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# Distance to treatment as a factor for loss to follow up of hepatitis C patients in North East England

H. Simpson<sup>1</sup>, P. Manley<sup>2</sup>, J. Lawler<sup>3</sup>, S. Morey<sup>4</sup>, E. Buchanan<sup>5</sup>, M. Hewett<sup>5</sup>, J. Knowles<sup>6</sup>, C. Miller<sup>5</sup>, B. McCarron<sup>6</sup>, M. Valappil<sup>7</sup>, S. McPherson<sup>8</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

<sup>2</sup>Field Epidemiology Service Newcastle, National Infection Service, Public Health England, Newcastle upon Tyne NE1 4WH, UK

<sup>3</sup>Public Health England, North East Health Protection Team, Newcastle upon Tyne NE1 4WH, UK

<sup>4</sup>Department of Health and Life Science, Northumbria University, Newcastle upon Tyne NE7 7XA, UK

<sup>5</sup>Viral Hepatitis Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

<sup>6</sup>Centre for Infection, James Cook University Hospital, Middlesbrough, UK

<sup>7</sup>Viral Hepatitis Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Public Health Laboratory North East, PHE, Newcastle upon Tyne, UK

<sup>8</sup>Viral Hepatitis Service, Newcastle upon Tyne Hospitals NHS Foundation Trust (Institute of Cellular Medicine, Newcastle University), Newcastle upon Tyne, UK

Address correspondence to H. Simpson, E-mail: hopesimpson@hotmail.co.uk

## ABSTRACT

**Background** A large proportion of the 200 000 HCV-infected individuals in the UK are undiagnosed or lost to follow-up. Engaging known infected individuals in treatment is essential for elimination.

**Methods** Using PHE surveillance data and HCV treatment registers from North East of England (NE) treatment centres for 1997–2016, we estimated the number of HCV cases not linked to treatment and the proportion with active infection. We compared distances of treated and untreated cases to treatment services, and assessed the effect of expanding HCV treatment into existing drug and alcohol treatment centres in the NEE on treatment accessibility.

**Results** The odds of being treated was associated with distance to treatment services. Confirmatory results for ~50% were not reported to PHE NE. Overall, 3385 patients reported to PHE NE had no record of treatment; we estimated 1621 of these may have been lost to follow-up after confirmation of active infection.

**Conclusions** Poor access to healthcare services may contribute to under-diagnosis or loss to follow-up. Expanding HCV treatment delivery into NEE drug and alcohol treatment centres would improve the accessibility of treatment services to people infected with/at risk of HCV. This may increase the proportion receiving treatment and support progress towards elimination.

**Keywords** communicable diseases, geography, secondary and tertiary services

## Introduction

Hepatitis C virus infection (HCV) is a major cause of liver-related morbidity and mortality in the Western world<sup>1</sup> and an important public health burden in the UK, with an estimated 200 000 people living with chronic infection, of whom a significant proportion are undiagnosed.<sup>2</sup> Most HCV infection in the UK is associated with injecting drug use. Approximately 70% of those infected with HCV develop chronic infection which is frequently asymptomatic. Consequently, HCV often remains undiagnosed for many years after infection and is sometimes only identified

H. Simpson, Research Assistant

P. Manley, Consultant Epidemiologist

J. Lawler, Specialty Registrar in Public Health

S. Morey, Senior Lecturer

E. Buchanan, Hepatitis Nurse Specialist

M. Hewett, Hepatitis Nurse Specialist

J. Knowles, Nurse Consultant in Blood Borne Viruses

C. Miller, Hepatitis Nurse Specialist

B. McCarron, Consultant Physician

M. Valappil, Consultant Virologist

S. McPherson, Consultant Physician

following complications related to end stage liver disease.<sup>1</sup> Chronic HCV patients are infectious and a potential source of onward transmission irrespective of symptoms. Untreated HCV results in persistent hepatitis that progresses to cirrhosis in ~20% of cases after 20–30 years.<sup>3</sup> HCV may result in extra-hepatic manifestations, and people with chronic infection report poorer quality of life compared with the general population.<sup>4,5</sup>

Therapeutic advances mean HCV is now eminently treatable with >95% of patients achieving sustained virological response (SVR; persistent clearance of HCV = ‘cure’) following an 8–12-week course of oral direct acting antiviral (DAA) drugs.<sup>6</sup> This provides an unprecedented opportunity to reduce HCV-associated morbidity and mortality and ultimately eliminate HCV as a public health threat, identified as a World Health Organisation target by 2030.<sup>7</sup> Elimination requires successful treatment of a critical proportion of infected individuals, alongside implementation of other available control measures.<sup>7</sup> For maximum impact, control and treatment strategies should focus on populations at highest risk, which in the UK is people who inject drugs.<sup>2</sup>

The large proportion of infected individuals unaware of their HCV status or lost to follow-up (LTFU), limits elimination efforts.<sup>7</sup> The typical treatment journey for HCV is long and complex,<sup>8</sup> with potential for loss to follow-up at all stages from testing through to treatment completion. In the UK, those at risk of HCV are diagnosed by detection of HCV antibody (anti-HCV Ab), alone or in combination with HCV antigen (HCV Ag). Presence of anti-HCV Ab indicates current or recovered infection, while HCV Ag and/or RNA indicate active infection.

To increase treatment coverage and completion rates, the identification and re-engagement of LTFU individuals is a priority for HCV Operational Delivery Networks (ODNs), which co-ordinate treatment delivery in England.<sup>9</sup> Improved understanding of the reasons for loss to follow-up is urgently required to address this problem. Public health surveillance datasets are a resource for the identification of previously diagnosed and notified cases, of which those with no corresponding treatment record represent potentially LTFU cases.

The North East and North Cumbria (NENC) HCV ODN coordinates HCV treatment in the North East of England (NEE), delivered through treatment centres in six acute NHS Trusts. Patients are also treated in prisons and some drug and alcohol treatment services (DAS). Treatment of NE patients in health facilities outside of NEE is uncommon.

We sought to estimate the burden of known active HCV infection among untreated individuals in NEE using the

PHE NE infectious disease surveillance system (EpiNorth3) and treatment registers compiled by NHS HCV treatment centres in NEE. We compared the proximity of existing treatment services to individuals known and not known to be treated and estimated the potential effect on treatment accessibility of expanding treatment delivery into all NEE DAS.

## Methods

This project was registered as a service evaluation project with the Newcastle upon Tyne Hospitals NHS Foundation Trust Clinical Governance Department.

### Data sources

#### Surveillance dataset

All HCV infections reported from 1 January 1997 to 31 December 2016 in NEE were identified from EpiNorth3. Reported infections included positive screening results for anti-HCV Ab, and positive results of tests for HCV Ag, RNA and genotype. Each reported infection was linked to its patient identifier to produce a dataset of patient records. Individual records were reviewed to identify laboratory confirmed active infection (those with a positive HCV Ag, RNA or genotype). The remainder had no recorded test to confirm active infection and hence active infection could not be distinguished from spontaneously resolved cases in this group.

#### Exclusions

Anonymised records, including those referred from sexual health clinics without patient identifiable data were excluded from further analysis. Non-NEE residents, cases from prisons (as HCV treatment services are currently delivered within prisons) and those without a valid postcode were excluded from spatial analysis (see below) after linking.

#### Treatment datasets

Treatment outcome data was available for patients who received antiviral treatment for HCV at four of the six NEE treatment centres: the County Durham and Darlington, Gateshead Health, South Tees and Newcastle-upon-Tyne Foundation Trusts, accounting for ~95% of patients treated in the NEE from 1997 to 2016. Outcomes were categorised as SVR, failed treatment, LTFU or died.

#### Record linkage

The surveillance and treatment datasets were linked to categorise those in the surveillance dataset with active infection as ‘treated’ or ‘untreated’. Individuals in the surveillance

dataset matched to cases in the treatment datasets were classified as having started treatment ('treated'), and individuals not matched to cases in the treatment datasets were classified as not known to be treated ('untreated').

A fuzzy matching function was implemented in R<sup>10</sup> to compare each case in the surveillance dataset with each case in each treatment dataset. This function calculates a similarity score for each potential match based on edit distances between corresponding fields. Edit distances can be based on the minimum number of character transpositions (Jaro–Winkler distance<sup>11</sup>) or the minimum number of character edits (Levenshtein distance<sup>12</sup>) between fields, and are adjusted so a score of zero represents no similarity and a score of one indicates an exact match. Jaro–Winkler distance was used to score the similarity of first name and surname fields; Levenshtein distance was used to compare date of birth and NHS number. A match in the sex field scored one and a mismatch scored zero. String distance scores for each field were weighted according to the relative discriminatory power of the field: NHS number was considered the most specific; followed by surname and date of birth, which were weighted equally; then by first name; and finally by sex. For each potential match, the weighted edit distances for each field were summed to derive an overall similarity score, and adjusted to a percentage.

All comparisons between the two datasets were ranked by similarity score. Each record from the surveillance dataset was linked to a single 'potential match' in the treatment dataset which was the record with the highest similarity score. A cut-off similarity score of 80% was used to define matches; potential matches below 80% were examined manually.

### Estimating the under-reporting of laboratory results

Given that all 'treated' cases would require laboratory confirmation prior to treatment initiation, matched treated cases with no recorded confirmatory test in the surveillance dataset were defined as 'non-recorded' confirmations. The ratio of 'treated' cases with 'non-recorded' confirmations to those with a recorded confirmatory result was calculated and defined as the 'non-recorded' ratio. The non-recorded ratio was applied to the number of 'untreated' individuals in the surveillance dataset without recorded confirmatory tests to estimate the number of non-matched individuals that were likely to be HCV confirmed but not recorded as such.

### Spatial analysis

Records from the surveillance cohort without a home postcode recorded were dropped from spatial analysis. Home

postcodes of all remaining individuals were geocoded and integrated in a geographical information system (ArcGIS (version 10.3, ESRI Inc., Redlands CA, USA)<sup>13</sup>) with HCV treatment service and DAS locations. Those DAS not currently providing HCV treatment were categorised as alternative treatment locations. Euclidean (straight-line) distances from individual home postcodes to current and alternative treatment locations were calculated.

Average annual rates of 'treated' and 'untreated' cases were calculated at ward-level, using 2015 ward-level populations from the Office for National Statistics<sup>14</sup> as denominators.

### Statistical analysis

For both 'treated' and 'untreated' case, Euclidian distance from home to nearest existing treatment services were used to investigate the association between proximity of services and the likelihood of having started treatment. We used the non-parametric  $k$ -sample  $\chi^2$  test for equal medians, and calculated Fisher's exact  $P$ -value (two-sided) to test the null hypothesis that the two groups were drawn from populations with the same median.

We defined two categories of proximity to the nearest treatment facility, by splitting the group at the median distance, rounded to the nearest kilometre and used univariate logistic regression analysis to estimate the effect of distance on the odds of having started treatment. The effect of distance (log-transformed) as a continuous predictor was also tested using logistic regression.

To explore the potential effect of expanding treatment delivery into all DAS in NEE, we calculated the average percentage change in median distance from the 'untreated' cases' home addresses to the nearest treatment centre, including both alternative and existing treatment locations. The null hypothesis that including the alternative treatment locations would not change the median distance to treatment was assessed with a median test (as above).

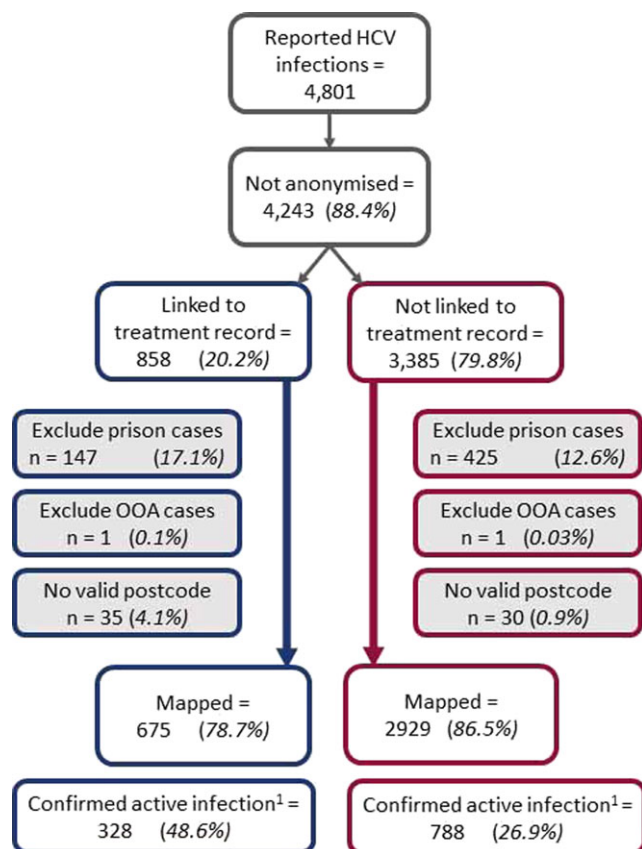
All statistical analysis was conducted in STATA 14.<sup>15</sup>

## Results

A total of 4801 reported HCV infections were recorded in the PHE NEE surveillance dataset over the study period. After exclusion of anonymised records, 4243 individuals remained in the surveillance cohort. Over the same period, 1447 patients were recorded as having received treatment at one of the NHS-Trusts included in the study. From the surveillance dataset, 858 (20.2%) were matched to a case with record of treatment ('treated'), while 3385 records could not be matched

(‘untreated’). Figure 1 shows reasons why cases were excluded or not mapped. Proportions of cases in prisons and out-of-area were similar between the matched and unmatched cases. The proportion of individuals with invalid or missing postcodes was higher amongst ‘treated’ cases (4.1 versus 0.9% missing postcode). Overall, 675 (78.7%) of the ‘treated’ cases and 2929 (86.5%) ‘untreated’ individuals were mapped.

Of the ‘treated’ individuals in the surveillance dataset, 328 (48.6%) had laboratory evidence of active HCV infection recorded within EpiNorth3, equating to a ‘non-recorded’ ratio of 1.06. In total, 788 (26.9%) ‘untreated’ individuals from the surveillance dataset had a confirmatory test result (indicating active HCV infection) recorded within the EpiNorth3 during the study period. Applying the ‘non-recorded’ ratio to this figure, we estimated ~833 additional ‘untreated’ individuals may have had HCV infection confirmed, but not recorded in EpiNorth3. This represented 1621 cases, out of 3385 ‘untreated’ records, estimated or known to have confirmed HCV infection.



**Fig. 1** Inclusion and exclusion of individuals with evidence of past or current HCV infection notified to the PHE NEE 1997–2016, numbers known to have started treatment in North East Trusts and numbers of confirmed active infections reported to PHE NEE. <sup>1</sup>Cases with positive confirmatory test results (HCV Ag or RNA detection) recorded in the surveillance system.

Figure 2 shows the distribution of rates of hepatitis C reported in the surveillance dataset from 1997 to 2016; (A) ‘treated’ and (B) ‘untreated’, at ward level, with the locations of existing treatment services in secondary care treatment hubs and drug and alcohol treatment centres, and other drug and alcohol treatment centres into which treatment delivery could be expanded.

The distributions of linear distances from home postcode to nearest existing treatment facility were highly positively skewed for both ‘treated’ and ‘untreated’ cases. The median distance to the nearest existing treatment facility for the entire surveillance cohort was 3.93 km: we categorised cases living within 4 km as ‘close proximity’.

The median distance among ‘treated’ cases was 3.43 km (interquartile range (IQR): 2.26–10.5 km), and the median among ‘untreated’ individuals was 4.20 km (IQR: 2.28–9.17 km). The Pearson  $\chi^2$  statistic for equality of medians was 5.35, with a Fisher’s exact *P*-value (two-sided) of 0.02.

Logistic regression analysis showed the odds of being treated was 1.22 (95% CI: 1.02–1.44) higher among individuals within close proximity of the nearest existing treatment facility, compared to those living further away (Table 1). There was no effect of distance as a continuous predictor.

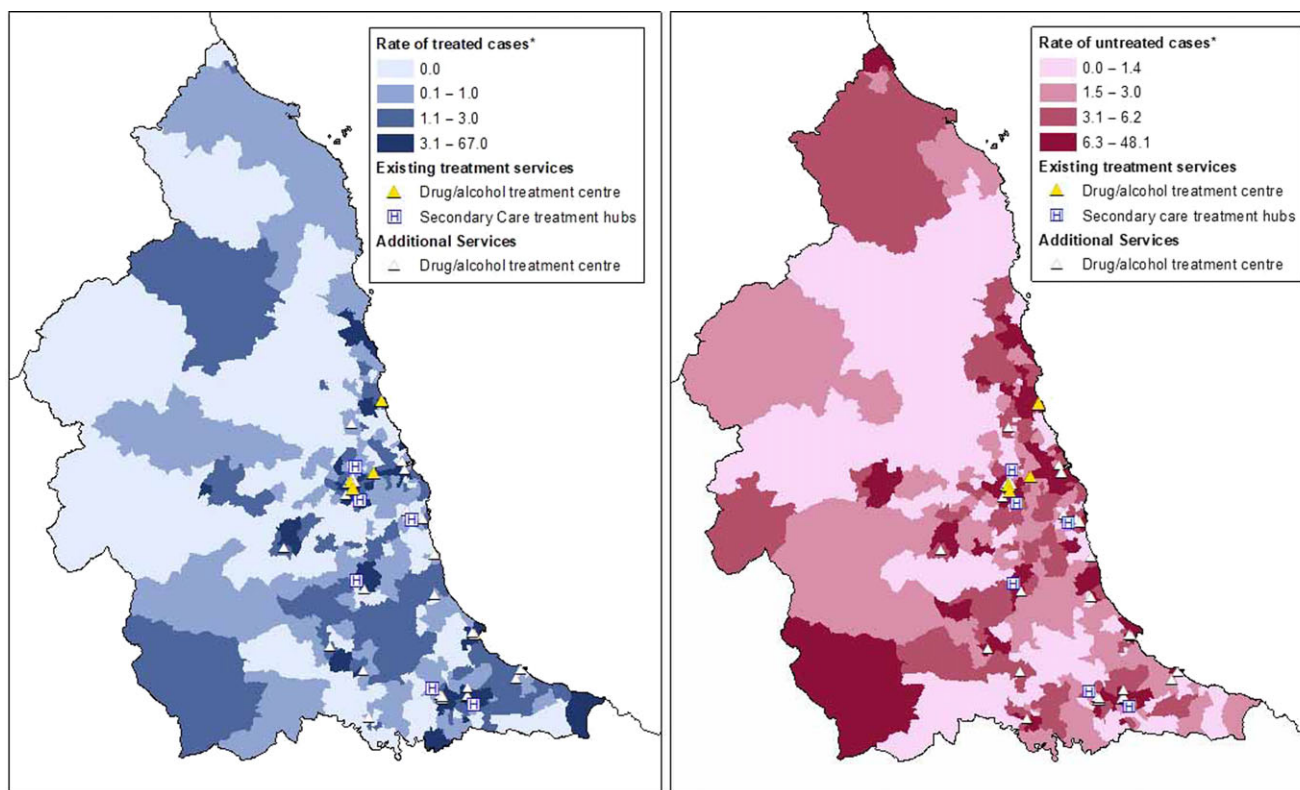
When all DAS were considered potential treatment delivery locations, the median distance to the nearest facility decreased from 3.93 to 1.79 km (IQR: 0.81–3.74 km), representing a decrease of 57.3%. The Pearson  $\chi^2$  statistic for the equality of medians was 446.64, with a Fisher’s exact *P*-value (two-sided) of <0.001.

## Discussion

### Main findings of this study

We identified 788 confirmed cases reported to PHE but with no record of treatment, and significant underreporting of confirmatory test results to PHE: of 858 patients who were notified to PHE and started treatment at one of included the NHS-Trusts over the study period, ~50% had not been reported as confirmed cases to PHE NE. Applying this scale of underreporting to the number of confirmed cases with no treatment record, we estimated the potential burden of diagnosed active HCV cases in the NEE LTFU prior to treatment initiation to be ~1621 over the study period, out of 3385 individuals with no record of treatment.

The remaining 1764 with no treatment record will include individuals with unreported negative tests, and cases LTFU before having a test to confirm active HCV infection. Some of this group will have been treated previously but, because ~70% of those with detected anti-HCV will have chronic



**Fig. 2** The average annual rate of hepatitis C reported to PHE NEE 1997–2016 and (A) who started treatment and (B) with no record of treatment, at ward level. \*Number of cases per 100 000 population per year (population figures from ONS for 2015).

**Table 1** Univariate logistic regression analysis of the effect of distance to the nearest HCV treatment service on the odds of being treated for HCV, in individuals with evidence of current or past HCV infection.

Predictor	OR of being treated <sup>b</sup>	Std. Err.	P > z	95% CI
>4 km <sup>a</sup>	1			
<4 km <sup>a</sup>	1.22	0.11	0.03	1.02–1.44
Constant	0.24	0.02	0	0.21–0.27

OR = odds ratio.

<sup>a</sup>Distance to the nearest facility offering HCV treatment.

<sup>b</sup>Defined by record of treatment for HCV in one of the North East Trusts.

infection if untreated, a large proportion are expected to have undiagnosed active HCV infection.

We found evidence that ‘treated’ individuals lived closer to HCV treatment services, compared to those who were LTFU before treatment initiation or confirmation of infection. Living within 4 km of a treatment facility was a strong predictor of having started treatment. Expanding HCV treatment into DAS in the NEE would significantly increase the geographical accessibility of HCV treatment services to untreated individuals.

### What is already known on this topic

HCV is known to be grossly under-diagnosed worldwide and in the UK,<sup>1,2</sup> although the scale of this problem is unknown. The geographical accessibility of health services is associated with uptake of various healthcare services in the UK and other high-income settings.<sup>16–18</sup> A study of HCV patients in Tayside, Scotland, found those living further from a specialist centre were less likely to be referred for treatment (although not more likely to be LTFU after referral).<sup>19</sup> HCV patients tend to be among the most deprived population sectors in the UK,<sup>20</sup> thus, the personal costs of treatment completion may be felt particularly strongly by this group.

HCV patients favour outreach clinics over the hospital setting, concordance with treatment being higher in those treated in DAS.<sup>21</sup>

### What this study adds

The evidence of the association between the distance to HCV treatment services and potential loss to follow-up has important implications for the strategic development of HCV services. The maps presented here have facilitated the strategic expansion of HCV treatment outreach services by

the NENC HCV ODN, prioritising areas with higher rates of untreated HCV. At the time of writing, the number of NEE outreach clinics has increased to 17, which has helped significantly increase treatment rates to >600/year in 2017/18. Further expansion of outreach services using the maps to identify viable treatment locations is planned.

Integrating HCV treatment with DAS in a holistic approach to managing addiction is likely to improve treatment uptake by targeting this particularly vulnerable group who are at highest risk of HCV infection. If HCV treatment services were expanded into all NEE DAS, more than 75% of 'untreated' individuals would live within close proximity of a treatment location. Delivery of HCV treatment from general practitioners' surgeries would also increase proximity of patients to treatment services. If proximity is a driver of LTFU, such service reorganisation could significantly reduce loss to follow-up.

The results of this exercise are also being used to re-engage potential LTFU cases in treatment or confirmatory testing: patients identified in this study as untreated or with unknown HCV status are being followed-up by Hepatology Assistants within the NENC HCV ODN. This is in line with recommendations from a recent All-Party Parliamentary Group on 'Eliminating Hepatitis C in England',<sup>22</sup> advising that PHE provide ODNs with data on known untreated HCV cases, so these individuals can be contacted to engage them in treatment. Targeting of testing to individuals without laboratory confirmation is expected to be a cost-effective approach to increasing treatment coverage, compared to a less targeted approach, which would result in re-testing of individuals who may already be known to have active HCV.

This work has illustrated the scale of underreporting of confirmatory results for HCV tests to PHE. Improving the reporting of HCV confirmatory testing is vital to ensure that surveillance data gives a more accurate account of HCV infection rates in the community, and is of maximum value to supporting healthcare and public health action. This exercise could be repeated in other regions through collaboration between PHE and HCV ODNs, which each maintain equivalent datasets to those in the NEE. This would provide a nation-wide estimate of the potential burden of known active, untreated HCV infection, and possible cases LTFU before confirmation.

### Limitations of this study

This study is subject to some limitations related to linking routine datasets. The group we defined as 'untreated' is likely

to contain some cases who had been treated, for example through another NHS-Trust, or under a different name. The scale of this misclassification is not possible to estimate without further data collection, but its potential impact could make the two analysis groups more similar: potentially resulting in an underestimate of the difference in proximity of treatment services between the two groups.

Around 12% of records from the surveillance database were anonymised, largely due to reporting of the infection from sexual health clinics. A proportion of this group is expected to be treated. These cases were excluded from the analysis, so anonymisation would have had little impact on the spatial analysis results, if the distributions of distances to treatment services among treated and non-treated cases are assumed to be equivalent among anonymous and identifiable cases.

Some cases could not be mapped as their home post-codes were not available. However, this information was assumed to be missing at random and thus unlikely to affect the spatial analysis results. In addition, linear distance does not give a direct indication of time or monetary costs of accessing healthcare. However, we believe this measure to be a good indicator of accessibility as it has been shown to correlate closely with drive-time in the UK.<sup>23,24</sup> We used a cut-off of 4 km to divide the cases into two approximately equal-sized groups with higher and lower levels of access to treatment. Although this categorisation is relatively crude, a 4 km radius has previously been used to define populations with better and worse access to health facilities in the UK,<sup>18,25</sup> with evidence that the latter group show lower attendance rates at general practitioners' clinics.<sup>18</sup> Further analysis would be required to validate the relationship between treatment proximity and access rates in this specific context, and to assess the true impact of interventions to reduce proximity on treatment completion rates.

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