of these districts were outside our institution's catchment area. The data were also analysed with and without the Isles of Scilly, as this is a small archipelago 28 miles off the southwest tip of Cornwall with a population of approximately 2000, and not representative demographically or geographically.

Ethics

This study had ethical approval from the SW regional ethics committee.

RESULTS

Forty cases of hepatitis E were identified during the study period. Of these 40 cases, 7 cases were excluded from the study as evidence suggested the infection was contracted from outside Cornwall. This included four cases in holidaymakers who had been resident in Cornwall for less than 2 weeks, and three cases in Cornish residents who had travelled abroad in the previous 8 weeks (Spain, n=2; southern France, n=1). The remaining 33 patients had a median age of 63 years (range 41-86 years) and 24 were male. 20/33 patients were identified at the Jaundice Hotline clinic, and 13 were hospital in-patients. One hundred and thirty two age and sex matched controls were included in the study. The diagnoses in these patients were: common bile duct stones (n=40), pancreatic carcinoma (n=18), drug-induced hepatitis (n=16), cholangiocarcinoma (n=13), hepatic metastases (n=10), miscellaneous (n=35).

The geographical distribution of cases and controls is shown in Figure 2 and Table 1. The geographical spread of cases was not even, with 20/33 cases in the two most

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western districts (Penwith and Kerrier). Analysis of the complete dataset showed a borderline significant increase (OR= 2.1, 95% CI= 1.0 to 4.7, p= 0.056) in cases in west Cornwall (Penwith and Kerrier), compared to central Cornwall (Carrick and Restormel). Analysis of the dataset excluding N Cornwall, Caradon and the Isles of Scilly showed the above difference to be significant (OR= 2.7, 95% CI= 1.1 to 6.5, p= 0.023). Prevalence of hepatitis E did not vary between quintiles of SES (top quintile excluded as only one participant).

The district-level incidence of HEV had a negative association with the number of pig holdings (IRR per increase of 100 pig holdings=0.53, 95% CI= 0.34-0.84, p=0.006), and a positive association with the number of people per pig holding (IRR per increase of 100 people per pig holding=1.36, 95% CI= 1.07-1.73, p=0.01). However, no association was seen between the incidence of HEV and the number of pig holdings per km^2 (IRR per increase of 0.1 pig holdings per km^2= 1.00, 95% CI= 0.75-1.33, p=0.99).

Compared to controls, cases were more likely to live within 2000m of the coast (OR=2.49, 95% CI= 1.13 to 5.4, p=0.022, table 2A, figure 2). This association remained after accounting for a variety of potential risk factors including age, sex, SES, rural living and proximity to pig farms (Table 2B).

The geographical relationship between place of residence and the nearest pig-holding is shown in Figure 3. There was no difference in the median distance from the homes of the cases and controls to the nearest pig holding, which was 625 m (range 0-2560 m), and 626 m (range 0-45312 m) respectively (p=NS).

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In the 8 weeks prior to presentation there was no difference between cases and controls in total local rainfall (p=0.15), total local rainfall as a percentage of long term average rainfall (p=0.66), or mean weekly rainfall (p=0.15). Logistic regression analysis showed no relationship between weekly excessive local rainfall in the 8 weeks prior to presentation (categorised as average weekly rainfall of up to 200%, 200-300%, 300-400% and >400% of expected weekly average) and cases of HEV.

The seroprevalence of anti-HEV IgG in 611 Cornish residents increased gradually with age (p<0.001; Figure 4). After adjusting for age and sex, there was no difference in anti-HEV IgG seroprevalence between west Cornwall and either central Cornwall (p=0.57) or east Cornwall (p=0.53).

DISCUSSION

The findings of this study show that, compared to controls, cases of locally acquired hepatitis E infection in Cornwall are not randomly geographically distributed, but occur more commonly in individuals who live within 2000 m of the coast and who live in the west of the peninsula. The reasons for these observations are uncertain. A previous study suggested that locally acquired hepatitis E is more common in coastal and estuarine areas of England [15]. Our study confirms these provisional findings. It has been previously postulated that this clustering is explained by the fact that older people tend to live near the coast, and HEV has a predilection for the middle aged and elderly. Our case control data would argue against this hypothesis, as the cases and controls were age and gender matched.

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There are a number of other possible explanations for the observation that cases of HEV3 cluster around the coast. These include dietary habits such as the consumption of shell fish. However, there was no difference in shell fish consumption in those cases that lived less than 2000m from the coast compared to those that lived further away [data not shown]. Coastal areas of Cornwall, with their steep sided valleys, are prone to higher levels of flooding which may increase exposure to waterborne pollutants in bathing water. Flood water could be contaminated with HEV, particularly if downstream from pig farm 'run-off'. However, we found no relationship between cases and proximity to pig farms or excessive local rainfall.

The incidence of hepatitis E infection was found to be higher in west Cornwall, compared to other parts of the county. In fact, one village in west Cornwall (population of 1200 inhabitants) experienced three cases of hepatitis E in 2 years. This higher frequency of infection appears not to be due to increased exposure at a population level, as there were no geographical differences in anti-HEV IgG seroprevalence between differing parts of Cornwall. The higher incidence of cases in west Cornwall could have a number of explanations. Firstly, it might be due to exposure to HEV at higher viral loads, as there appears to be a relationship between viral load and severity of illness, at least in non-human primates [22]. Secondly, the route of exposure might influence clinical disease expression. Thirdly, host factors may play a role, as clinically overt hepatitis E infection appears to be more common in individuals who consume more than 22 units of alcohol per week [19]. We were unable to explore this latter possibility and its effect as a confounding variable as there are no local data on geographical differences in alcohol consumption. Finally, the geographic shape of Cornwall is such that the ratio of length of coast to inland land area increases the further west you travel, as the north and south coastlines

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converge at the southwestern tip of the peninsula, i.e. most residents of west Cornwall live quite close to the coast because of the local topography.

Geographical clustering of hepatitis E is poorly documented in other developed countries. The best data comes from France, where seroprevalence studies suggest that there is a north:south gradient. Anti-HEV IgG seroprevalence in northern France is very low [23], but is very high in the south [24]. HEV appears to be hyperendemic in Midi Pyrennes (the area around Toulouse in southwestern France), with seroprevalence in blood donors of 52% [11] and an incidence in transplant patients of 3.2% [24]. In the Toulouse area, it has been suggested that the main route of infection is via the consumption of infected meat products, as high viral loads of HEV have been found in local sausage which is consumed without cooking [10,11]. It is impossible to apply our findings regarding coastal mapping of cases of hepatitis E to the Toulouse area, as Toulouse is more than 200Km from the nearest coast. However, this does not exclude the possibility of waterborne infection, as there are two major watercourses that run through this region.

There was no relationship between cases of hepatitis E and proximity of residence to pig-holdings. This suggests that contamination of the local environment adjacent to pig farms is not an important route of infection. However, very close proximity to pigs is thought to be a possible route of infection as anti-HEV IgG seroprevalence is high in pig-handlers and swine veterinarians [25,26,27]. We were surprised at the very large number of pig farms that exist in Cornwall, and very few of the cases or controls lived more than a few kilometres from the nearest pig-holding. As we had a relatively small number of cases of hepatitis E, the study may have not had enough power to show a true difference. Some of these pig-holdings rear many hundreds of pigs, and

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some only one or two. This was not accounted for in the analysis, and it could be that environmental risk of hepatitis E infection relates to the size of the pig-holding, with large farms potentially producing the greatest risk in terms of the quantum of HEV contaminating the immediate environment.

Little is known about the influence of SES in hepatitis E infection. We found no influence of SES in patients with hepatitis E, but this may be partially due to lack of power with the limited numbers of cases. Inclusion of SES of participants had little effect on the strength of the relationship between distance from coast of domicile and risk of HEV infection and detection.

The study has a number of strengths. It was conducted using a very well characterised and documented cohort of cases of locally acquired hepatitis E. The study area was discrete, geographically isolated, with mainly one provider of secondary care services. Finally, the controls and most of the cases were identified from a well-established fast-track clinic that over the study period prospectively recorded clinical, laboratory and outcome data on all patients.

This study has some weaknesses. For instance, the number of cases was small and so the study may not have sufficient power to show true relationships. It would have been preferable to have performed a nested case control study with all patients identified from the same source. This was not possible due to the small number of cases, therefore some of the cases were identified from the hospital in-patient population. All proximity measurements were made using the patient's domiciled address. Whilst it would have been useful to have undertaken a similar exercise with the patient's place of work, it was felt that this would only have a marginal effect at best, as most patients were elderly and retired. The consumption of undercooked pork

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is known to be a risk factor for contracting Hepatitis E [10]. None of the patients with hepatitis E in our study were vegetarian, and all ate pork or pork products (data not shown). However, dietary details from the control cohort were not available, precluding dietary analysis. Direct exposure to pigs has also been shown to be a risk factor for hepatitis E. This study did not examine the strength of association between patients and pig farm workers. Both these analyses may provide an alternative explanation to the environmental hypothesis of disease transmission.

In conclusion, compared to controls, patients with hepatitis E are more likely to live within 2000m of the coast and cases cluster in the west of Cornwall. Proximity to pig farms, local rainfall levels, and socio-economic status appear not to be important factors in patients with hepatitis E. These findings suggest that environmental factors may be important in HEV genotype 3 exposure in humans. Detailed environmental studies are underway to explore this possibility.

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Table 1.

Distribution of cases of hepatitis E, pigs and people, by district council, Cornwall 1998-2011

	Scilly Isles	Penwith	Kerrier	Carrick	Restormel	North Cornwall	Carradon
Population*	2,111	64,331	101,219	93,924	104,218	87,658	83,984
Cases HEV (n=)	0	12	8	5	4	2	2
Incidence of HEV**	0	0.15	0.066	0.044	0.032	0.018	0.02
IMD 2007 score (sd)	Na	29.17 (6.7)	24.40 (7.1)	19.50 (6.6)	22.99 (7.6)	25.68 (10.6)	22.99 (2.96)
Pig holdings (n=)	0	99	239	251	175	348	240
People/pig/holding	Na	649	423	347	595	251	349
Land area (Km2)	Na	310	479	472	458	683	1200
Pig holdings/Km2	0	0.32	0.5	0.53	0.38	0.51	0.2

Notes:
Penwith and Kerrier = west Cornwall, Carrick and Restormel = central Cornwall, North Cornwall and Caradon = east Cornwall
** 2010 figures [16]*
*** Annual incidence over the study period per 10^5 population*
Na = not available

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Table 2.

2A. Logistic regression models comparing age, sex and distance from the place of residence to the coast in HEV cases and controls.

	All data				Excluding data for Caradon, North Cornwall and Isles of Scilly			
	N	Odds Ratio	95% CI	p-value	N	Odds Ratio	95% CI	p-value
Male	118				106			
Female	45	0.98	0.42, 2.31	0.962	43	1.14	0.47, 2.75	0.773
Age at diagnosis								
Up to 60	59				55			
Over 60	104	0.99	0.45, 2.19	0.982	94	0.79	0.35, 1.81	0.579
Distance from the coast								
> 2,000m	98				86			
< 2,000m	65	2.49	1.13, 5.40	0.022	63	2.72	1.18, 6.29	0.019

2B. Logistic regression models comparing age, sex and distance from the place of residence to the coast in HEV cases and controls, accounting for SES

	All data				Excluding data for Caradon, North Cornwall and Isles of Scilly			
	N	Odds Ratio	95% CI	p-value	N	Odds Ratio	95% CI	p-value
Male	118				106			
Female	45	0.94	0.40, 2.22	0.884	43	1.08	0.44, 2.61	0.869
Age at diagnosis								
Up to 60	59				55			
Over 60	104	0.99	0.44, 2.20	0.979	94	0.98	0.34, 1.81	0.576
Distance from the coast								
> 2,000 m	98				86			
< 2,000 m	65	2.52	1.15, 5.51	0.020	63	2.77	1.19, 6.41	0.018

SES = socioeconomic status. Data included from 33 cases of HEV and 130 controls (data from 2 controls were missing).

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LEGENDS TO FIGURES

Fig. 1. The geography of Cornwall UK

Fig. 1 (A)

Cornwall is a geographically isolated maritime peninsula at the tip of southwest Britain, shaded in yellow.

Fig. 1(B)

Topographically Cornwall resembles an isosceles triangle, with the apex of the triangle pointing west, and the base of the triangle facing east and forming a border with the neighbouring county of Devon. The county is administered by a single local council (Cornwall County Council), but prior to April 2009 there were six district councils: Penwith and Kerrier (west Cornwall), Carrick and Restormel (central Cornwall), and North Cornwall and Carradon (east Cornwall)

Fig. 1(C)

The catchment area for the Royal Cornwall Hospital includes the population living to the west of the dashed horizontal line (figure 1c).

Fig. 2

The geographical distribution of the residences of the cases and controls

Fig. 3

The geographical distribution of the residences of the cases, controls and pig-holdings

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Fig. 4

Seroprevalence of anti-HEV IgG amongst the Cornish population as a whole and separately by region: west Cornwall (Penwith and Kerrier); central Cornwall (Carrick and Restormel); east Cornwall (Caradon and N Cornwall).

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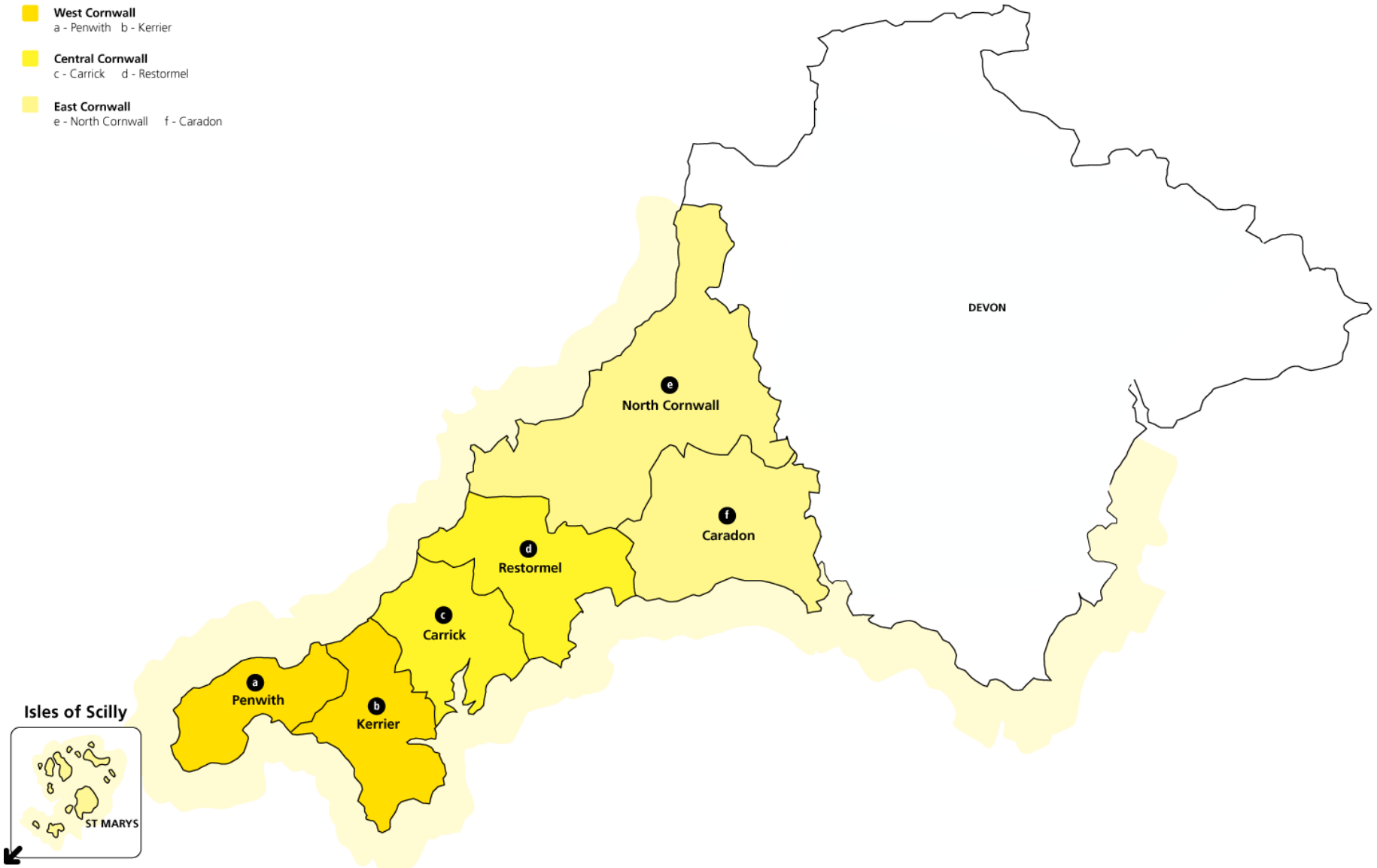
Figure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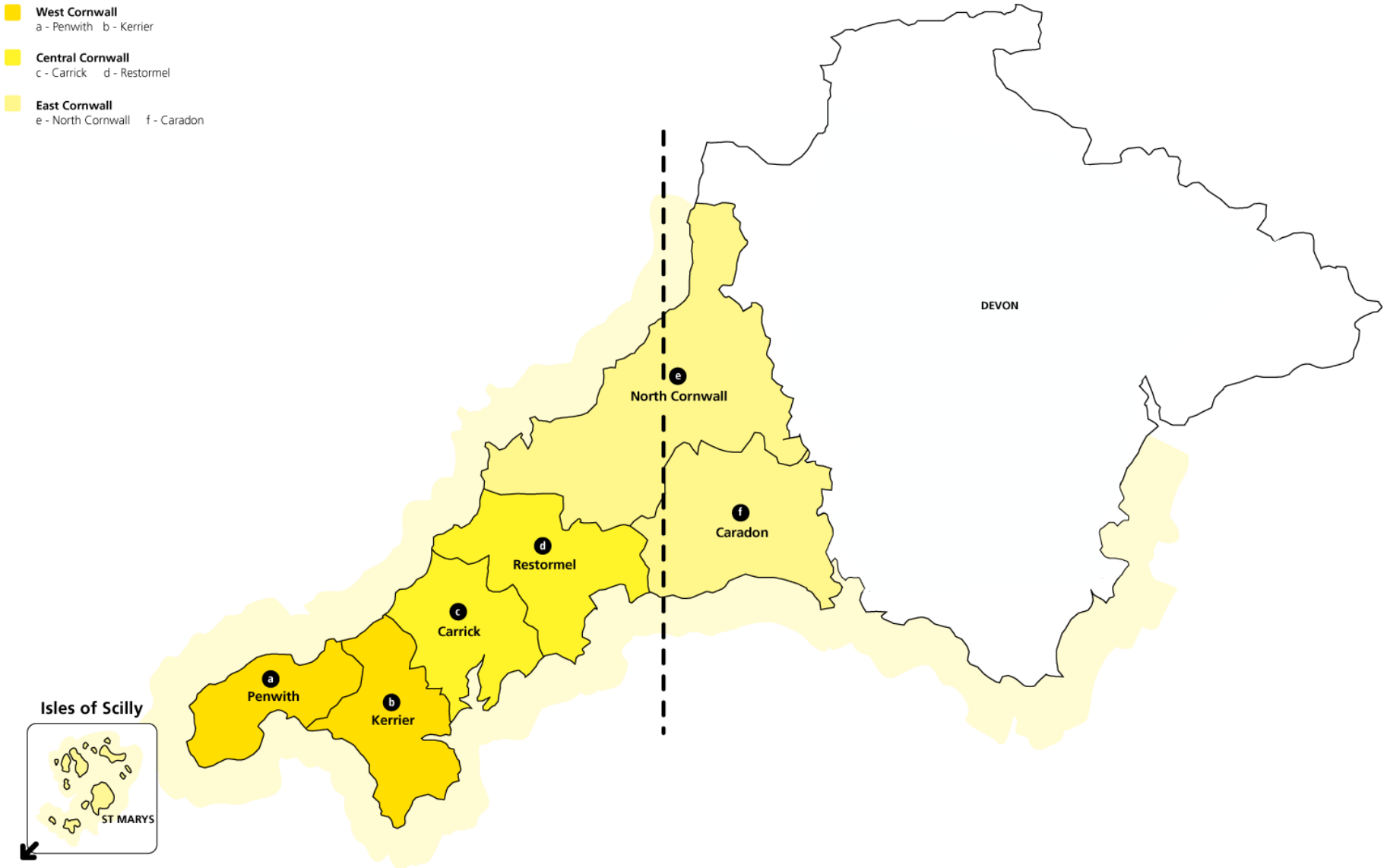
a - Penwith b - Kerrier
Central Cornwall
c - Carrick d - Restormel
East Cornwall
e - North Cornwall f - Caradon
DEVON
North Cornwall
Caradon
Restormel
Carrick
Penwith
Kerrier
Isles of Scilly
ST MARYS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DEVON
North Cornwall
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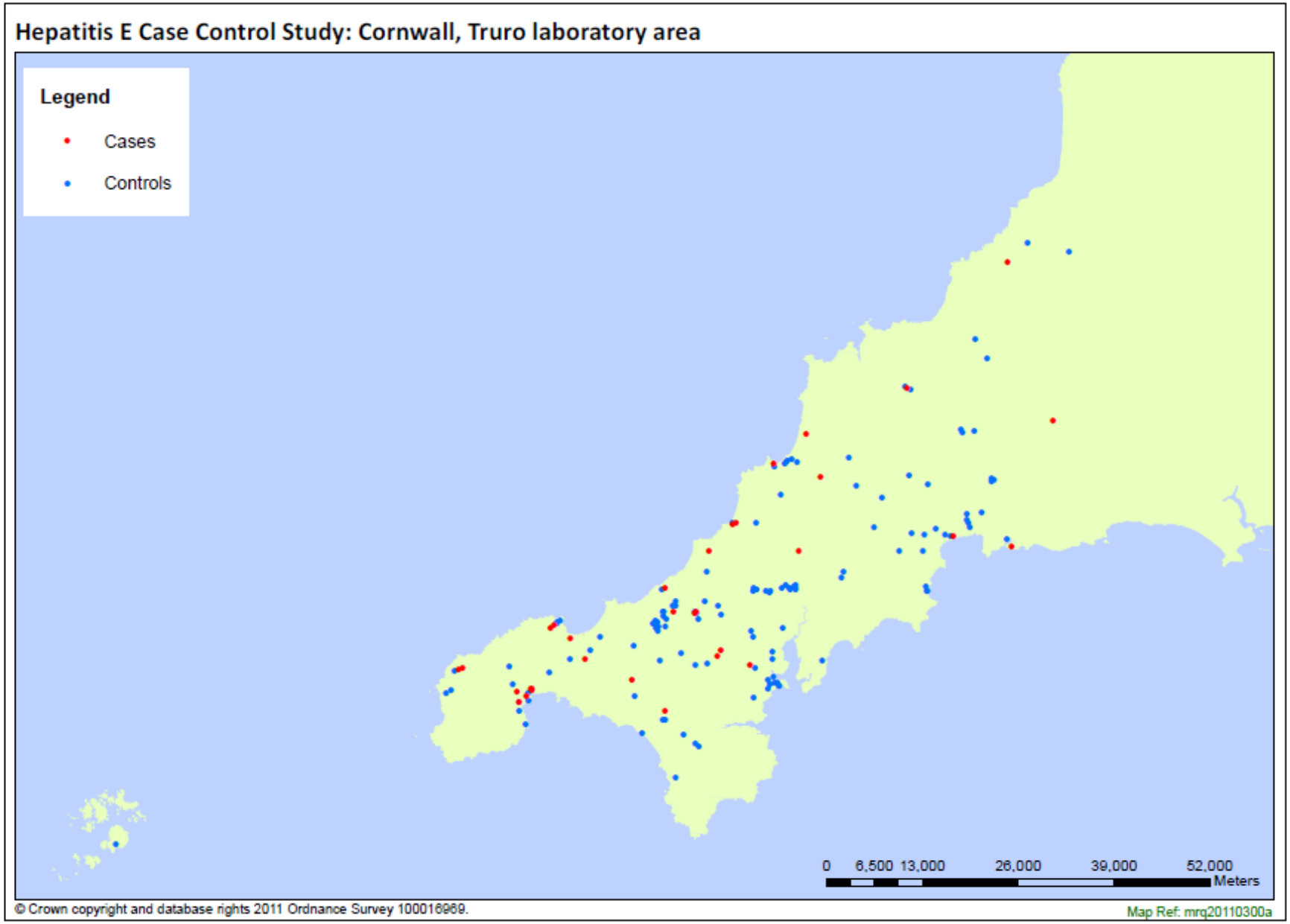
Carrick
Penwith
Kerrier
Isles of Scilly
ST MARYS

Figure


Hepatitis E Case Control Study: Cornwall, Truro laboratory area
Legend
Cases
Controls
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Meters
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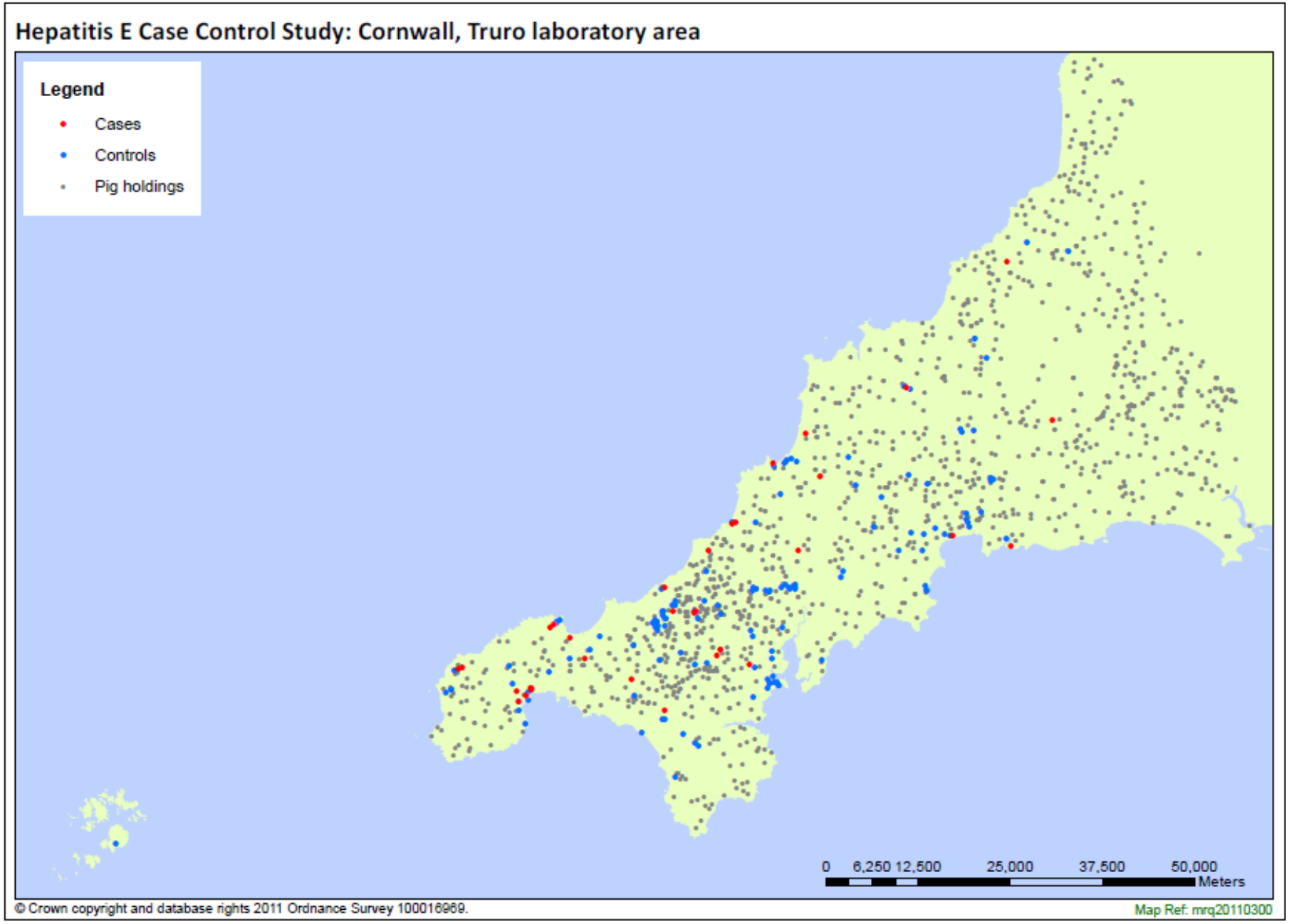
Map Ref: mrq20110300a

Figure


Hepatitis E Case Control Study: Cornwall, Truro laboratory area
Legend
Cases
Controls
Pig holdings
0 6,250 12,500 25,000 37,500 50,000
Meters
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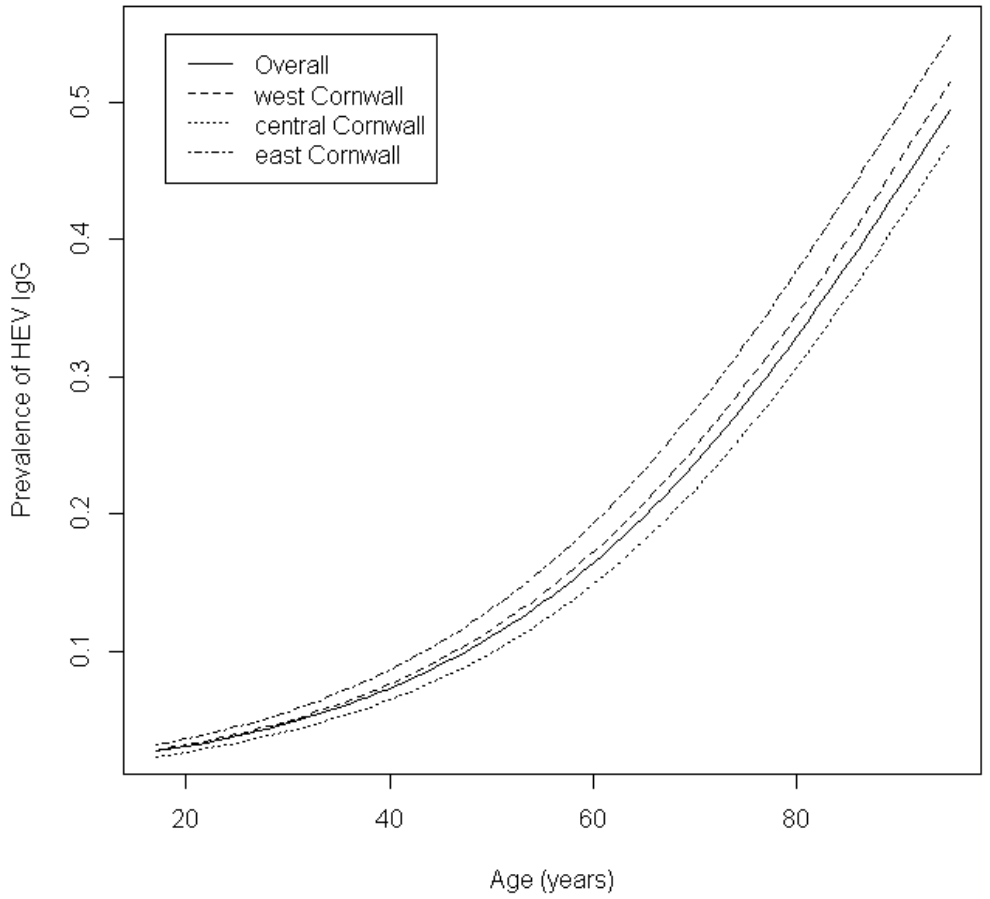
Map Ref: mrq20110300

Figure



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