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Original Contribution

Hepatitis C Infection Among Injecting Drug Users in England and Wales (1992–2006): There and Back Again?

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Changes in hepatitis C virus (HCV) prevalence from 1992 to 2006 were examined by using 24,311 records from unlinked anonymous surveillance of injecting drug users in England and Wales. Bayesian logistic regression was used to estimate annual prevalence, accounting for changing recruitment patterns (age, gender, injecting duration, geographic region, interactions) and the sensitivity and specificity of different oral fluid testing devices. After controlling for these differences, the authors found that the adjusted HCV prevalence decreased from 70% (95% credible interval: 62, 78) in 1992 to 47% (95% credible interval: 43, 51) in 1998 before rising again to 53% (95% credible interval: 48, 58) in 2006. Women injecting drug users had a higher HCV risk than did men (odds ratio = 1.50, 95% credible interval: 1.31, 1.73). Two regions (London and North West) had a markedly higher HCV prevalence than did the rest of England and Wales. Among individuals who had injected for less than 1 year, the adjusted HCV prevalence in 2006 was higher than that in 1992 (28% vs. 19%, respectively). HCV infection can be prevented. The public health challenge in England and Wales is to increase action in order to regain a downward trend in HCV risk and the benefit that has been lost since 1998.

England; hepatitis C; prevalence; sentinel surveillance; substance abuse, intravenous; Wales

Abbreviations: AIC, Akaike Information Criterion; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug user.

Hepatitis C virus (HCV) infection is preventable and treatable. In most developed and transitional countries, HCV transmission has been concentrated among injecting drug users (IDUs) (1–4), who typically experience high rates of infection. For example, in England and Wales, an estimated 80% of all HCV cases are due to injecting drug use (5, 6). Preventing infection in this population is thus a key component of public health responses to reduce HCV-related harm and morbidity. The main primary interventions include the provision of sterile injecting equipment and reducing and stopping injection through opiate substitution therapy (7, 8). Interpreting HCV surveillance data in order to assess the impact of prevention is complicated by difficulties associated with recruiting representative samples of IDUs. Although better methods are being developed (9), most survey data will suffer from recruitment or selection

bias, which needs to be properly accounted for when comparing trends in HCV prevalence over time.

Although many studies have reported a high HCV prevalence among IDUs, few have reported trends over time, and these have revealed contrasting pictures. In Australia, the prevalence of human immunodeficiency virus (HIV) is low, the availability of interventions is good, but HCV prevalence remains persistently above 50% and has increased among recent injectors (10). In Glasgow, Scotland, HCV prevalence was estimated to have fallen during the early 1990s but remains above 50% (11). In the United States, evidence for a decrease in HCV prevalence has been found in a number of cities (Baltimore, Maryland; Los Angeles, California; and New York, New York) (12, 13).

In this paper, we use surveillance data collected from approximately 50 sampling sites per year from 1992 to

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2006 and comprising 24,311 participations. We examine trends in HCV prevalence and investigate whether, after adjustment for changing recruitment patterns (age at test, gender, injecting duration, geographic region, interactions) and test accuracy, HCV prevalence has declined.

MATERIALS AND METHODS

The survey

A national unlinked anonymous surveillance of IDUs was started in 1990 to monitor trends in HIV infection by using specialist services for IDUs as a pragmatic sampling frame. Detailed methods have been published elsewhere (14, 15). Briefly, voluntary oral-fluid samples and an accompanying questionnaire are collected annually from consenting IDUs attending representative services across England and Wales providing needle exchange, opiate substitution therapy, and treatment for drug use. Since 1998, the samples have been routinely tested for anti-HCV antibodies, and a recent extension has allowed retrospective anti-HCV testing of stored samples from the 1992, 1994, and 1996 surveys. Those aged 15–59 years who had injected in the previous 4 weeks were included in the analyses in this paper.

Estimating trends in anti-HCV prevalence presents a number of difficulties. First, the participating services and their geographic distribution have changed over time, reflecting changing patterns of drug use and service provision. For example, in the earlier years, there were many services in the North West region of England, an area with historically high rates of HCV infection among IDUs but also one of the areas most affected by injecting drug use in the early 1990s (16, 17). Hence, regional variations in data collection occur over time and must be adjusted for in the analysis. Second, the device used to collect oral fluids has also changed over time, and this affects the sensitivity and specificity of the assay in detecting anti-HCV antibodies. Prior to 1998, the Salivette (Sarstedt, Ltd., Leicester, United Kingdom) collection device was used in the survey, while from 1998 onward, the OraSure (OraSure Technologies, Inc., Bethlehem, Pennsylvania) device has been used. In a population whose anti-HCV prevalence is 30%, the Salivette device has been estimated to have a sensitivity of only 74.1% (95% confidence interval (CI): 68.2, 79.4) with 99.0% (95% CI: 97.4, 99.7) specificity, while the OraSure device has an estimated sensitivity of 91.7% (95% CI: 87.5, 94.8) and specificity of 99.2% (95% CI: 97.8, 99.8) (18). Therefore, the sensitivity of detecting anti-HCV is higher in the 1998–2006 surveys compared with those conducted before 1998.

This paper uses logistic regression to estimate the shape of the prevalence trend, while adjusting for variables that may explain the changing recruitment in unlinked anonymous data. The analysis accounts for differential misclassification of the infection status; that is, the sensitivity and specificity are different for samples collected before and since 1998. Failure to acknowledge sensitivities and specificities in the analysis would result in an underestimate of anti-HCV prevalence and a severe underestimation in the years prior to 1998.

Regression model

A classical logistic regression model is first implemented, with the observed anti-HCV test result as the binary response variable. This is regressed against the year in which the test is taken in order to estimate a period effect. To account for changing recruitment effects, the following demographic variables are included in the analysis: age, gender, injecting duration, and geographic region of recruitment (London, Midlands and Wales, North East and Yorkshire, North West, Southern and Eastern). We do not attempt to adjust for other variables that may explain the period effect, for example, injecting risk behaviors. Adjustment for these variables will dilute the HCV risk trend that we are attempting to infer.

Nonlinear relations are investigated for all continuous variables (year of test, age, injecting duration) through the use of polynomials. For each variable, the degree of the polynomial is chosen by selecting the model with the lowest Akaike Information Criterion (AIC). Polynomial functions up to degree 4 (quartic) were assessed for each continuous variable. To further improve the fit of the model, all 10 possible 2-way interactions of the 5 variables are considered. Variable selection is performed, and the model with the lowest AIC is chosen. A global goodness-of-fit test for the final binary logistic model is performed by using the method proposed by le Cessie and van Houwelingen (19). To judge the effect of missing data on model estimates, we conducted multiple imputation using chained equations (20) in a sensitivity analysis. The prevalence trend estimated from the final model is plotted over the study period by setting all other covariates to their mean values in the data set.

Prevalence in recent initiates (those with injecting duration of <1 year) is strongly associated with HCV incidence, and hence we also considered an additional model where injecting duration is expressed as a binary variable (recent vs. nonrecent initiates).

Accounting for imperfect sensitivity and specificity of the test device

As discussed above, the anti-HCV test sensitivity and specificity are not perfect and differ over time as the result of a change in the testing device. From the law of total probability, a positive test result occurs with probability,

$$p = \pi \text{ Sens} + (1 - \pi)(1 - \text{Spec}),$$

where π is the true prevalence of disease, and “Sens” and “Spec” are the sensitivity and specificity of the test, respectively. If the sensitivity and specificity are known exactly, then one can estimate the true probability of disease from the observed test results. Magder and Hughes (21) suggest an expectation-maximization algorithm to do this in the context of logistic regression.

In this setting, the sensitivity and specificity of the assay using the 2 collection devices are not known exactly, and we wish to incorporate this uncertainty in the model. Their estimated values together with 95% confidence intervals are given above and as reported by Judd et al. (18). To

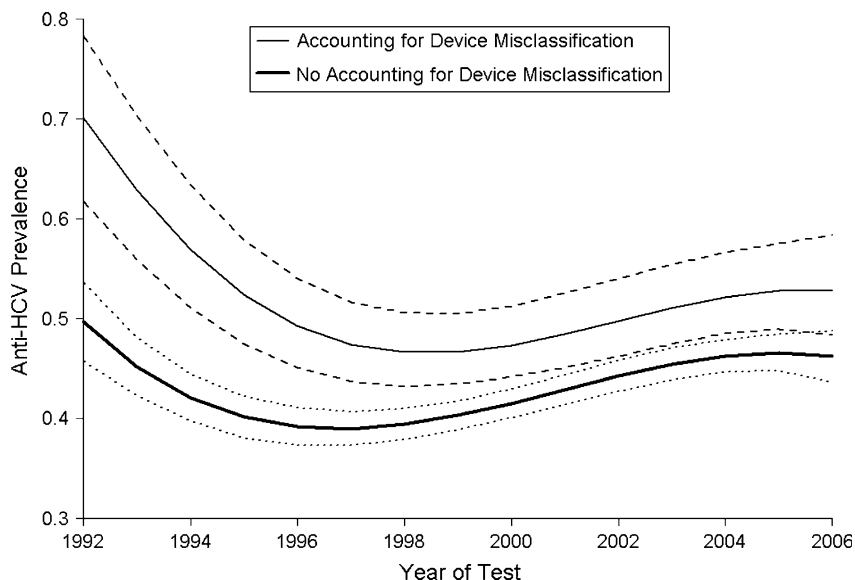


Figure 1. Estimated hepatitis C virus (HCV) antibody prevalence trend for injecting drug users before and after accounting for test device sensitivities and specificities, England and Wales, 1992–2006. All other covariates are set to their mean values. Dashed lines show 95% credible intervals for the model accounting for device misclassification. Dotted lines show 95% credible intervals for the model not accounting for device misclassification.

incorporate this additional uncertainty, a Bayesian analysis is implemented with the same choice of variables as from the best-fitting classical logistic model. The sensitivity and specificity of each device are given informative prior probability distributions to reflect the uncertainty surrounding their values. To achieve this, the log-odds of both “Sens” and “Spec” are assumed to follow normal distributions with means equal to the log-odds of the estimated values, and variances were calculated from the corresponding confidence intervals. Regression parameters in the logistic model are given noninformative prior distributions, and inferences are made from the posterior distributions of these parameters. A similar approach is described in detail by McInturff et al. (22). The Bayesian analysis provides a posterior distribution for each parameter of the logistic model and, hence, a posterior distribution for the predicted HCV prevalence from each combination of covariate values and for differences in HCV prevalence between subgroups. This, in turn, allows calculation of posterior probabilities of any quantity of interest, for example, the difference between HCV prevalence in 2006 compared with that in 1992.

Implementation

All classical analyses were carried out by using the “glm” function in R. Bayesian analyses were performed by using Markov chain-Monte Carlo techniques implemented in WinBUGS (23), and for which the model code is available from the authors upon request. Inferences were based on 32,000 iterations from 2 chains running in parallel, and convergence was assessed through the use of the Brooks-Gelman diagnostic (24).

RESULTS

In total, 24,311 participations were available from England and Wales over the years 1992, 1994, 1996, and 1998–2006. Appendix Table 1 in the Appendix shows the observed number and proportion testing positive for anti-HCV by year, sex, region, injecting duration, and age.

The final classical logistic regression model (with the lowest AIC) included all main effects and six 2-way interactions (year of test \times region, year of test \times injecting duration, region \times injecting duration, region \times gender, region \times age, gender \times injecting duration). The main effects of the continuous covariates, year of test and injecting duration, were found to be best modeled by use of cubic polynomials, while age was found to be best modeled by use of a quadratic. The final model showed a good fit to the data (global test for lack of fit, $P = 0.862$). Parameter estimates from this model are shown in the Appendix (Appendix Table 2).

There were 1,087 (4.5%) individuals missing information on injecting duration, 504 (2.1%) missing HCV test status, 465 (1.9%) missing age, 140 (0.6%) missing gender, and 2 (0.008%) missing region of recruitment. All individuals missing anti-HCV test status were from participations in 1992, 1994, or 1996 (stored sample either could not be located or was insufficient for testing). A multiple imputation analysis was undertaken, and results were almost identical to those from the complete case analysis (results not shown but available on request); therefore, the findings from the unimputed analyses are reported here.

Figure 1 shows the change in estimated prevalence from the Bayesian logistic model before and after accounting for the sensitivity and specificity of the oral-fluid test.

Table 1. Multivariate Bayesian Model of Hepatitis C Virus Infection Risk for Injecting Drug Users, England and Wales, 1992–2006

Variable	Odds Ratio ^a	95% Credible Interval
Region		
London	1.00	
Midlands and Wales	0.47	0.39, 0.57
North East and Yorkshire	0.45	0.36, 0.55
North West	1.67	1.41, 2.01
Southern and Eastern	0.37	0.31, 0.44
Gender		
Male	1.00	
Female	1.50	1.31, 1.73
Injecting duration, year(s)		
<1	1.00	
1	1.27	1.23, 1.34
5	2.84	2.47, 3.38
10	6.84	4.99, 9.99
15	9.11	7.39, 11.80
Age, years		
20	1.00	
30	1.63	1.44, 1.85
40	2.33	1.98, 2.76
50	2.90	2.23, 3.91

^a Odds ratios are presented for the mean characteristics of the study population.

Accounting for anti-HCV test misclassification has the effect of increasing the estimated prevalence, especially before 1998, when the sensitivity was lower. The uncertainty surrounding the estimated prevalence also increases to account for the uncertainty in the level of test sensitivity and specificity. In Figure 1, the estimated prevalence is shown, with all the other variables set to their mean levels, and can therefore be interpreted as the average adjusted prevalence in the study population. Results suggest that the adjusted HCV prevalence among IDUs decreased from 70% (95% credible interval: 62, 78) in 1992 to 47% (95% credible interval: 43, 51) in 1998, before slowly rising again to a level of 53% (95% credible interval: 48, 58) in 2006. Using this predicted trend, we estimate a 99.9% chance that the HCV prevalence in 2006 is greater than that in 1998.

Table 1 shows the odds ratio of HCV infection for region, gender, injecting duration, and age, when all other covariates are at their mean level. After adjustment, there is evidence for higher HCV prevalence among female IDUs than among males (odds ratio = 1.50, 95% credible interval: 1.31, 1.73). HCV prevalence also increases with injecting duration, with the odds ratio for those injecting for 5 years compared with <1 year estimated as 2.84 (95% credible interval: 2.47, 3.38).

Figure 2 shows the estimated prevalence trends from the model in which individuals are classified as recent and non-recent initiates. Results reveal a comparatively high HCV

adjusted prevalence in individuals who have injected for less than 1 year—at 19% (95% credible interval: 10, 34) in 1992 approximately halving by 1998 and then increasing to 28% (95% credible interval: 17, 41) in 2006. The increase from 1998 has been more marked in recent than non-recent initiates. The probability that HCV prevalence is higher in 2006 than in 1992 for recent initiates is estimated as 83.9%.

Strong regional effects are identified, and Figure 3 shows the estimated prevalence trend by geographic region. HCV prevalence in London and the North West is markedly higher than in the other regions and, by 2006, had risen on average to 70%. In London, there is an 8.3% probability that prevalence in 2006 is as high as it was in 1992. The trends from the other regions all overlap, with the estimated prevalence especially uncertain in the early years (because of small samples from some areas), and in general suggest that HCV risk fell in the early 1990s and from 1998 flattened out. Analyses that further subdivided the regions in the rest of England and Wales (without London and the North West region) gave a similar picture but also increased the uncertainty surrounding the average estimates (results not shown).

The effect of age on the risk of HCV infection is presented in Table 1 for selected ages. Despite adjustment for injecting duration, so that at each age the average duration is the same, there is still a clear age effect, with older individuals having a higher risk of infection than younger IDUs.

DISCUSSION

Our analysis of public health surveillance data suggests that, in England and Wales, HCV risk prevalence among IDUs declined during the 1990s but that the trend reversed after 1998 such that, in 2006 in some areas and among some subgroups of IDUs, HCV prevalence was approaching or even greater than that in 1992. In addition, we suggest that, in England and Wales, marked geographic differences in HCV prevalence remain, and prevalence among recent injectors of <1 year has increased rapidly since 1998 and is higher than the HCV prevalence in 1992. This is consistent with results from some studies in the United Kingdom that suggest increased HCV prevalence among recent initiates (25, 26) and that any change in HCV risk would occur more quickly among recent injectors. In our models, the risk of infection was estimated to increase monotonically with injecting duration, after adjustment for age and year of test (i.e., any cohort effect). This is to be expected, because the risk of current or past infection, as measured through anti-HCV antibodies, can only accumulate with exposure.

We found that, even after adjustment (for age, injecting duration, and year of test), women are more likely to be infected than men, and older injectors with the same average injecting duration are more likely to be infected than younger injectors. In contrast, a recent meta-analysis of HCV prevalence studies reported no significant difference in prevalence between men and women (27). The difference in HCV prevalence risk experienced by older injectors may be due to residual cohort effects that have not fully been accounted for or, alternatively, may reflect differential

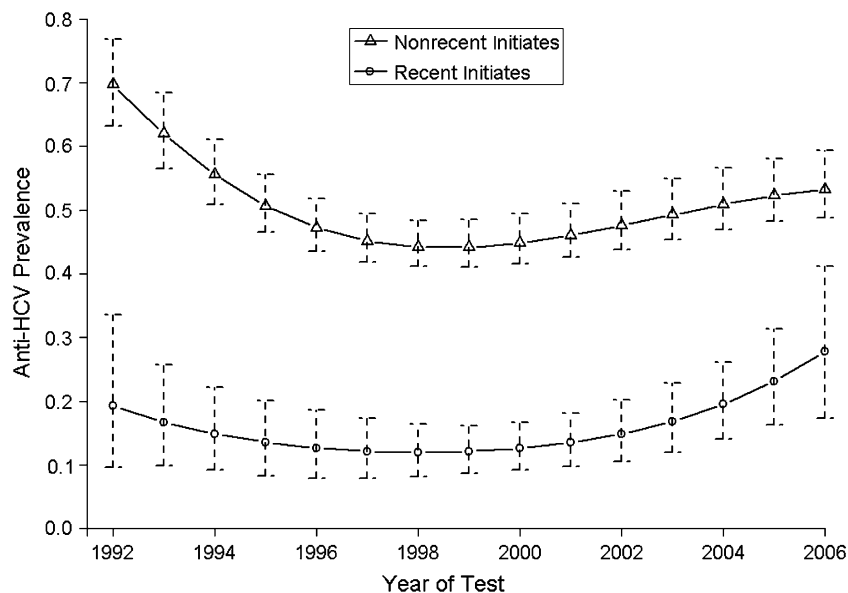


Figure 2. Estimated hepatitis C virus (HCV) antibody prevalence trend for injecting drug users by recent and nonrecent initiates, England and Wales, 1992–2006. All other covariates are set to their mean values. Error bars show 95% credible intervals.

exposure to other injectors with a higher risk of HCV. Differential exposure could also explain why we found a higher adjusted prevalence in females. That is, women may tend to inject with older men with a longer injecting duration and therefore are at greater risk of exposure to HCV. Such a pattern has been observed in a network of New York IDUs (28). An alternative hypothesis is that women also may be more

vulnerable and may be less able to control their injecting environment and risk than men (29–31). Equally, people who start injecting at an older age (after 25 years) may have greater comorbidity and/or other risks, such as homelessness and prison history, that increase their HCV risk, or there may be a greater misclassification of injecting duration among older injectors. These hypotheses and

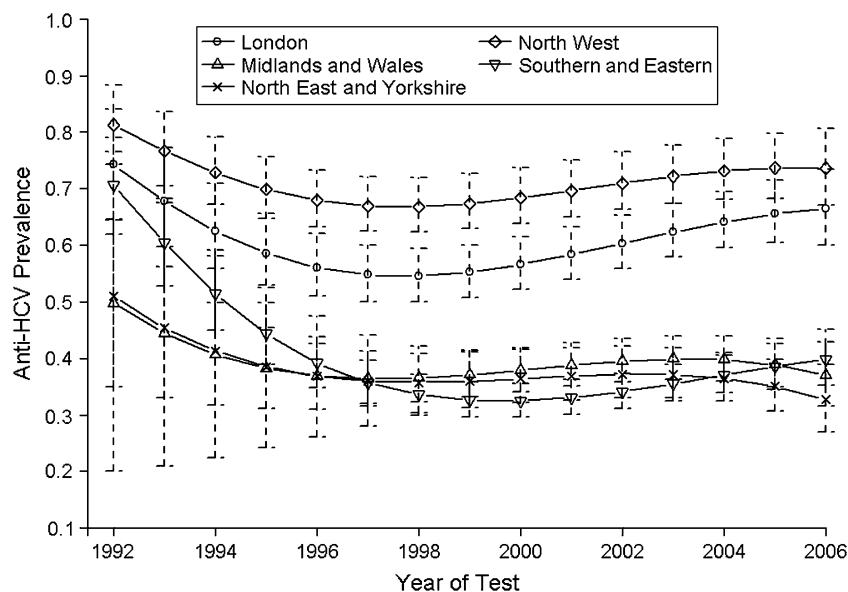


Figure 3. Estimated hepatitis C virus (HCV) antibody prevalence trend for injecting drug users by region, England and Wales, 1992–2006. All other covariates are set to their mean values. Error bars show 95% credible intervals for each region.

explanations need to be explored in future research and targeted prevention.

Strengths and limitations

Two key strengths of this work are the sources of data and analytical approach. First, the data were obtained from an ongoing surveillance program that has recruited reasonably sized ($n \approx 2,000$) annual samples by using the same methodology over time, although the service provision from which samples are drawn has necessarily changed over the time period. Second, we deployed innovative statistical methodology to adjust for changes in the accuracy of the testing device by allowing uncertainty in the knowledge of the level of sensitivity and specificity in the adjustment process. We also modeled age and injecting duration as continuous variables using polynomials. This approach provides a better fit to the relation between age/duration of injecting and HCV risk, which is not linear, and reduces the number of parameters compared with introducing categorical data (16).

The resulting estimated HCV prevalence overall and among subgroups is based on the average characteristics of the sample, and therefore the emphasis of this work is on relative changes in HCV risk over time, which we feel are more readily interpretable and the appropriate focus of routine surveillance. However, the estimates do not provide direct information on the true HCV prevalence in the IDU population, which can be addressed only if we assumed that we had recruited a representative sample of IDUs or had external information to generate specific sample weights that could be applied to the routine surveillance data. Such an assumption is not warranted, and data for the latter are unavailable.

We acknowledge several related limitations. First, although we sampled from similar sites ($n \approx 50$ low threshold treatment and syringe exchanges) each year, these have changed over time broadly reflecting changes in service provision. The changes in distribution and types of services provided will, in part, reflect changing patterns of drug use and the types of drug being used, as well as developments in drug policy, such as expanded provision of specialist drug treatment. Although we adjusted for several potential confounders, it is possible that the case-mix and other unmeasured factors (such as severity of dependence, proportion of former prisoners, and quicker access to treatment) relating to HCV risk have also changed over time.

Second, we lacked power and continuous surveillance data to investigate a more refined classification of geographic areas. There are cities in the defined geographic regions (such as Bristol and Brighton in the Southern and Eastern region and Leeds in the North East and Yorkshire region) that have higher levels of HCV than other cities, towns, and rural areas in these regions (16). Preliminary investigations suggested that, in the Southern and Eastern region, the proportion of high prevalence sampling sites did not remain constant over time. However, further analyses subdividing this region into "high," "medium," and "low" prevalence sites found a generally consistent overall picture of trend (data not shown).

Third, we do not attempt to explain the differences in HCV prevalence, for example, by fitting additional covariates on injecting risk behavior or the availability and intensity of prevention services. In part, this is because full data on risk behavior and other predictors are unavailable, but primarily because the main purpose of our analyses was to provide basic public health evidence on whether HCV risk (as measured by estimated anti-HCV prevalence) has changed over time.

Our work attempts to estimate trends in HCV prevalence and models prevalence in recent (<1 year) injectors as a measure of incidence, but another possible approach would be to estimate incidence directly from serial prevalence and exposure information (e.g., refer to references 32 and 33). These approaches directly address issues concerning incidence and transmission. Nevertheless, results from our model still provide useful information concerning the underlying epidemic among IDUs.

Interpretation—public health intelligence

There are 2 key messages for policy makers and practitioners in England and Wales and elsewhere. First, HCV among IDUs can be controlled: There are some places with low HCV prevalence and HCV risk fell during the early to mid-1990s, even in sites with a high background prevalence of HCV. The declines in risk support the hypothesis that the health education, needle exchange, and opiate substitution treatment widely used in the United Kingdom in the late 1980s changed behavior and injecting risk for HCV as well as HIV infection among IDUs (34–36).

Second, increased action and prevention services are required. Since 1998, HCV risk has remained stable or increased and, among some IDUs (particularly recent injectors), any benefits of the risk reduction achieved in earlier years have been lost. There are several potential and overlapping reasons for the increase in risk that cannot be explored by these data alone. These include increases in the prevalence of injecting over and above any increase in prevention services (37, 38) and/or changes in the characteristics of the IDU population (such as increased homelessness and crack-cocaine injection) that may have led to increased injecting risk (16). Whatever the explanation, and it is likely to be a combination of reasons, the key public health challenge is to reverse the currently rising HCV risk through increasing effective intervention coverage (8, 39, 40). The challenge to our public health surveillance program is to improve information collected on the characteristics of IDUs so that we can develop better models of HCV risk in order to inform and measure the impact of public health action.

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Appendix Table 1. Observed Hepatitis C Virus Antibody Prevalence by Covariate Level, England and Wales, 1992–2006

Variable	No. Positive	No. Tested	Proportion Positive
Year of test			
1992	850	1,800	0.47
1994	868	2,134	0.41
1996	640	1,810	0.35
1998	896	2,306	0.39
1999	830	2,485	0.33
2000	791	2,362	0.33
2001	716	2,063	0.35
2002	741	1,819	0.41
2003	743	1,693	0.44
2004	704	1,572	0.45
2005	824	1,828	0.45
2006	824	1,935	0.43
Sex			
Male	7,196	18,162	0.40
Female	2,171	5,510	0.39
Region			
London	2,329	4,418	0.53
Midlands and Wales	865	2,868	0.30
North East and Yorkshire	611	2,999	0.20
North West	3,254	6,089	0.53
Southern and Eastern	2,368	7,431	0.32
Injecting duration, years			
0–4	1,619	7,897	0.21
5–9	2,201	6,077	0.36
10–14	2,008	4,032	0.50
≥15	3,119	4,755	0.66
Age, years			
15–24	1,155	5,773	0.20
25–29	2,071	6,100	0.34
30–34	2,381	5,331	0.45
35–59	3,600	6,158	0.58

Appendix Table 2. Parameter Estimates From a Classical Logistic Regression Model With Lowest AIC Statistic for Injecting Drug Users, England and Wales, 1992–2006

Parameter	Estimate	Standard Error	z Value	P Value
Intercept	-0.105	0.058	-1.82	0.069
Year of test				
Linear	0.081	0.012	6.57	<0.001
Quadratic	0.0045	0.0022	2.05	0.041
Cubic	-0.00112	0.00026	-4.38	<0.001
Age, years				
Linear	0.0124	0.0066	1.87	0.061
Quadratic	-0.00069	0.00027	-2.52	0.012
Gender, females	0.262	0.085	3.07	0.002
Injecting duration, years				
Linear	0.1131	0.0072	15.79	<0.001
Quadratic	-0.00394	0.00061	-6.48	<0.001
Cubic	0.000061	0.000025	2.43	0.015
Region, baseline London				
Midlands and Wales	-0.593	0.085	-6.97	<0.001
North East and Yorkshire	-0.713	0.095	-7.54	<0.001
North West	0.404	0.069	5.83	<0.001
Southern and Eastern	-0.876	0.070	-12.42	<0.001
Gender × injecting duration				
Females × linear effect	-0.0169	0.0080	-2.13	0.033
Females × quadratic effect	-0.0036	0.0012	-3.12	0.002
Females × cubic effect	0.000190	0.000063	2.99	0.003
Injecting duration × region				
Linear × Midlands and Wales	-0.014	0.010	-1.35	0.178
Linear × North East and Yorkshire	0.039	0.013	2.97	0.003
Linear × North West	-0.0230	0.0082	-2.79	0.005
Linear × Southern and Eastern	0.0064	0.0078	0.83	0.409
Year of test × injecting duration				
Linear × linear	-0.00142	0.00075	-1.91	0.057
Quadratic × linear	-0.00084	0.00017	-5.02	<0.001
Linear × quadratic	0.000110	0.000061	1.82	0.069
Quadratic × quadratic	0.000028	0.000014	1.98	0.048
Year of test × region				
Linear × Midlands and Wales	-0.039	0.015	-2.63	0.009
Linear × North East and Yorkshire	-0.057	0.025	-2.29	0.022
Linear × North West	-0.000	0.012	-0.00	0.999
Linear × Southern and Eastern	-0.055	0.011	-4.91	<0.001
Quadratic × Midlands and Wales	-0.0045	0.0033	-1.35	0.177
Quadratic × North East and Yorkshire	-0.0043	0.0052	-0.82	0.413
Quadratic × North West	-0.0036	0.0026	-1.39	0.164
Quadratic × Southern and Eastern	0.0046	0.0026	1.75	0.079
Age × region				
Linear × Midlands and Wales	0.025	0.011	2.40	0.017
Linear × North East and Yorkshire	-0.002	0.012	-0.20	0.841
Linear × North West	0.0268	0.0084	3.17	0.002
Linear × Southern and Eastern	0.0381	0.0082	4.63	<0.001
Gender × region				
Females × Midlands and Wales	-0.16	0.13	-1.19	0.233
Females × North East and Yorkshire	0.04	0.15	0.28	0.777
Females × North West	-0.01	0.10	-0.13	0.894
Females × Southern and Eastern	0.25	0.10	2.49	0.013

Abbreviation: AIC, Akaike Information Criterion.