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Age- and time-dependent prevalence and incidence of hepatitis C virus infection in drug users in France, 2004–2011: model-based estimation from two national cross-sectional serosurveys

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SUMMARY

Hepatitis C virus (HCV) infection is a public health issue worldwide. Injecting drug use remains the major mode of transmission in developed countries. Monitoring the HCV transmission dynamic over time is crucial, especially to assess the effect of harm reduction measures in drug users (DU). Our objective was to estimate the prevalence and incidence of HCV infection in DU in France using data from a repeated cross-sectional survey conducted in 2004 and 2011. Age- and time-dependent HCV prevalence was estimated through logistic regression models adjusted for HIV serostatus or injecting practices. HCV incidence was estimated from a mathematical model linking prevalence and incidence. HCV prevalence decreased from 58·2% [95% confidence interval (CI) 49·7–66·8] in 2004 to 43·2% (95% CI 38·8–47·7) in 2011. HCV incidence decreased from 7·9/100 person-years (95% CI 6·4–9·4) in 2004 to 4·4/100 person-years (95% CI 3·3–5·9) in 2011. HCV prevalence and incidence were significantly associated with age, calendar time, HIV serostatus and injecting practices. In 2011, the highest estimated incidence was in active injecting DU (11·2/100 person-years). Given the forthcoming objective of generalizing access to new direct antiviral agents for HCV infection, our results contribute to decision-making and policy development regarding treatment scale-up and disease prevention in the DU population.

Key words: Drug users, hepatitis C virus, incidence, mixture model, prevalence.

INTRODUCTION

Hepatitis C virus (HCV) infection is a public-health issue worldwide and injecting drug use is still the major mode of HCV transmission, especially through the sharing of injecting equipment [1, 2]. Although public health prevention measures have been introduced in a large number of high-income countries (syringe-exchange programmes, opioid substitution treatments, consumption rooms and, to a lesser extent, treatment for prevention), the level of HCV transmission in drug users (DU) is still a public health issue as current harm reduction intervention strategies on HCV transmission have had mixed success [2–4]. A marked decrease in incidence has been observed

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in some countries [2, 5]. One example is the city of Amsterdam which has seen a marked decrease tending towards zero, partly thanks to harm reduction measures combined with changes over time in the type of drugs used and the consumption patterns of injecting drug users (IDU) [5]. Despite these positive developments, HCV incidence remains high in IDU [4] and consequently regular estimation of HCV prevalence and incidence in the DU population is crucial to assess the impact of harm reduction measures.

The most suitable way to estimate incidence is to conduct a prospective cohort where high-risk individuals are followed up over time and are tested for anti-HCV seroconversion [6–9]. Such a cohort would need to follow a large number of hard-to-reach subjects for a long time. This is difficult, expensive and time consuming.

Alternative approaches exist, for example implementing sentinel surveillance and using one or repeated cross-sectional surveys. Essential to all these alternatives is the collection of blood samples [plasma, serum, or dried blood spots (DBS)] for anti-HCV antibodies and/or HCV RNA testing.

There are several different ways cross-sectional surveys can be used. The first is to estimate HCV incidence from retrospective cohorts built from cross-sectional surveys when only HCV antibodies are collected [2]. Another is the use of mathematical models [3, 10–13]. In general, supplementary data are needed to build these models, including disease-related mortality, annual number of new DU and clinical and behavioural data (e.g. lifetime history of injecting drug use). Yet another cross-sectional approach involves HCV RNA testing of anti-HCV-negative samples. Using the proportion of new infected persons (i.e. HCV RNA positive in anti-HCV-negative persons) and the window period (i.e. the mean number of days during which HCV RNA is detectable before HCV antibodies develop) [10–13], HCV incidence is estimated using a simple formula [9, 14]. Finally, another way to estimate incidence is to apply an anti-HCV avidity-testing algorithm to identify samples compatible with recent primary infection [15, 16].

In France, no cohort studying HCV infection in DU at the national level is currently in place. Although an anti-HCV IgG avidity assay to identify recent HCV infection has recently been developed in France it has not yet been applied in practice [17, 18].

The aims of this paper were to estimate age- and time-dependent prevalence and incidence of HCV infection in DU in France from 2004 to 2011 using two national cross-sectional surveys (ANRS-Coquelicot studies) conducted in 2004 and 2011, based on blood testing [19, 20]. We built a mathematical model based on the relationship between prevalence and incidence. HCV antibodies were used as biological markers to estimate both prevalence and incidence, as HCV RNA was not available in the first survey.

METHODS

Data sources

The French ANRS-Coquelicot survey is a repeated cross-sectional serosurvey conducted in 2004 [19] and 2011 [20] in DU recruited in five French metropolitan cities (Lille, Strasbourg, Paris, Bordeaux, Marseille). In the 2011 survey two additional administrative departments (Seine-Saint-Denis and Seine-et-Marne, which are suburbs of Paris) were also included. The surveys' objectives were to estimate the prevalence of anti-HIV and anti-HCV antibodies, to assess at-risk practices associated with HCV transmission and to evaluate the dynamics of the HIV and HCV epidemics in this population.

For each survey and in each city (and department in 2011), time-location sampling was used (described in a previous paper [21]). Briefly, a comprehensive inventory was built of all the centres providing services to DU (including high- and low-threshold services). We then constructed a sampling frame based on half-day opening times of centres. All listed centres participated in the survey. Half-days were randomly drawn in all centres using simple random sampling without replacement. At each centre/half-day visit, DU were selected using systematic random sampling, except for residential centres where all users were included in the survey.

Information on participants' socio-demographic situation, health status, access to HCV screening, knowledge of HCV transmission modes, drug use, and at-risk practices was collected.

In order to have similar populations, we excluded DU interviewed in general practitioners' offices in 2004, as these locations were not used in the 2011 survey. We also excluded those interviewed in the two administrative departments only in 2011 for the same reason.

Studied variables

We focused on certain variables known to be associated with HCV infection: age, HIV serostatus and injecting practices [injected drugs at least once during lifetime (yes/no), injected drugs in the month before

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the study interview (yes/no)], and crack use (yes/no) [19, 20]. Crack use was defined as the consumption of crack (sniffing, snorting, injecting, smoking) in the month before the interview. Although injecting drug use and the sharing of syringes and injecting equipment remains the major mode of transmission, crack use is suspected to be a possible risk for HCV infection [19] as chipped or hot glass pipes can cause lesions in the mouth and hands, exposing users to infection. An IDU was defined as someone who reported injecting drug use at least once in her/his lifetime. An active injecting drug user (AIDU) was defined as someone who reported injecting drug use in the month before the study interview.

Laboratory data

Blood samples on blotting papers were collected during the interview by participants who agreed to provide self-obtained finger-prick blood samples on DBS for anti-HIV and HCV antibody testing. Six drops, corresponding to ~50 µl capillary whole blood, were spotted onto filter paper card (Whatman 903™, GE Healthcare Europe GmbH, Germany).

DBS samples in 2004 and in 2011 were screened using the same assays: HCV 3.0 Ortho ELISA and Ortho HIV1/2 Ab capture ELISA for HCV and HIV antibodies, respectively [19]. Positive anti-HIV samples (i.e. defining HIV positivity in a DU) were confirmed by serotyping and/or Western blot [22]. Details of the serological data analysis are provided in Supplementary Appendix 1.

Analyses

Statistical analyses were based on a five-step process:

Step 1. Anti-HCV data were modelled using a mixture of normal distributions to discriminate between HCV-seronegative and HCV-seropositive individuals.

Step 2. We deduced the global HCV prevalence from the classification obtained in step 1.

Step 3. We estimated age- and time-dependent HCV prevalence using regression models.

Step 4. We deduced age- and time-dependent HCV incidence from the prevalence estimated in step 3 using a model-based approach.

Step 5. We estimated the global HCV incidence for the year of each survey (i.e. 2004 and 2011), using the incidence estimated in step 4 and the estimated proportion of DU.

Mixture model

To avoid inconclusive classifications arising from the use of specified biological thresholds (e.g. a cut-off value provided by the manufacturer), the distribution of the quantitative results of antibody tests was modelled using an underlying mixture model – also called the direct method – rather than the usual threshold method [23]. We used a six-component and five-component mixture model on data from the 2004 and 2011 surveys, respectively, to identify persons who were seronegative or seropositive for HCV, according to reactivity level in the anti-HCV assay. Details of the model selection strategy are provided in Supplementary Appendix 2. Component densities were assumed to be normally distributed. We assumed that levels 1–3, corresponding to the lowest reactivity, represented the negative results of the anti-HCV test. Levels 4–6 (for 2004) and levels 4–5 (for 2011) were assumed to represent the positive results of the anti-HCV test.

Sampling weights

To produce estimates in the DU population, all the analyses took into account the sampling designs (sampling weights, stratifications, primary sampling units) of the two surveys.

As these surveys were based on time-location random sampling, DU attendance frequency in centres was incorporated into the sampling weights [21]. We appended the two datasets and adapted the sampling weights according to year of each survey, gender and age group (dichotomized into age >30 years or not) [24]. We decided to create this dichotomization as individuals aged <30 years in the 2004 sample were able to benefit from all the harm reduction measures available in France in 2004.

Estimation of age- and time-dependent prevalence

From our mixture model, each individual was classified as seropositive or seronegative. For each individual i, let us consider a binary variable of interest Y_i corresponding to the HCV classification ($Y_i = 1$ if i is seropositive and 0 if not). $P(Y = 1|a, t)$ is the probability of being seropositive at age a at calendar time t. A multivariate regression mel was used to estimate age- and time-dependent HCV prevalence, including age as a continuous covariate. The two most popular approaches to deal with a continuous covariate are to use splines or fractional polynomials. In the former, a generalized additive model is used. In

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the latter, a generalized regression model is performed. As we expected a simple shape reflecting a simple relationship between HCV infection and age, we chose this latter approach to build the multivariable model [25]. The generalized linear model can be expressed by:

$$g\big(E[Y|a,t]\big) = g(P(Y=1|a,t)) = \alpha + \eta(a) + ct, \quad (1)$$

where g is a link function, α is the intercept, c is the regression coefficient associated with time t and $\eta(a)$ a fractional polynomial function for age a. Fractional polynomials are an extension to classic polynomials, and are used for possible improvements in fit where the powers can be real values [26]. Different power transformation models are used instead of a straight line to estimate the relationship between the outcome variable and a continuous covariate, and to select the best-fitting model (i.e. the one with the highest likelihood value).

The fractional polynomial of degree m for the linear predictor, associated with age a, is defined as: $\eta_m\big(a, b, p_1, p_2, \ldots, p_m\big) = \sum_{j=0}^{m} b_j H_j(a)$, where m is an integer, b is a vector of regression coefficients, $p_1 \leqslant p_2 \ldots \leqslant p_m$ is a sequence of powers and $H_j(a)$ is a transformation function given by:

$$H_j(a) = \begin{cases} a^{p_j} & \text{if } p_j \neq p_{j-1} \\ H_{j-1}(a) \times \ln(a) & \text{if } p_j = p_{j-1} \\ & \text{with } p_0 = 0 \text{ and } H_0 = 1. \end{cases}$$

In our study, two link functions were tested: the complementary log-log link [log(−log [1 − x])] and the logit link [log(x/[1 − x])], also used in previous studies [27]. The best model was selected using Akaike's Information Criterion (AIC). Using a logit link, age- and time-dependent prevalence from equation (1) is expressed as:

$$P(Y=1|a,t) = \frac{\exp\big(\alpha + \eta(a) + ct\big)}{1 + \exp\big(\alpha + \eta(a) + ct\big)}. \quad (2)$$

Using a complementary log-log link, $P(Y=1|a,t) = 1 - \exp(-\exp(\alpha + \eta(a) + ct))$. It is straightforward to include additional covariates to adjust for any specific characteristics of interest such as the HIV serostatus or at-risk behaviors (e.g. injecting practices, crack use). Five regression models were performed to estimate HCV prevalence as a function of age and time (models 1 and 2), on age, time and injecting practices (model 3), on age, time and crack use (model 4) and finally, on age, time and HIV serostatus (model 5). We considered these five different models instead of one global model in order to estimate prevalence and incidence in each sub-population.

Estimation of age-dependent incidence

$\lambda(a,t)$ is the age- and time-dependent incidence of HCV infection. $N(a,t)$ is the proportion of anti-HCV negative persons of age a at time t, and $P(a,t)$ the proportion of anti-HCV positive persons (i.e. the prevalence) of age a at time t. We assumed that HCV transmission could be represented by a two-state compartmental model [28], corresponding to the anti-HCV negative (N) and the anti-HCV positive (P) states, as illustrated in Figure 1, and expressed by the following differential equations:

$$\left.\begin{aligned} \frac{\mathrm{d}N(a,t)}{d(a,t)} &= -\lambda(a,t)N(a,t) - \mu_1 N(a,t) + \beta N(a,t) \\ &\quad + \gamma P(a,t) \\ \frac{\mathrm{d}P(a,t)}{d(a,t)} &= \lambda(a,t)N(a,t) - \mu_2 P(a,t) - \gamma P(a,t). \end{aligned}\right\} \quad (3)$$

Parameters presented in Figure 1 and introduced in equation (3) are shown in Table 1 [19, 29, 30].

Given that $N(a,t) + P(a,t) = 1$ for each age and time, we can express incidence from equation (3) by:

$$\begin{aligned} \lambda(a,t) = \Big(&\frac{\partial}{\partial a}P(a,t) + \frac{\partial}{\partial t}P(a,t) + (\beta - \mu_1) \\ &- (\beta - \mu_1 - \gamma)P(a,t)\Big) \\ &/(1 - P(a,t)), \end{aligned}$$

where $P(a,t)$ represents the prevalence estimated in the previous section. We can thus replace $P(a,t)$ by $P(Y=1|a,t)$ hereafter. With a logit link, age-dependent prevalence, for a given time t, can be derived from equation (2):

$$\begin{aligned} \frac{\partial P(a,t)}{\partial a} &= \frac{\partial P(Y=1|a,t)}{\partial a} \\ &= \frac{\eta'(a)\exp\big(\alpha + \eta(a) + ct\big)}{\big[1 + \exp\big(\alpha + \eta(a) + ct\big)\big]^2}, \end{aligned}$$

where $\eta'(a)$ is the first derivative of the fractional polynomial $\eta(a)$ with respect to age a. The estimated age-dependent incidence for a given time t is therefore:

$$\begin{aligned} \lambda(a|t) = \big(&\eta'(a)p(a|t)(1 - p(a|t)) + (\beta - \mu_1) \\ &- (\beta - \mu_1 - \gamma)p(a|t)\big) \\ &/(1 - p(a|t)), \end{aligned} \quad (4)$$

where $p(a|t) = P(Y=1|a,t)$ is the estimated prevalence for age a calculated at a given time t. Using a

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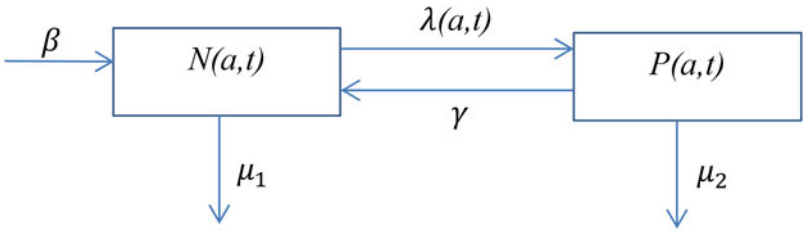

Fig. 1. Two-state compartmental model for HCV transmission. β is the proportion of new drug users; γ is the seroreversion (defined as the absence of HCV antibodies in a person previously known to be HCV positive) rate; μ_1 is the all-cause mortality rate in those without HCV infection; μ_2 ($=\mu_1+\mu_{HCV}$, μ_{HCV} is the HCV-related mortality rate) is the all-cause mortality rate in those with HCV infection and λ is the incidence rate.

Table 1. *Annual parameters in the two-state compartmental model*

Parameter	Parameter value	Reference
β: proportion of new drug users	2%	ANRS-Coquelicot data [19, 20]
γ: HCV seroreversion* rate	0·001	Le Page *et al.* [29]
μ_1: all-cause mortality rate in those without HCV infection	0·7%	Smit *et al.* [30]
μ_2: all-cause mortality rate in those with HCV infection	1·3%	Smit *et al.* [30]

* Defined as the absence of HCV antibodies in a person previously known to be anti-HCV positive.

complementary log-log link, the estimated age-dependent incidence at time t is given by:

$$\lambda(a|t) = \big(-\eta'(a)\log(1-p(a|t))(1-p(a|t)) + (\beta-\mu_1) - (\beta-\mu_1-\gamma)p(a|t)\big) /(1-p(a|t)).$$

Estimation of global incidence

Using the previous estimation of age-dependent incidence $\lambda(a|t)$ and the estimated proportion of DU by age, we calculated the global incidence of HCV infection for each time survey. The proportion of DU of age a at time t, noted $q(a|t)$, was estimated using the Horvitz–Thompson estimator $\hat{q}(a|t) = \sum_i^n w_i x_i(a,t) / \sum_i^n w_i$, where w_i is the sampling weight of the individual i, $x_i(a,t) = 1$ if the individual i is of age a at time t and 0 otherwise, and where n is the survey sample size [31].

For a given survey time, the global incidence can thus be expressed by the weighted arithmetic mean of the age-dependent incidences $\lambda(t) = \sum_a \hat{q}(a|t)\lambda(a|t)$.

A bootstrap method was used to estimate the variance of estimates, detailed in Supplementary Appendix 3. All analyses were performed using Stata v. 12.1 (StataCorp., USA) and the R 3.1.2 program (R Foundation for Statistical Computing, Austria).

RESULTS

Descriptive characteristics of DU

In the ANRS-Coquelicot surveys, 1462 and 1568 DU were included in 2004 and 2011, respectively, and blood samples were available in 79% and 92% of the participants [19, 20]. The final dataset combining these two surveys included 813 DU in 2004 and 1242 DU in 2011, after excluding individuals surveyed in general practitioners' offices only in 2004, and those surveyed in the two administrative departments only in 2011. In addition, DBS from 2004 were deemed invalid when there was insufficient material (i.e. DBS <6 mm in diameter). Table 2 presents descriptive statistics about the participants for both of the surveys after exclusion. The majority of the participants were men (~77%) aged 26–45 years (83% in 2004 and 67% in 2011).

From both surveys, we estimated that most DU reported injecting drug use [72·0% (95% confidence interval (CI) 63·4–80·7) in 2004 and 65·7% (95% CI 61·7–69·7) in 2011] and that <50% had used crack in the previous month (Table 2). HIV prevalence was estimated at 10·8% (95% CI 5·4–16·2) in 2004 and 9·4% (95% CI 6·8–12·0) in 2011.

Using the threshold method, HCV prevalence in DU was estimated at 58·9% (95% CI 50·4–67·4) in 2004 and 43·4% (95% CI 39·0–47·9) in 2011. Using the mixture model, HCV prevalence in DU was estimated at 58·2% (95% CI 49·7–66·8) in 2004 and 43·2% (95% CI 38·8–47·7) in 2011.

Estimated age- and time-dependent prevalence

The logit link provided the lowest AIC for all regressions when modelling prevalence. Table 3 presents the

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Table 2. *Descriptive statistics of participants, France, 2004 and 2011, ANRS-Coquelicot*

	2004 ($N = 813$)			2011 ($N = 1242$)		
Participants	Unweighted (proportion)	Weighted (proportion)	95% CI	Unweighted (proportion)	Weighted (proportion)	95% CI
Age, years						
18–19	0·9	0·4	0·1–1·1	0·9	0·6	0·3–1·4
20–25	11·6	6·9	4·7–10·2	10·3	7·6	5·9–9·9
26–35	43·7	48·5	39·9–57·2	25·9	26·1	22·6–29·9
36–45	39·0	39·7	32·3–47·6	40·7	41·9	38·1–45·8
46–55	4·7	4·2	2·6–6·5	19·9	21·3	17·5–25·7
⩾56	0·2	0·3	0·00–1·9	2·3	2·5	1·6–4·0
Men	77·0	72·2	64·3–80·0	77·9	79·5	76·0–82·9
Reporting injecting drug use	73·3	72·0	63·4–80·7	63·9	65·7	61·7–69·7
Reporting injecting drug use in the month previous to the study interview	39·0	44·1	33·7–54·6	32·2	36·1	30·2–42·1
Crack use in the previous month	24·6	41·0	30·3–51·6	27·8	34·4	29·7–39·1
HIV prevalence	10·1	10·8	5·4–16·2	8·0	9·4	6·8–12·0
HCV prevalence (threshold method)	54·1	58·9	50·4–67·4	39·1	43·4	39·0–47·9
HCV prevalence (direct method)	52·5	58·2	49·7–66·7	39·2	43·2	38·9–47·7

CI, Confidence interval.

results obtained from the different regression models. For each model (except model 2), age and time were significantly associated ($P < 0·05$) with HCV infection.

For all the Figures below (except Fig. 1), the left panel represents the prevalence according to age from the two surveys, estimated from the regression model (curves) and from the pointwise design-based prevalence estimates (circles).

In all DU, prevalence monotonically increased with age until reaching a plateau at age ~50 years. A marked decrease in prevalence was observed regardless of age between 2004 and 2011 (Fig. 2, left panel).

Age- and time-dependent HCV prevalence was higher in IDU than in those who did not report injecting drug use [odds ratio (OR) 17·7, 95% CI 10·0–31·4; Table 3; Fig. 3, left panel]. Most DU were IDU (68·9%, 95% CI 64·7–72·7).

In AIDU, prevalence sharply increased with age until it reached a plateau at age ~40 years, then stabilized at ~80% (Fig. 4, left panel). The results and the shape of the prevalence according to the year of the survey, were not significantly different (OR 0·9, 95% CI 0·8–1·0, Table 3). No significant association with age or with time was found (model 2, Table 3). No significant association with crack use was found (model 4, Table 3).

Estimated age- and time-dependent prevalence was higher in HIV-positive DU than in HIV-negative DU (OR 5·3, 95% CI 2·9–9·9, Table 3, model 5), with the global HCV prevalence exceeding 80% (Fig. 5, left panel).

Estimated age- and time-dependent incidence

In Figures 2–5, the middle panel represents the estimated HCV incidence expressed as the rate of new anti-HCV positive persons/100 person-years, according to age both in 2004 and 2011, with their confidence intervals. The right panel represents estimated incidence according to age for each year between 2000 and 2020.

Overall, incidence decreased over time. It increased until a given age (for example, in 2011, age 34 years in all DU) before decreasing thereafter (Figs 2–5).

In all DU, the highest incidence was estimated at 10·0/100 (95% CI 7·8–11·6) in those aged 31 years in 2004, and at 6·1/100 (95% CI 4·4–7·5) in those aged 34 years in 2011 (Fig. 2, middle panel).

HCV incidence in non-IDU decreased faster over time than in IDU (Fig. 3, middle and right panels). The highest incidence in non-IDU was estimated at 3·9/100 (95% CI 2·4–5·2) in those aged 35 years in 2004, and at 2·3/100 (95% CI 1·0–3·4) in those aged 37 years in 2011. HCV incidence was always higher in IDU than in their non-injecting counterparts. The highest HCV incidence was estimated at 15·1/100 (95% CI 12·0–17·9) in those aged 29 years in 2004, and at 9·5/100 (95% CI 7·2–11·2) in those aged 32 years in 2011 (Fig. 3, middle panel).

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Table 3. *Logistic regression models performed to estimate anti-HCV prevalence in drug users, France, 2004 and 2011, ANRS-Coquelicot*

Variable	Fractional polynomial transformation $\eta(a)$	Regression coefficient estimate (s.e.)	*P*	95% CI	OR
Model 1					
Age	$(age/10)^{-1} - 0{\cdot}27$	−18·15 (2·59)	<0·001	−23·25 to −13·06	
	$(age/10)^{3} - 49{\cdot}14$	−0·008 (0·004)	0·023	−0·016 to −0·001	
Time (ref.: 2004)		−0·15 (0·03)	<0·001	−0·21 to −0·09	0·86 (0·81–0·92)
Intercept		0·81 (0·20)	<0·001	0·42 to 1·20	
Model 2 (AIDU)					
Age	$(age/10)^{-2} - 0{\cdot}08$	−4·05 (22·53)	0·857	−48·27 to 40·18	
	$(ag\ (age/10)^{-2} \ln(age/10) - 0{\cdot}10$	−44·66 (36·46)	0·221	−116·245 to 26·91	
Time (ref.: 2004)		−0·10 (0·06)	0·091	−0·21 to −0·02	0·91 (0·81–1·02)
Intercept		1·52 (0·38)	<0·001	0·78 to 2·27	
Model 3					
Age	$\ln(age/10) - 1{\cdot}30$	17·49 (4·12)	<0·001	9·38 to 25·60	
	$\ln(age/10)^{2} - 1{\cdot}68$	−5·22 (1·54)	0·001	−8·28 to −2·20	
Time (ref.: 2004)		−0·16 (0·04)	<0·001	−0·23 to −0·09	0·85 (0·79–0·92)
Reporting injecting drug use (ref: no)		2·88 (0·29)	<0·001	2·30 to 3·45	17·73 (10·02–31·36)
Intercept		−1·22 (0·33)	<0·001	−1·87 to −0·58	
Model 4					
Age	$(age/10)^{-1} - 0{\cdot}27$	−18·14 (2·57)	<0·001	−23·18 to −13·09	
	$(age/10)^{3} - 49{\cdot}14$	−0·008 (0·004)	0·031	−0·015 to −0·000	
Time (ref.: 2004)		−0·15 (0·03)	<0·001	−0·21 to −0·09	0·86 (0·81–0·91)
Crack user (ref.: no)		0·26 (0·19)	0·159	−0·10 to 0·63	1·30 (0·90–1·89)
Intercept		0·71 (0·18)	<0·001	0·35 to 1·06	
Model 5					
Age	$(age/10)^{-1} - 0{\cdot}27$	−17·60 (2·59)	<0·001	−22·68 to −12·52	
	$(age/10)^{3} - 50{\cdot}14$	−0·009 (0·004)	0·010	−0·016 to −0·002	
Time (ref.: 2004)		−0·16 (0·04)	<0·001	−0·24 to −0·09	0·85 (0·79–0·91)
HIV (ref: HIV-negative)		1·68 (0·31)	<0·001	1·07 to 2·29	5·35 (2·90–9·86)
Intercept		0·82 (0·26)	0·002	0·31 to 1·32	

AIDU, Drug user reporting active injecting drug use; OR, odds ratio; CI, confidence interval.

For example, for model 1: $\text{logit}(P(Y = 1|a, t) = -18{\cdot}15\left[(a/10)^{-1} - 0{\cdot}27\right] - 0 \cdot 01\left[(a/10)^{3} - 49{\cdot}14\right] - 0{\cdot}15t + 0{\cdot}81$, for age a at time t.

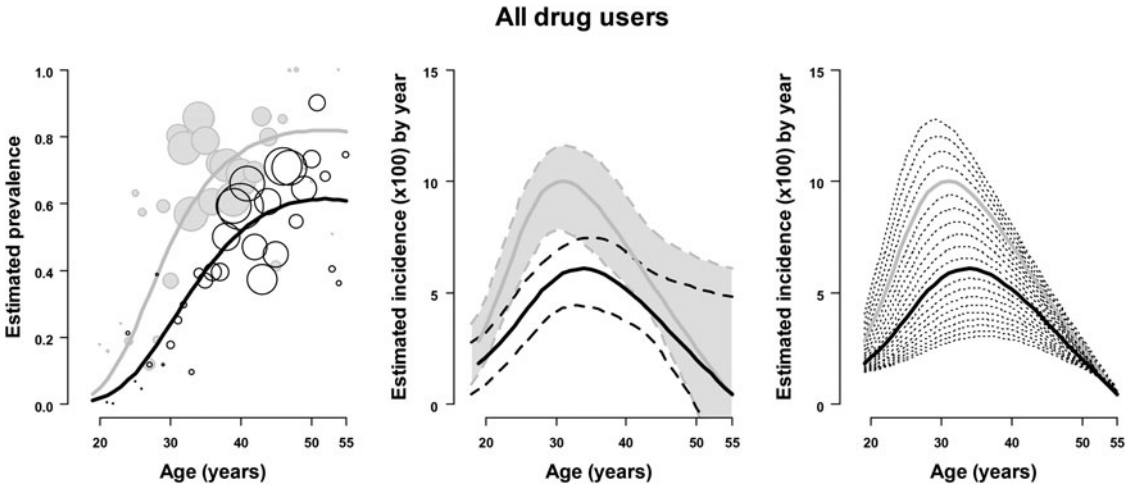

Fig. 2. *Left panel*: Curves represent the age-dependent HCV prevalence estimates from the logistic models in drug users in 2004 (grey) and 2011 (black). Circles represent the estimated prevalence by age. Their size is proportional to the number of persons in 2004 (solid grey circles) and 2011 (open circles). *Middle panel*: Curves represent the age-dependent HCV incidence estimates in drug users in 2004 (grey) and 2011 (black) with their confidence intervals (dashed curves). *Right panel*: Age-dependent HCV incidence estimates in drug users over 2000–2020. Curves were obtained from the model in 2004 (grey curves), 2011 (black curves) and the other years (dotted curves).

Estimates in AIDU showed that HCV dynamic infection was relatively similar between 2004 and 2011, as expected from the regression model (Fig. 4, model 2, Table 3).

In HIV-positive DU, HCV incidence increased until age 25 years in 2004 and until age 27 years in 2011 before decreasing thereafter (Fig. 5, middle and right panels). Even age-dependent HCV incidence consistently drifted towards older ages with time, the corresponding DU being younger in this subpopulation than the other subpopulations.

Estimated global incidence in those aged 18–55 years

We estimated a global incidence in those aged 18–55 years because of the very small number of older participants.

In all DU, HCV incidence was lower in 2011 (4·4/100, 95% CI 3·3–5·9) than in 2004 (7·9/100, 95% CI 6·4–9·4) (Table 4). For each DU subpopulation studied, we observed that HCV incidence was lower in 2011 than in 2004.

HCV incidence was found to be twice as high in AIDU as in other DU, decreasing from 15·4/100 (95% CI 11·9–19·3) in 2004 to 11·2/100 (95% CI 9·0–19·0) in 2011 (Table 4).

DISCUSSION

We estimated age- and time-dependent prevalence and incidence of HCV infection in DU in France by first modelling prevalence data from two repeated cross-sectional surveys and then building a model linking prevalence and incidence. We estimated that HCV prevalence in DU in France increased with age in 2004 and 2011, and decreased over time in all DU. HCV incidence was also dependent on age and declined from 11/100 person-years in 2004 to 6/100 person-years in 2011.

Prior to this work, the only published HCV incidence estimate available in France came from a 2000–2001 cohort of injecting DU in the northeast region of France (excluding Paris and its suburbs) and equalled 9/100 person-years [32].

The present study exhaustively recruited harm reduction facilities and care services for DU in five French metropolitan cities. We included both high- and low-threshold services, which enabled us to obtain a wide range of services serving different profiles within the DU population attending specialized services. Furthermore, the ANRS-Coquelicot survey is the only study that includes biological data to measure HCV prevalence.

Our estimates are consistent with those from some other European countries. In England, Wales and Northern Ireland, the incidence of HCV infection in IDU was estimated at 4–12 infections/100 person-years in 2011 [15] and between 6 and 18/100 person-years in 2013 [33], using an anti-HCV avidity testing method. In Scotland, HCV incidence in IDU was estimated at 10 infections/100 person-years in 2013–2014 [33]. In Australia, HCV incidence in IDU declined over

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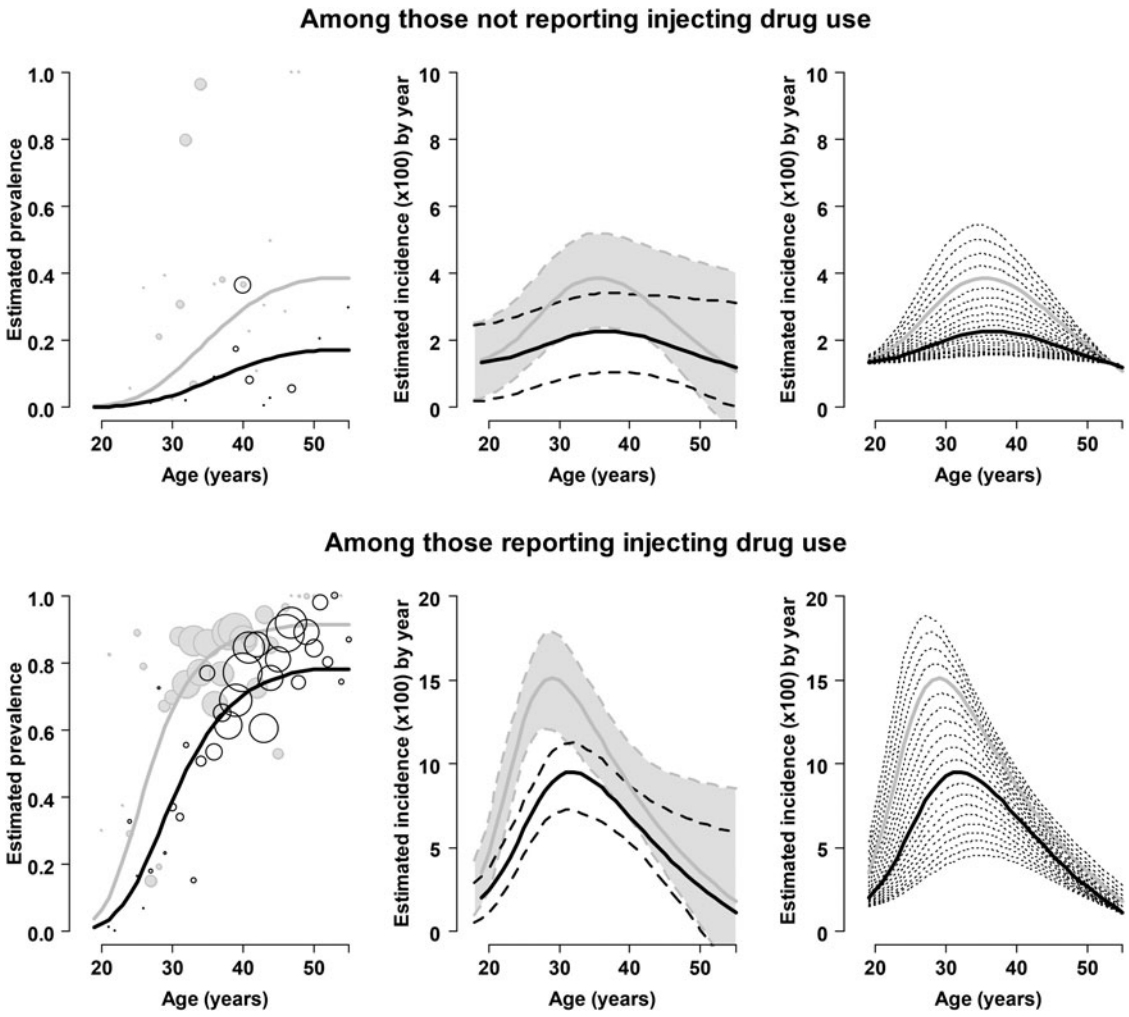

Fig. 3. *Left panels*: Curves represent the age-dependent HCV prevalence estimates from the logistic models in 2004 (grey) and 2011 (black) in those not reporting injecting drug use (*top panels*) and those reporting injecting drug use (*bottom panels*). Circles represent the estimated prevalence by age. Their size is proportional to the number of individuals in 2004 (solid grey circles) and 2011 (open circles). *Middle panels*: Curves represent the age-dependent HCV incidence estimates in 2004 (grey) and 2011 (black) with their confidence intervals (dashed curves) in those not reporting injecting drug use (*top panels*) and those reporting injecting drug use (*bottom panels*). *Right panels*: Age-dependent HCV incidence estimates over 2000–2020 in those not reporting injecting drug use (*top panels*) and those reporting injecting drug use (*bottom panels*). Curves were obtained from the model in 2004 (grey curves), 2011 (black curves) and the other years (dotted curves).

time, between 10 and 15/100 person-years in 2004 to 4/100 (95% CI 1·3–12·3) person-years in 2009 [2].

Our study shows that global HCV incidence was twice as high in AIDU as in IDU in 2011, which explains why the prevalence did not vary significantly between the two surveys in AIDU. Compared to other European countries such as The Netherlands [5] and Switzerland [34], HCV incidence in AIDU remains high in France. In parallel with this work, we estimated a HCV incidence of 49/100 person-years in 2011–2013 in AIDU in Paris and its suburbs, using a biological approach based on HCV RNA positives in negative anti-HCV tests, and an estimated window period of 56 days [35]. The two estimates (11% and 49%) are not directly comparable. The first came from five French cities throughout mainland France, each city having its own characteristics in terms of DU profiles, while the second focused on individuals surveyed in Paris and its suburbs [20]. Some authors have pointed out that in order to use this method effectively, a large sample size is needed due to the short window period unless incidence is very high [15]. Other authors have highlighted that variability in HCV RNA detection and the disease's natural history during early infection may also result in differences between methods [11].

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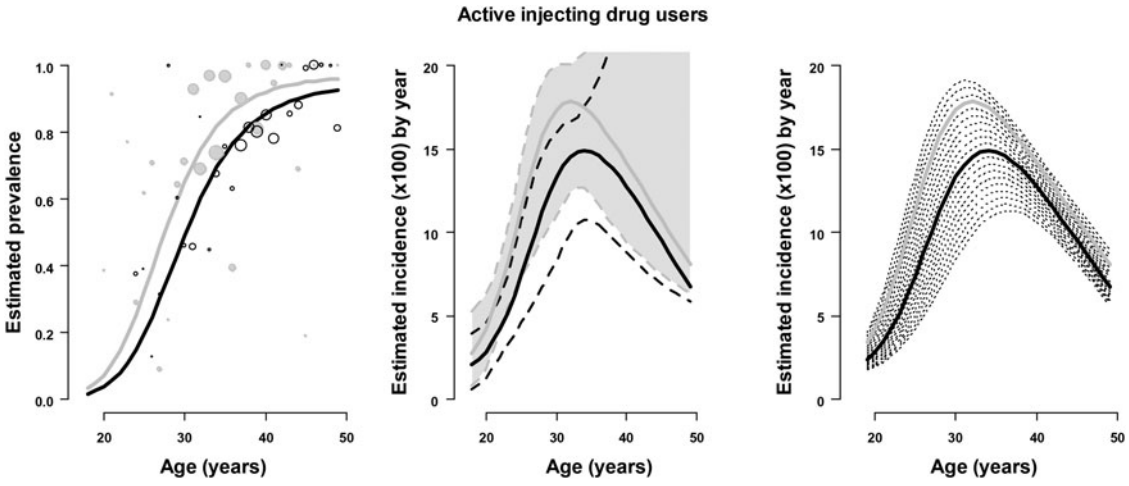

Fig. 4. *Left panel*: Curves represent the age-dependent HCV prevalence estimates from the logistic models in those reporting active injecting drug use in 2004 (grey) and 2011 (black). Circles represent the estimated prevalence by age. Their size is proportional to the number of individuals in 2004 (solid grey circles) and 2011 (open circles). *Middle panel*: Curves represent the age-dependent HCV incidence estimates in active injecting drug users in 2004 (grey) and 2011 (black) with their confidence intervals (dashed curves). *Right panel*: Age-dependent HCV incidence estimates in active injecting drug users over 2000–2020. Curves were obtained from the model in 2004 (grey curves), 2011 (black curves) and the other years (dotted curves).

Our results showed that crack use in the previous month is probably a poor proxy for lifetime risk from crack use. Indeed, it is not crack itself that exposes individuals to the risk of HCV transmission, but the oral lesions caused by chipped and very hot glass pipes. The use of glass pipes regularly results in burns and ulcerated lesions and cuts on lips and in oral cavities. Small amounts of blood may constitute a risk of infection when users share their glass pipes during crack consumption.

Harm reduction measures may contribute to a faster decline in incidence/prevalence and should be taken into account when modelling prevalence and incidence over time. At an international level, harm reduction measures have been greatly improved since the late 1980s [2, 5]. Today they include needle-and-syringe exchange programmes, access to opiate substitution treatment, HCV screening and HCV treatment [2, 3, 5, 36]. In France, access to opioid substitutive treatments has improved but some harm reduction measures, available in other countries, are still not available, such as supervised consumption rooms [37]. In the ANRS-Coquelicot surveys, the following question about needle-and-syringe cleaning (bleach) was included: '*Over the last month, did you at least once use the same water/bleach to clean your needle/syringe?*'. However, the percentage of missing data was high (70%). Furthermore, as the question '*Have you been cured of your HCV infection?*' was asked only in the 2011 survey, we were unable to consider HCV treatment for HCV-positive individuals in our modelling approach.

Our model-based estimates should also be interpreted with caution as they suffer from many potential limitations also present in other studies, some of which are listed by Cullen *et al.* [15]. First, in those not reporting injecting drug use, HCV incidence was estimated at 2/100 (95% CI 0·9–3·2) person-years in 2011. However, this estimation may be a reflection of misclassification bias due to the under-reporting of injecting drug use. Second, to model prevalence, it would have been interesting to include additional variables – such as migration – in the regression models, if that data had been available. Incidence estimation could be greatly improved as the transmission of HCV infection is driven by a basic two-state model. Third, we considered one homogeneous population of DU while other authors have considered two or more populations based on different IDU risk behaviours [3].

Many studies have developed compartmental models with more than two states, stratified by several factors including HIV serostatus, being an injector or not, being on HCV treatment or not, being cured (i.e. those who are anti-HCV positive and HCV-RNA negative) or not [3, 38, 39]. However biological results on HCV RNA to identify those individuals cured of the disease were not available in 2004. It would have been also useful to incorporate parameters depending

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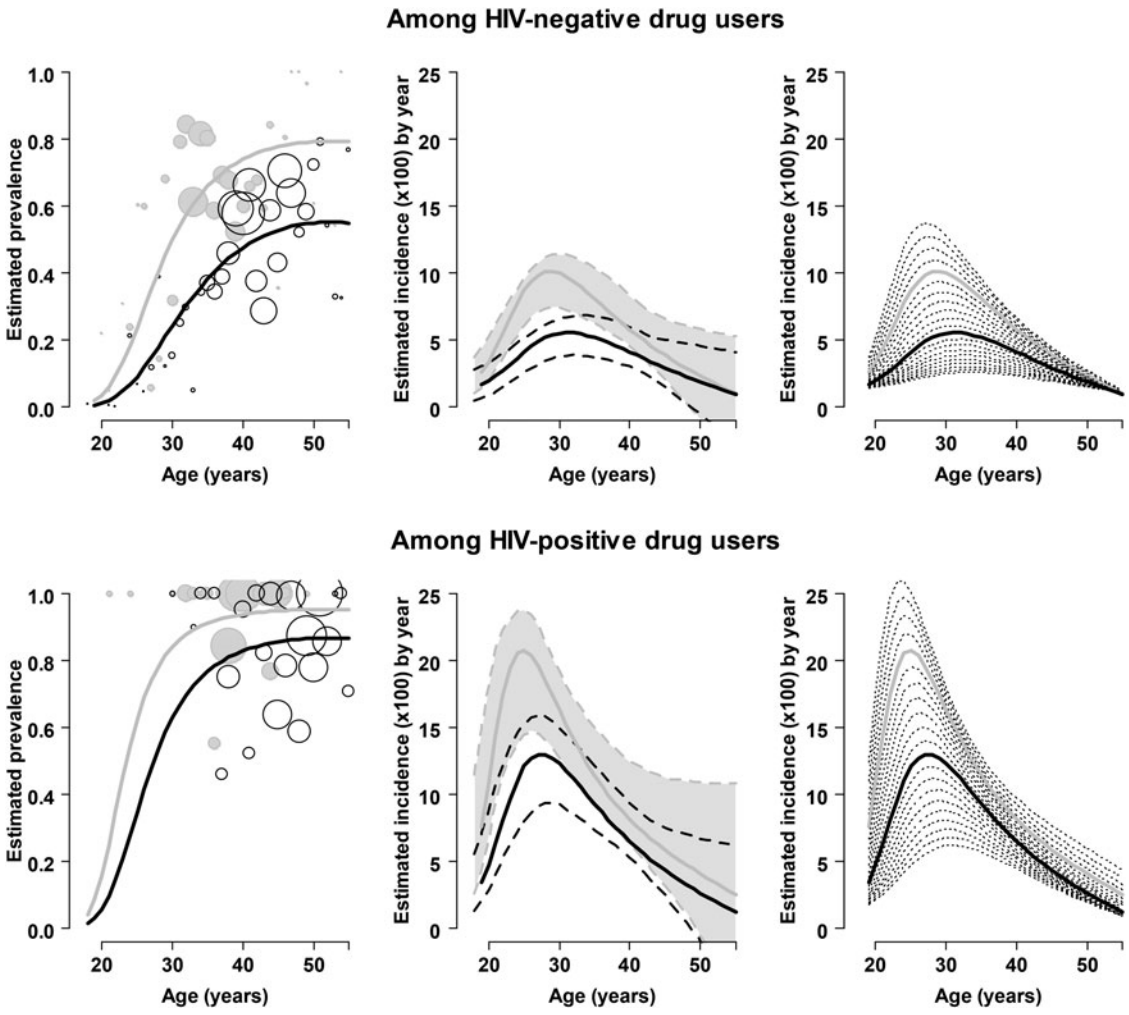

Fig. 5. *Left panels*: Curves represent the age-dependent HCV prevalence estimates from the logistic models in 2004 (grey) and 2011 (black) in HIV-negative drug users (*top panels*) and HIV-positive drug users (*bottom panels*). Circles represent the estimated prevalence by age. Their size is proportional to the number of individuals in 2004 (solid grey circles) and 2011 (open circles). *Middle panels*: Curves represent the age-dependent HCV incidence estimates in 2004 (grey) and 2011 (black) with their confidence intervals (dashed curves) in HIV-negative drug users (*top panels*) and HIV-positive drug users (*bottom panels*). *Right panels*: Age-dependent HCV incidence estimates over 2000–2020 in HIV-negative drug users (*top panels*) and HIV-positive drug users (*bottom panels*). Curves were obtained from the model in 2004 (grey curves), 2011 (black curves) and the other years (dotted curves).

on age (or age group), gender and/or time in the mortality rate, the proportion of new DU. However, precise data on the French DU population are not available [4, 40].

Despite these methodological limitations, we believe that our approach combining a regression model with a compartmental model is an alternative method to estimate incidence from cross-sectional data in the absence of cohort.

Implementing a third cross-sectional survey in DU should be considered, to evaluate whether the decline in HCV incidence has continued since 2011. Despite a potential increase of at-risk behaviours, such a decline is to be expected given recent developments in harm reduction measures and new therapeutic approaches. Since June 2016, all individuals at risk of HCV transmission in France, including IDU, have been eligible for HCV antiviral treatment with new direct-acting antivirals (DAA). Compared with anti-HCV regimens using pegylated interferon and ribavirin, DAA have a very high success rate, better tolerance, a shorter prescribed course and easier adherence. HCV transmission models have shown that even modest increases in successful treatment of HCV infection in persons who inject drugs can decrease prevalence and incidence [3]. Assessing DAA treatments' impact

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Table 4. *Estimation of HCV incidence (per 100 person-years) in drug users, 18–55 years age group, France, 2004 and 2011*

	2004			2011		
Participants	Sample size	Incidence per 100 py	95% CI	Sample size	Incidence per100 py	95% CI
All drug users	811	7·9	6·4–9·4	1209	4·4	3·3–5·9
Not reporting injecting drug use	216	3·1	1·9–4·5	434	2·0	0·9–3·2
Reporting injecting drug use	594	10·8	9·0–12·8	775	6·1	5·0–8·0
Reporting active injecting drug use (injected during month previous to study interview)	232	15·4	11·9–19·3	252	11·2	9·0–19·0
HIV-negative drug users	753	7·4	5·8–8·9	1111	3·9	2·8–5·4
HIV-positive drug users	58	9·1	7·4–13·3	98	4·6	2·4–7·8

py, Person-years; CI, confidence interval.
One individual did not report if he was an injecting drug user or not. Active injecting drug users are a subgroup of injecting drug users.

on prevalence and incidence in the French context is crucial. Furthermore, the declining trend of injecting drugs observed in most European countries, reflected in the two ANRS-Coquelicot surveys in France, could lead to a decline of prevalence and incidence of HCV.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0950268816002934.

DECLARATION OF INTEREST

None

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