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ORIGINAL ARTICLE

Investigating rates and risk factors for hepatitis C virus reinfection in people receiving antiviral treatment in England

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Abstract

England has committed to the World Health Organization target to eliminate hepatitis C virus (HCV) as a public threat by the year 2030. Given successful treatments for HCV in recent years, it is unclear whether HCV reinfection will impact England's ability to achieve HCV elimination. We aimed to estimate the HCV reinfection rate among a cohort of patients receiving antiviral treatment using available surveillance data. Linkage between a treatment dataset from 2015 to 2019 and an HCV RNA testing dataset were used to identify people who experienced reinfection using three criteria. A Cox proportional hazards model was used to determine risk factors associated with HCV reinfection among a cohort who received treatment and had follow-up HCV RNA testing. The reinfection rate among those receiving HCV treatment was 7.91 per 100 person-years (PYs, 95% confidence interval (CI) 7.37–8.49) and highest among current injecting drug users (22.55 per 100 PYs, 95% CI 19.98–25.46) and people who had been in prison (20.42 per 100 PYs, 95% CI 17.21–24.24). In the adjusted model, women had a significantly reduced risk of reinfection. Being of younger age, current injecting drug users, and receipt of first treatment in prison were each significantly associated with increased risk of reinfection. Two-fifths of those with reinfection (43%, $n = 329/767$) were linked to treatment after reinfection, and of those starting treatment, three quarters (75%, $n = 222/296$) achieved a sustained virologic response. Guidance for testing groups at risk of reinfection and harm reduction strategies to minimize transmission should be implemented if England is to achieve HCV elimination targets.

KEYWORDS
elimination, hepatitis C, people who inject drugs, reinfection, treatment

Abbreviations: BBV, blood borne virus; CI, confidence interval; DAA, direct-acting antivirals; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, Men who have sex with men; PWID, people who inject drugs; PY, person years; SSBBV, sentinel surveillance of blood borne viruses; SVR, sustained virological response; UKHSA, UK health security agency; WHO, world health organisation.

1 | INTRODUCTION

The World Health Organization (WHO) released a global health sector strategy that aimed to support the elimination of viral hepatitis as a public health threat by the year 2030.[1] The strategy notes that this should be achieved by reducing the incidence of, and death from, chronic viral hepatitis, as well as continued investment in prevention and harm reduction.[1] It is estimated that 95% of deaths from hepatitis are attributable to hepatitis B (HBV) and C (HCV) viruses and consequently these are the primary focus of elimination.[1] In England, there are approximately 81,000 people living with chronic HCV infection and the country has committed to the WHO strategy to eliminate viral hepatitis.[2]

Hepatitis C virus has a long progression time, with infected individuals often remaining asymptomatic for decades, before the possible development of liver cirrhosis.[3] As a result, regular testing of populations who are at risk of HCV, such as people who inject drugs (PWID) or men who have sex with men (MSM), is needed to identify those with the infection and link them to treatment. Direct-acting antivirals were accessible in England from 2014 and more widely available from 2016.[2] In this new era of HCV treatment, because DAAs are highly effective and tolerable, they also offer the potential to reduce HCV transmission.[4-6] However, given their higher treatment success rate,[2] those who successfully clear the virus may be at risk of reinfection due to ongoing risk behaviours. Additionally, reinfection is likely to occur first among those who remain at risk where there is still circulating virus, due to some people with HCV remaining untreated.[7] Without adequate prevention methods for those at risk of reinfection, and with groups of people with HCV who remain untreated, the effect of HCV reinfection on England's ability to achieve and sustain HCV elimination is unknown.[8]

A review of the HCV reinfection literature suggested that reinfection rates were low in the era of interferon treatment among all those who achieved a sustained virologic response (SVR) after treatment (0.48 per 100 person-years (PY)), although this was higher among PWID (1.21–12.4 per 100 PYs) and MSM living with HIV (5.3–13.2/100 PYs).[9] Additionally, with more treatment success using DAAs, the reinfection rate may be higher than previously reported for interferon treatment. Among a cohort of PWID in Tayside, Scotland, the reinfection rate was higher among those treated with DAAs (7.17 per 100 PYs) compared to those receiving interferon treatment (4.93 per 100 PYs).[10] Another study in Scotland also found a higher reinfection rate in the era of DAAs compared to the earlier interferon treatment era (8.8 per 100 PYs vs. 3.9 per 100 PYs), although low levels of retesting over 1 year after successful treatment were also observed (30%).[11] A meta-analysis found that receiving opioid-substitution therapy (OST) alongside treatment was associated with reduced HCV reinfection rates among PWID (1.4 per 100 PYs).[12] Similarly, findings from British Columbia, Canada, found higher reinfection rates among recent PWID (3.1 per 100 PYs) and ever PWID (1.4 per 100 PYs) compared to never PWID (0.3 per 100 PYs), and only one reinfection was found among PWID receiving daily OST during treatment.[13] Reinfection rates among prisoners in the North East of England have been found to be high post SVR (20%), although this study could not determine where reinfection occurred and the route of exposure.[14]

Given the importance of understanding HCV reinfection in reference to HCV elimination targets, the aim of this study is to estimate the rate of HCV reinfection among people with documented receipt of treatment for HCV using surveillance datasets in England and to understand the sociodemographic risk factors associated with HCV reinfection.

2 | METHODS

The National Health Service for England HCV treatment database contains people who initiate HCV treatment in England since 2015. The database is used to allocate funding for HCV treatment and therefore the database can be considered an accurate representation of people initiating HCV treatment in England. Data for individuals who initiated treatment between 2015 and 2019 was linked to testing data in the UK Health Security Agency's (UKHSA) sentinel surveillance of blood borne viruses (SSBBV) that captures all blood borne virus (BBV) testing in England from participating laboratories (2015–2019), accounting for 40% of all HCV testing in England.[15] Those who were treated in 2019 but who did not have follow-up of at least 196 days were excluded from analyses. Data collection methods for SSBBV have been described previously,[16] and SSBBV data were used to identify those testing positive for HCV RNA after treatment. Linkage between datasets was based on a unique patient identifier (National Health Service Number) used across healthcare services in England and on soundex (coding based on each person's surname), date of birth and gender.

Demographic information was extracted from the treatment database, which included gender, age at first treatment, ethnicity and exposure. A person was considered as a person who currently injects drugs (current PWID) at first treatment if they had engaged in injecting drug use over the past 3 years and anyone who had engaged in injecting drug use over 3 years prior to treatment initiation, but with no current PWID risk reported was considered a person who previously injected drugs (past PWID). Data were linked from SSBBV to a sexual health dataset for sexual health services in England (GUMCAD) at UKHSA,[17] using patient number and clinic code to further confirm MSM status where this may have been missed. People who received their first HCV treatment in prison were considered to be prisoners at first treatment. A person's index of deprivation score was obtained from using their postcode of residence and their deprivation score was divided into quintiles (lower score indicated higher levels of deprivation).

Three criteria were used to identify HCV reinfection (Figure 1), any one of which would establish a person as experiencing reinfection.

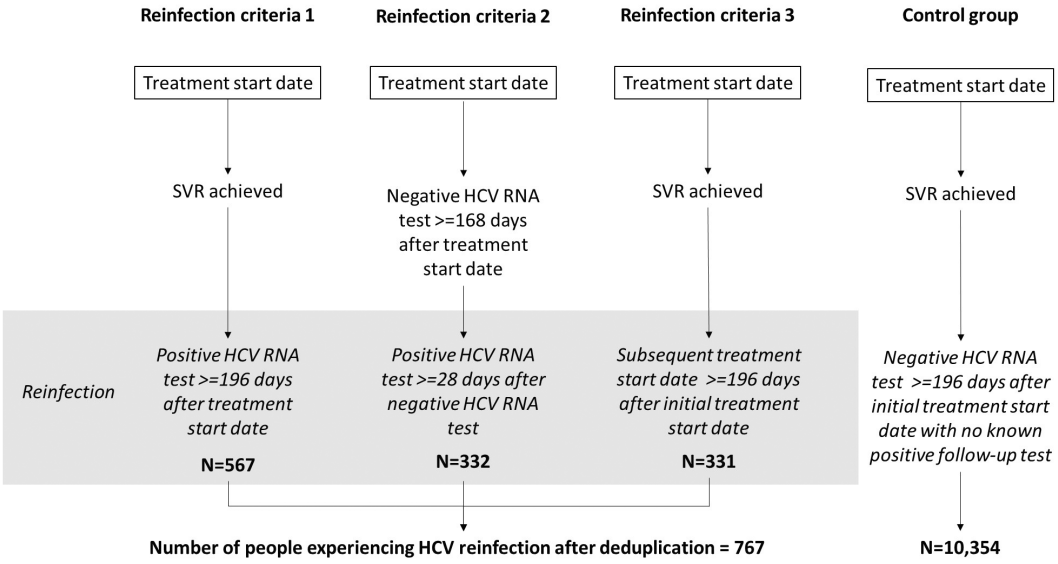

FIGURE 1 Summary of methods used to identify HCV reinfection and the control group.

2.1 | Criteria 1 ($n = 567$)

Hepatitis C virus reinfection was defined as a positive HCV RNA test at least 196 days (28 weeks) after treatment start date among those with a sustained virologic response (SVR) during their first treatment period. Twenty-eight weeks was used as the maximum treatment duration of patients identified through this criterion was 24 weeks (median duration 12 weeks, 91% completed treatment by 12 weeks); an additional 4 weeks was added to account for any delayed treatment start. The date of next positive HCV RNA test at least 196 days after the start of initial treatment was used as the date of known reinfection.

2.2 | Criteria 2 ($n = 332$)

Hepatitis C virus reinfection was defined as a positive HCV RNA test at least 28 days after a previous HCV RNA negative test, and where the negative HCV RNA test was taken at least 168 days (24 weeks) after treatment start. Here, the negative HCV RNA test was used as a proxy for an SVR where such information had not been reported. The date of next positive HCV RNA test at least 196 days after the start of initial treatment was used as the date of known reinfection.

2.3 | Criteria 3 ($n = 331$)

Hepatitis C virus reinfection was defined among individuals who received a subsequent period of treatment after an initial SVR, and where this subsequent treatment period was at least 196 days (28 weeks) after their first treatment start date. The date of the next treatment start date that was at least 196 days after the start of treatment was used as the date of known reinfection.

A control group ($n = 10,354$) was identified of people who received treatment, achieved an SVR and had a follow-up negative HCV RNA test at least 196 days after treatment with no known follow-up positive HCV RNA test. The control group was representative of those who received treatment for HCV when compared to a group who received treatment but were not included in analyses due to a lack of follow-up data ($n = 33,886$) in terms of gender (70% male vs. 72% male), ethnicity (76% White vs. 79% White) and age (median age at treatment start 50 years vs. 47 years). The control group had a smaller proportion of current PWID than those not included in analyses (13% vs. 25%).

2.4 | Reengagement in treatment

Reengagement in treatment was assessed for those who experienced HCV reinfection by identifying a subsequent treatment initiation after their HCV RNA positive test date. Treatment data between 2015 and 2021 were included. SVR achievement was calculated for those who initiated treatment after reinfection between 2015 and 2020 to account for reporting delays for treatment outcomes.

2.5 | Statistical analysis

Analyses were conducted using R (version 4.1.0). Time at risk was calculated from 196 days after first treatment start date, with reinfection rates being presented per 100 person-years (PY) for risk groups with 95% confidence intervals (95% CI). Kaplan–Meier curves were produced to display the cumulative time to HCV reinfection in years stratified by gender, age group, ethnicity, region of birth, sexuality (MSM and non-MSM), PWID status (never, previous or current), whether someone received their first treatment in prison, region of first treatment and deprivation quintile of residence.

A Cox proportional hazards regression model was used to determine whether the listed risk factors were associated with HCV reinfection. Risk factors with a *p*-value <.1 in these bivariable analyses were considered for inclusion in the model. Gender was included as an effect modifier for people who received their first treatment in prison as international research has found a higher HCV prevalence among women prisoners compared to men.[18,19]

3 | RESULTS

There were 11,121 people who had been successfully treated and had a follow-up HCV RNA test or a second treatment period more than 196 days after their initial treatment start date. The majority were men (70%, *n* = 7859), of White ethnicity (76%, *n* = 8489) and had ever injected drugs (59%, *n* = 4940). There were 551 people who met reinfection criteria 1, 332 that met reinfection criteria 2 and 331 that met reinfection criteria 3. There were similar proportion of men (81%, 78%, 79%, criteria 1, 2 and 3, respectively) and people of White ethnicity (82%, 82% and 84%, respectively) across the three criteria. After deduplication, 767 (7%) were identified as experiencing HCV reinfection.

Among those experiencing HCV reinfection, 79% (*n* = 605) were men, 59% (*n* = 450) reported ever injecting drugs, median age at first treatment was 43.5 years (interquartile range 36–52 years) and median time between first treatment start and reinfection was 16 months (range 6–50 months). When considering the time at risk from 196 days after treatment start, the median time to reinfection was 9 months (range 0–44 months). A first treatment regimen was available for 98% (*n* = 10,897) of participants, with 92% (*n* = 9983) having received DAA treatment, 6% (*n* = 704) having received DAA and pegylated interferon combination therapy and 2% (*n* = 210) ribavirin and pegylated interferon therapy, where data were available. There was no significant difference in mean number of follow-up HCV RNA tests between those experiencing reinfection (*mean = 1.8*, *Standard deviation = 1.4*) and those who did not (*mean = 1.8*, *standard deviation = 1.2*).

The overall reinfection rate was 7.91 per 100 PYs (95% CI 7.37–8.49). The reinfection rate was highest among current PWID (22.55 per 100 PYs, 95% CI 19.98–25.46) and people who had been in prison (20.42 per 100 PYs, 95% CI 17.21–24.24). Women who had been in prison (32.10 per 100 PYs, 95% CI 21.69–47.51) had a higher reinfection rate than men who had been in prison (18.85 per 100 PYs, 95% CI 15.57–22.83). Among MSM, the reinfection rate was 7.59 per 100 PYs (95% CI 5.21–11.07) and among past PWID the reinfection rate was 6.80 per 100 PYs (95% CI 5.89–7.84). Among people who were not identified as being in prison, a PWID or as a MSM, reinfection rate was 5.23 per 100 PYs (95% CI 4.65–5.88).

Figure 2 displays the Kaplan–Meier curves for variables considered for the Cox proportional hazards model and Table 1 displays findings from the Cox's proportional hazards model. In the adjusted model, women had a significantly reduced risk of reinfection compared to men. Being of younger age was significantly associated with increased risk of reinfection. Being a current PWID and receiving a first treatment in prison were significantly associated with increased risk of reinfection for both men and women. Also, receiving first treatment in the North of England was significantly associated with increased risk of reinfection compared to receiving treatment in London.

Among those that experienced reinfection, around two-fifths (43%, *n* = 329/767) were linked to treatment after reinfection between 2015 and 2021. Three quarters (75%, *n* = 222/296) of those restarting treatment after reinfection experienced a subsequent SVR among those restarting treatment between 2015 and 2020.

4 | DISCUSSION

This study aimed to identify and characterize HCV reinfection among those treated for HCV in England between 2015 and 2019 using available surveillance datasets. Previously, reinfection studies used prospective cohorts of people receiving treatment or high-risk groups and followed participants for a period of time after treatment completion.[4,9,20] Therefore, our study contributes to the relatively small number of studies that use routinely collected surveillance data to identify individuals experiencing reinfection.[10,11] Our overall reinfection rate for people initiating treatment in the DAA era was 7.91 per 100 PYs. This rate is similar to that reported from a study conducted in Australia and New Zealand in the interferon era (7.4 per 100 PYs),[20] although this was among a sample of MSM or PWID, and therefore the risk of reinfection may be higher among these groups than that among all HCV treated individuals. Notably, the reinfection rate observed in our study is much higher than that observed in a review of HCV reinfection in the interferon era (0.48 per 100 PYs).[9]

We found higher rates among current PWID during the DAA era of treatment compared to during the interferon era (22.55 per 100 PYs vs. 1.21–12.4 per 100 PYs).[9] We also found higher rates among PWID compared to similar studies in Scotland in the DAA era (22.55 per 100 PYs vs. 7.17/8.8 per 100 PYs).[10,11] However, these Scottish studies did not differentiate between current and past PWID, which may explain the higher reinfection rate observed in this study. The reinfection rate for current PWID in this study was similar to that seen in a study where participants were recruited from a needle and syringe programme, where recent injecting drug use may be more likely (22.55 per 100 PYs vs. 21.5 per 100 PYs),[21] although this study had a small sample size in comparison (*n* = 94). We also observed that the reinfection rate for past PWID was lower than that for current PWID. However, there was still a risk of reinfection among past PWID, which may be due to a misclassification of whether someone is a current or past PWID among a small number of individuals or could be due to people relapsing and reengaging in injecting drug use. Therefore, both current and past PWID may need harm reduction strategies, such as continuous testing for BBVs including HCV, needle exchange services and opioid substitution therapy to reduce the risk of reinfection in this population. It is recommended

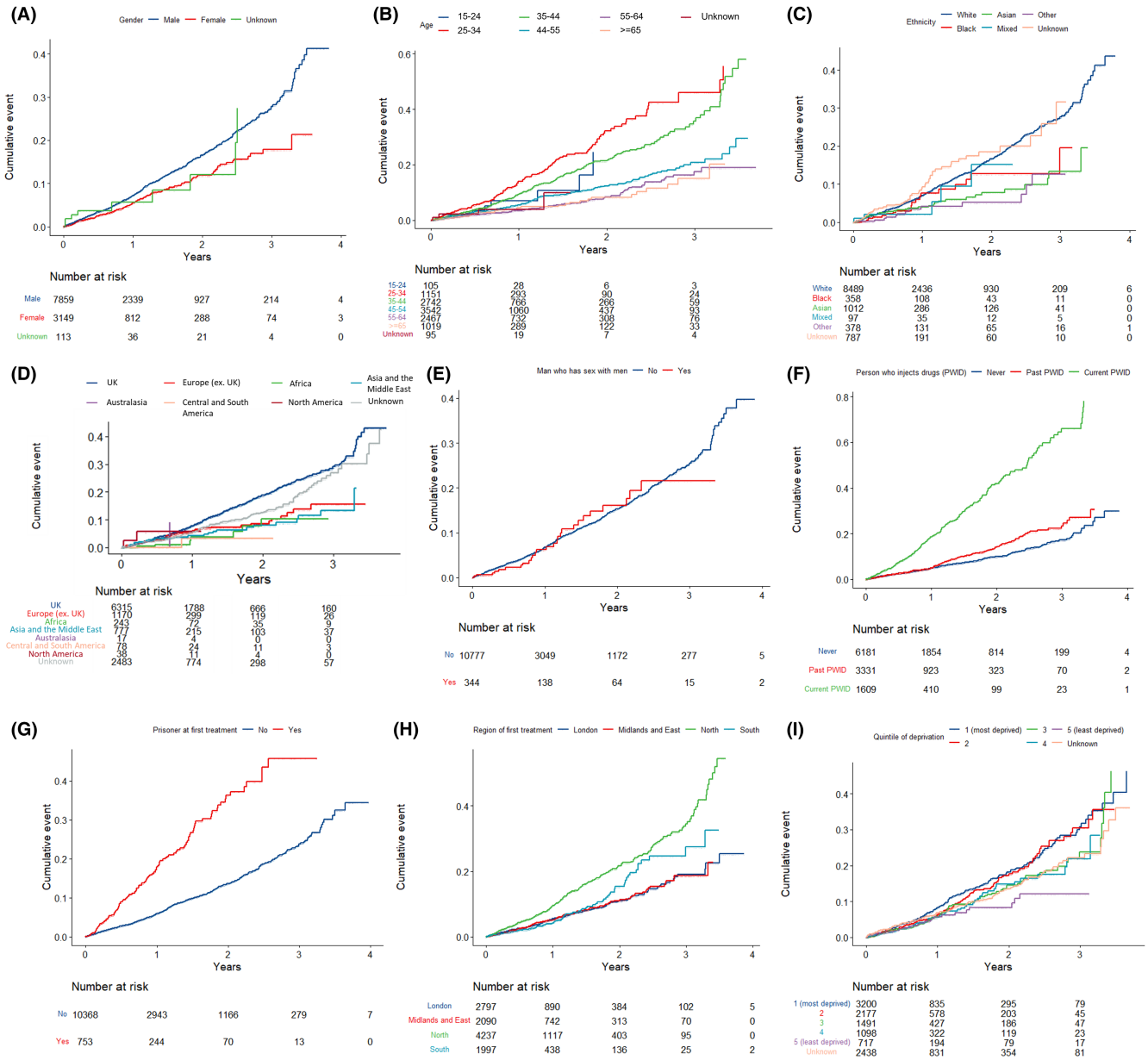

FIGURE 2 Kaplan–Meier curves displaying cumulative probability for HCV reinfection after successful treatment in years by (A). gender, (B). age group, (C). ethnicity, (D). region of birth, (E). sexuality (MSM or non-MSM), (F). injection drug use, (G). prisoner at first treatment, (H). region of treatment and (I). deprivation of residence quintile. PWID – person who injects drugs.

that PWID are tested annually for HCV,[22] and because we have observed an ongoing risk among past PWID, this guidance should be extended to past PWID as well. Our study has demonstrated a particularly high risk of reinfection for those who are current PWID at first treatment and therefore it is important that this group is tested annually for HCV, or more frequently if known to be engaging in high-risk behaviours, to minimize harm to the individual, and to prevent onward transmission.

Similar to a study conducted in the North East of England,[14] we found high rates of reinfection among people who were first treated in prison. It is unclear whether reinfection was experienced within prison or upon release. It has been found that stigma and a lack of knowledge are barriers to HCV testing in prisons and opt-out testing is an enabler to testing.[23] Opt-out testing for BBVs is recommended for prisons in England,[24] although research has suggested that in practice, testing rates are below the target of 50% of prisoners.[25] Additionally, drug availability in prisons and a lack of harm reduction services like needle syringe programmes,[26] as well as poor access to OST,[27] may leave people in prison at increased risk of reinfection after testing and treatment. Similar to previous international research on HCV prevalence in prisons,[18,19] our data suggest that women prisoners had a higher reinfection rate and risk of reinfection than male prisoners. Further research is needed to understand why this difference might be and whether women in prison are less likely to be identified as being at risk or reinfection or tested for BBV after initial treatment. Regardless of whether HCV reinfection occurs

TABLE 1 Rates of HCV reinfection by risk and Cox's proportional hazards for factors associated with HCV reinfection.

	Total	Reinfections (Row %)	Person Years (PY)	Reinfection rate per 100 PYs (95% CI)	Hazard Ratio (95% CI)	*p*-Value	adjusted Hazard Ratio (95% CI)
Total	11,121	767 (7%)	9693	7.91 (7.37–8.49)	-		-
Gender							
Male	7859	605 (8%)	6966	8.68 (8.02–9.41)	1	.0001	1
Female	3149	153 (5%)	2617	5.85 (4.99–6.85)	0.69 (0.58–0.82)		0.77 (0.63–0.93)
Unknown	113	9 (8%)	110	8.20 (4.27–15.76)	0.90 (0.46–1.73)		0.75 (0.36–1.53)
Age group at first treatment							
15–24	105	8 (8%)	87	9.21 (4.61–18.41)	1.44 (0.71–2.92)	<.0001	1.26 (0.61–2.57)
25–34	1151	143 (12%)	903	15.84 (13.44–18.66)	2.49 (2.02–3.09)		1.89 (1.51–2.37)
35–44	2742	258 (9%)	2287	11.28 (9.99–12.75)	1.75 (1.46–2.10)		1.47 (1.22–1.77)
45–54	3542	207 (6%)	3161	6.55 (5.72–7.51)	1		1
55–64	2467	104 (4%)	2273	4.57 (3.77–5.54)	0.70 (0.55–0.88)		0.87 (0.68–1.10)
> = 65	1019	42 (4%)	911	4.61 (3.41–6.24)	0.71 (0.51–0.98)		0.98 (0.70–1.38)
Unknown	95	5 (5%)	71	7.01 (2.92–16.85)	1.09 (0.45–2.65)		1.07 (0.44–2.62)
Ethnicity							
White	8489	627 (7%)	7354	8.53 (7.88–9.22)	1	<.0001	1
Black	358	19 (5%)	329	5.77 (3.68–9.04)	0.66 (0.42–1.04)		0.97 (0.59–1.61)
Asian	1012	43 (4%)	925	4.65 (3.45–6.26)	0.54 (0.39–0.73)		0.66 (0.42–1.03)
Mixed	97	5 (5%)	99	5.04 (2.10–12.10)	0.57 (0.24–1.37)		0.67 (0.32–1.62)
Other	378	14 (4%)	384	3.65 (2.16–6.15)	0.41 (0.24–0.70)		0.56 (0.32–0.97)
Unknown	787	59 (8%)	600	9.83 (7.62–12.69)	1.18 (0.90–1.54)		1.08 (0.81–1.45)
Region of birth							
UK	6315	506 (8%)	5390	9.39 (8.60–10.24)	1	<.0001	1
Europe (ex. UK)	1170	55 (5%)	949	5.79 (4.45–7.55)	0.62 (0.47–0.82)		0.81 (0.61–1.09)
Africa	243	7 (3%)	232	3.02 (1.44–6.34)	0.31 (0.15–0.66)		0.58 (0.25–1.32)
Asia and Middle East	777	35 (5%)	706	4.95 (3.56–6.90)	0.51 (0.36–0.72)		1.01 (0.61–1.67)
Australasia	17	2 (12%)	13	15.92 (3.98–63.65)	1.91 (0.48–7.68)		1.72 (0.43–6.93)
Central and South America	78	1 (1%)	72	1.39 (0.20–9.88)	0.14 (0.02–1.01)		0.24 (0.03–1.72)
North America	38	2 (5%)	33	6.14 (1.54–24.55)	0.68 (0.17–2.74)		1.15 (0.29–4.66)
Unknown	2483	159 (6%)	2298	6.92 (5.92–8.08)	0.74 (0.62–0.88)		1.05 (0.85–1.31)
Men who has sex with men (MSM)							
No	10,777	740 (7%)	9337	7.93 (7.37–8.52)	1	.6100	-
Yes	344	27 (8%)	356	7.59 (5.21–11.07)	0.91 (0.62–1.33)		-

(Continues)

TABLE 1 (Continued)

	Total	Reinfections (Row %)	Person Years (PY)	Reinfection rate per 100 PYs (95% CI)	Hazard Ratio (95% CI)	*p*-Value	adjusted Hazard Ratio (95% CI)
PWID status							
Never/unknown	6181	317 (5%)	5755	5.51 (4.93–6.15)	1	<.0001	1
Past	3331	189 (6%)	2781	6.80 (5.89–7.84)	1.27 (1.06–1.52)		1.05 (0.87–1.28)
Current	1609	261 (16%)	1157	22.55 (19.98–25.46)	4.29 (3.64–5.05)		2.57 (2.09–3.13)
Prisoner at first treatment							
No	10,368	636 (6%)	9051	7.03 (6.50–7.59)	1	<.0001	1
Yes	753	131 (17%)	641	20.42 (17.21–24.24)	2.94 (2.43–3.54)		-
Male prisoner	647	105 (16%)	557	18.85 (15.57–22.83)	1		1.39 (1.11–1.74)
Female prisoner	101	25 (25%)	78	32.10 (21.69–47.51)	2.54 (1.58–4.10)		2.42 (1.53–3.83)
Unknown prisoner	5	1 (20%)	7	15.22 (2.14–108.03)	0.83 (0.10–6.70)		1.67 (0.21–13.48)
Region of first treatment							
London	2797	150 (5%)	2544	5.90 (5.03–6.92)	1	<.0001	1
Midlands and East	2090	124 (6%)	2079	5.96 (5.00–7.11)	1.02 (0.80–1.29)		0.85 (0.66–1.09)
North	4237	401 (9%)	3558	11.23 (10.22–12.43)	2.01 (1.67–2.43)		1.28 (1.03–1.59)
South	1997	92 (5%)	1512	6.09 (4.96–7.47)	1.12 (0.87–1.47)		0.89 (0.68–1.17)
Deprivation of residence quintile							
1 (most deprived)	3200	248 (8%)	2638	5.70 (5.03–6.45)	1.34 (1.06–1.70)	.0020	1.16 (0.90–1.48)
2	2177	147 (7%)	1783	8.24 (7.01–9.69)	1.19 (0.92–1.54)		1.23 (0.94–1.59)
3	1491	95 (6%)	1336	7.11 (5.82–8.69)	1		1
4	1098	64 (6%)	954	6.71 (5.25–8.57)	0.96 (0.70–1.32)		1.04 (0.76–1.44)
5 (least deprived)	717	32 (5%)	637	5.02 (3.55–7.10)	0.72 (0.48–1.07)		0.98 (0.65–1.47)
Unknown	2438	181 (7%)	2344	7.72 (6.67–8.93)	1.07 (0.83–1.37)		1.00 (0.78–1.29)

inside or outside of prison, it appears that people who receive HCV treatment within prison are at high risk of reinfection and continuous HCV testing and harm reduction strategies within and outside of prison are needed in this population.

In this study, the reinfection rate among MSM was 7.59 per 100 PYs. Previous studies conducted in both the interferon and the DAA era of treatment found MSM living with HIV were at increased risk of reinfection.[9,28] We were not able to accurately report whether MSM in this study were or were not living with HIV, so reinfection rates among MSM living with HIV in England may be higher than what is reported here. HCV reinfection has been reported to be high among all people living with HIV who have received an HCV diagnosis, although higher among MSM.[29] Therefore, living with HIV is an important consideration for HCV reinfection among people receiving HCV treatment and future HCV reinfection research. High risk behaviour among MSM for HCV, HIV and other STIs can be both sexual and drug related, such as injecting drug use associated with chemsex (e.g. crystal methamphetamine, mephedrone),[30,31] or non-injecting drug use (e.g. cocaine, γ-hydroxybutyrate/ γ-butyrolactone (GHB/GBL)), which is associated with unprotected anal intercourse and a high number of sexual partners.[32–34] Therefore, it is important that MSM continue to be tested for HCV in services such as sexual health and HIV treatment services after completion of DAA treatment and are also offered harm reduction services for drug use if needed and offered safe injecting packs.[28,35]

It is important to note that there was still a risk of reinfection among people who were not known to be PWID, MSM or had been in prison (5.23 per 100 PYs). It is unclear whether these people may have not reported any risk, that it was not asked, documented or whether there are other groups of people at risk of reinfection who are not identified by current testing guidance and harm reduction strategies.

Linkage to treatment after reinfection was low (43%). Ensuring those that have been identified as reinfected reengage in treatment is important for their own health and wellbeing. Understanding who this population is and whether those who experience reinfection are less likely to engage in care or whether they experience any barriers to reengagement, compared to people diagnosed for the first time, would help contextualize the potential impact HCV reinfection may have on elimination targets. Among those who restart treatment, SVR rates were similar to rates nationally (75% vs. 79%),[2] but lower than the WHO target of 90%.[36] It is currently unknown whether an HCV reinfection may be more difficult to treat than the initial infection, or whether experiencing reinfection with the same genotype may be more difficult to treat than reinfection with a different genotype. Therefore, further research is needed to understand whether reinfection affects SVR achievement. Due to inconstancies in the reporting of HCV genotype over the study period, whether a genotype switch had occurred could not be incorporated into the reinfection criteria.

There are a number of biases and limitations that should be considered when interpreting these data. First, SSBBV covers approximately 40% of the HCV testing in England considering the registered population at general practice surgeries. Therefore, a limitation of these data may be that individuals who were tested for HCV in non-participating labs, would not have been linked to treatment data. However, sentinel surveillance includes the two laboratories who offer BBV testing for the majority of the drug services in England, and therefore estimates of reinfection among PWID are unlikely to be impacted by missing data in SSBBV. Second, the need for sufficient identifiers for linkage between SSBBV and the treatment database will impact the ability to identify a reinfection, particularly with criteria 1 and 2. Therefore, this may be a conservative estimate of the number with a positive HCV RNA test post HCV treatment. Third, it is possible that relapses may be misclassified as reinfections, although measures were taken to minimize this risk. If an individual met the criteria for reinfection (including having an SVR reported) and a clinician reported a relapse during their first treatment, their treatment duration was obtained. All treatment durations (median 12 weeks, range 8–27 weeks) for those where a relapse had been reported but met the criteria for reinfection ($N = 58$), completed their treatment prior to the time at risk for reinfection in this study, and so were included. Although it is difficult to distinguish between late relapse and reinfection without genetic sequencing,[37] 28 weeks (196 days) after treatment initiation was chosen as the beginning of time at risk to minimize risk of misclassifying relapse as reinfection, as relapse 12 weeks after SVR achievement is uncommon (<0.5%)[38] and over 90% of successful treatments were completed by 12 weeks, thereby accounting for an additional 14 weeks where relapse would most commonly occur. Finally, there is the risk of a missing data bias, as it is unclear whether those at higher risk may be more likely to be followed up, and therefore reinfection is more likely to be identified, or whether reinfection may be higher among those lost to follow-up who remain undiagnosed. The low rate of retesting among this cohort who did have at least one follow-up HCV RNA test may also contribute to an under estimation of reinfection. It has been suggested that a local integrated approach with mental and physical health, social and housing services may be necessary to identify those with complex needs who are at risk of reinfection and suitable for testing.

Despite our study's limitations, this is the first attempt to identify and characterize HCV reinfection in England using surveillance data. Although this study was conducted in the era of DAA treatment, not all participants included received DAA treatment. However, those not receiving DAA treatment still met the inclusion criteria for successful initial treatment and were therefore still at risk of reinfection. If England is to achieve the WHO targets for hepatitis elimination, preventing HCV reinfection should be a priority in harm reduction strategies, such as continuous testing, needle exchange services and OST, aimed at groups who are at increased risk. This study has highlighted key groups that are at risk of reinfection, such as PWID and people who have been in prison. Therefore, the guidance and recommendations in place regarding treatment and annual HCV testing for these populations should be implemented to aid England's target of reducing HCV incidence, morbidity and mortality by the year 2030.

AUTHOR CONTRIBUTIONS

MH linked the datasets, carried out the analysis and drafted the manuscript. SM, MD, HH and RS conceived the initial concept, SM, MD, HH, RS and CS provided critical input into the methodological approach and all authors reviewed and approved all revisions.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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