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Meta-Analysis

Meta-Regression of Hepatitis C Virus Infection in Relation to Time Since Onset of Illicit Drug Injection: The Influence of Time and Place

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The authors examined the relation between time since onset of illicit drug injection (time at risk) and rates of hepatitis C virus (HCV) infection by using meta-regression. In 72 prevalence studies, median time since onset of injection was 7.24 years and median prevalence was 66.02%. The model showed statistically significant linear and quadratic effects of time at risk on HCV prevalence and significantly higher prevalence in developing and transitional countries and in earlier samples (1985–1995). In developed countries post-1995, mean fitted prevalence was 32.02% (95% confidence interval: 25.31, 39.58) at 1 year of injection and 53.01% (95% confidence interval: 40.69, 65.09) at 5 years. In developing/transitional countries post-1995, mean fitted HCV prevalence was 59.13% (95% confidence interval: 30.39, 82.74) at 1 year of injection. In 10 incidence studies, median time at risk was 5.29 years and median cumulative HCV incidence was 20.69%. Mean fitted cumulative incidence was 27.63% (95% confidence interval: 16.92, 41.70) at 1 year of drug injection. The authors concluded that time to HCV infection in developed countries has lengthened. More rapid onset of HCV infection in drug injectors in developing/transitional countries resembles an earlier era of the HCV epidemic in other regions.

harm reduction; hepatitis C; HIV; meta-analysis; substance abuse, intravenous

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user.

Hepatitis C virus (HCV) infection is endemic in injection drug user (IDU) populations throughout the world (1, 2). HCV is efficiently transmitted via blood exposures, including by injection with a syringe used by another IDU, shared use of drug preparation equipment, and potentially via other blood exposures in the injection setting (3, 4). Rates of HCV infection in IDUs are highly variable, with prevalence reported between 10% and 100% and incidence ranging from 2 to 45 infections per 100 person-years (5–8).

A number of early cross-sectional studies in the United States and Europe suggested very rapid acquisition of HCV following onset of drug injection (9–12), but, in more recent years, there have been reports of low or declining prevalence in young injectors (13–15). Understanding variability in the interval between onset of drug injection and HCV infection may lead to advancements in HCV prevention and in estimating the future burden of disease.

In this study, the relation between time since onset of drug injection and HCV prevalence and incidence was examined with data from the HCV Synthesis Project, a meta-analysis of research studies of HCV epidemiology and prevention in drug users throughout the world (16, 17). Calendar time (study period) and place (study location) were examined as potential modifiers of this relation.

MATERIALS AND METHODS

The scope of the HCV Synthesis Project includes published and unpublished reports describing the epidemiology of HCV infection in drug users—IDUs and non-IDUs who sniff or smoke heroin, cocaine, or amphetamine. These 2 groups of drug users have been identified as having a biologically plausible risk of HCV infection related to drug use,

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through percutaneous exposure (via injection) or mucous membrane exposure to blood via sharing of straws or pipes used to administer drugs (noninjection drug use) (18, 19). To be eligible for inclusion in the HCV Synthesis Project, studies must have reported HCV prevalence or incidence rates, measures of association, human immunodeficiency virus (HIV)/HCV coinfection rates, or HCV genotype distributions in eligible samples of drug users. In addition, HCV status must have been determined by serologic testing of either sera or saliva.

Data collection and abstraction methods have been described in detail elsewhere (17). Briefly, automated searches of published literature were carried out with electronic databases of the published medical literature and by using government and other websites related to public health and drug control. Manual search methods included follow-up of information provided in footnotes and searching of journals and proceedings from scientific conferences related to drug use, hepatitis, and HIV. Reports published or released between January 1989 and December 2006 were included in the search. A total of 2,375 reports were identified and screened for eligibility, of which 628 were determined to be eligible and were included in the HCV Synthesis Project sample.

Data were abstracted by senior research assistants who had graduate training in research methods; all coding was reviewed by the project director and principal investigator. Overlapping reports, for example, duplicate data from a single study, were identified based on matching study names, setting, and authors; this step was followed by comparing sample sizes, years of data collection, and other study characteristics to select the most complete and informative report in terms of our research question of interest. A number of reports included multiple studies (e.g., HCV prevalence or incidence estimates were given for samples recruited by using different study methods or with different demographic characteristics). In this paper, multiple studies in the same report are indicated in the tables by appending ''study 1,'' ''study 2,'' and so forth, to the citation.

Studies were included in the current analysis if HCV infection rates (prevalence or incidence) in IDUs were reported in relation to categories of time since onset of drug injection (hereafter referred to as ''time at risk''). Mucous membrane exposure (sniffing or smoking drugs) in the absence of injection-related exposure was not examined in this analysis; thus, the analysis included samples of only those individuals who had injected drugs. Time at risk is an approximation of accrued risk of HCV acquisition by exposure to infected blood in shared syringes or other implements used to inject drugs. It is typically measured by asking participants the date of or age at their first illicit drug injection and calculating the time between that date and the date of study participation or interview.

The midpoint of time-at-risk categories was calculated so that each category could be represented by a single value. For the upper boundaries of open-ended categories, 10 years was added to the lower boundary to calculate a midpoint; the 10-year interval was selected on the basis of the distributions of the data reviewed in the HCV Synthesis Project. Twenty-two percent of category upper boundaries were open ended. Substituting other realistic values for open-ended upper boundaries did not appreciably alter the results. Since, by definition, drug injectors have been injecting for more than 0 years, the lower boundary of the minimum-duration-of-injecting category was set to 0.08 years, equivalent to 30 days since onset of injection. Thus, for example, data in a time-at-risk category of ''5 years or less'' would be represented by a value of 2.54, the midpoint between 0.08 and 5 years.

Time-at-risk categories represented partially aggregated data, reflecting increased precision compared with summary measures at the study level (i.e., mean or median time since onset of injection in relation to HCV prevalence or incidence for the entire sample) but less precision than would have been provided by individual data. Median values at the study level were calculated by summing across categories and dividing by study sample size. Preliminary analyses also examined the associations in data from studies that reported only summary measures of HCV infection and time at risk at the study level. However, results from these preliminary analyses exhibited relatively larger standard errors for the time-at-risk measurement (data not shown) and smaller effects compared with those from studies that reported rates in relation to time-at-risk categories, reflecting the relative lack of precision in the time-at-risk measure when summarized at the study level. Thus, to maximize precision in the models, we focused on the studies that reported results in relation to time-at-risk categories.

Several factors were examined as potential confounders or modifiers of the relation between time at risk and HCV infection rates. Studies were classified according to whether data collection was completed in 1985–1995 versus later (1985 was the earliest year of data collection reported in the studies). This year (1995) was chosen a priori to represent a division between an early period and a later period characterized by increased HCV awareness among IDUs and the expansion of HIV/HCV prevention programs in the United States, Europe, and Australia (20–22). For studies that did not report the time frame of data collection, year of publication minus 2 years was used to approximate the end of data collection. Place was also evaluated as a modifier of the time-at-risk relation. A lack of public health resources in developing and transitional countries was expected to shorten the time to HCV infection in comparison to developed countries. Thus, studies were coded according to whether data were from a developing/transitional country or from a developed country; calendar time and place were represented in the analysis with single dichotomous indicator variables. We could not assess the interaction between place and calendar time because only 1 study from developing/transitional countries collected data before the end of 1995. Two indicators of potential sampling bias were also examined as covariates—recruitment method and recruitment location. To develop final models, nested models were tested by using likelihood ratio tests of the -2 pseudo-log-likelihoods.

To assess the association between time since onset of injection and HCV rates, generalized mixed-effects meta-regression models were developed with SAS PROC

GLIMMIX software (SAS Institute, Inc., Cary, North Carolina). The data were in 2-level hierarchical form. The level 1 unit of analysis was defined by the time-at-risk category, representing partially aggregated data within each study. Some reports contained data for more than 1 study. The level 2 unit of analysis was defined by report rather than study level because sampling characteristics were typically constant for reports that included more than 1 study. Results (data not shown) did not change meaningfully when the study was used to define the level 2 unit of analysis. The models specified binomial distributions of the dependent variables and random intercepts to account for shared variance within reports. Events/trials syntax was used to represent the dependent variables. Events represented prevalent or incident cases, whereas trials represented the total sample. Thus, the models reflected the actual sample sizes and were not otherwise weighted. The number of cases and the total sample size, representing cumulative incidence over the follow-up periods and aggregated by time-at-risk categories, were available for all incidence studies. To control for the precision of the time-at-risk category intervals, a variable representing the interval width was initially included in the models. Robust sandwich estimation of the covariance matrix of the fixed effects was used to provide estimates that may be less biased by model misspecification that is unavoidable because of the limited number of variables available in the data (23).

This approach enables estimation of the effects of potential covariates at the study level, as well as the effects of the main exposure of interest (time at risk) at the most precise level of aggregation available, while accounting for the shared variance within studies. These methods maximize the quantity and the comparability of the data. Methods requiring more than 2 categories per study would have reduced our sample by 25% for prevalence studies and 50% for incidence studies (24). The plots of time at risk in relation to HCV prevalence and incidence showed evidence of nonlinearity, so quadratic time-at-risk terms were added to the models to evaluate this possibility. To reduce multicollinearity, time at risk was centered by subtracting the mean from each score and dividing the result by the standard deviation before squaring. Since the analysis included samples of only those individuals who had injected drugs, the intercept term should not be interpreted as the average HCV rate among unexposed persons (25). Heterogeneity was assessed by likelihood ratio tests of the random-effect variance parameters.

Potential publication bias was assessed by inspection of a funnel plot and Begg and Egger formal tests of funnel plot asymmetry (26). To create the funnel plot, log odds were calculated for the subset of 55 prevalence studies and 5 incidence studies with at least 3 time-at-risk categories and were plotted against the inverse of the standard errors. There was no evidence of publication bias among the prevalence studies as indicated by the symmetry of the funnel plot (not shown) and nonsignificant Begg's test ($P = 0.33$) and Egger's test ($P = 0.09$). There was also no evidence of publication bias in the funnel plot of the incidence studies (not shown) and nonsignificant Begg's test ($P = 0.63$) and Egger's test ($P = 0.87$).

RESULTS

HCV prevalence in relation to time at risk

Seventy-two studies (63 reports) (9, 15, 27–85; B. R. Edlin, unpublished study; A. Egeland, unpublished study) reported HCV prevalence in relation to categories of time since onset of drug injection; a total of 293 categories were available for analysis. Median HCV prevalence across these studies was 66.02% (minimum, 22.30; maximum, 97.89; interquartile range: 47.43, 76.62). Median time at risk across prevalence studies was 7.24 years (minimum, 0.75; maximum, 23.27; interquartile range: 4.95, 9.53). Twenty-two studies (30.6%) were from 1995 or earlier, and 14 studies (19.4%) were from developing or transitional countries. Characteristics of the 72 studies are shown in Table 1.

The final meta-regression model of these data showed statistically significant linear and quadratic effects of time at risk on HCV prevalence rates (Table 2). The coefficient for the quadratic term was less than 0; thus, the quadratic effect reduced the slope increasingly as time at risk accrued. The test for heterogeneity using the random-effect variance parameter estimate was significant ($P < 0.01$). Higher prevalence was predicted in developing and transitional countries ($P < 0.05$) and among studies with enrollment in 1985–1995 ($P < 0.01$). The variable representing the interval width of the time-at-risk category was not significant and did not achieve data-based criteria for confounding; it was not retained. To further explore the potential effect of precision in the time-at-risk measure, we conducted analyses stratified by length of time at risk. Since shorter time-at-risk intervals presumably were reported more reliably, results from analyses of such data should be more precise. Results of these stratified analyses (data not shown) were similar, with differences explainable by the focus on different lengths of time at risk (i.e., the shortest times at risk showed the steepest slopes). Covariance parameter estimates and parameter standard errors were not meaningfully different by length of time at risk. Terms representing study methods (recruitment location and recruitment method) were not significant, did not meet data-based criteria for confounding or effect modification, and were not included in this model.

A plot of the observed HCV prevalence by time at risk, with the fitted regression line overlaid, is presented in Figure 1. Fitted values were calculated by using results from models of the data in the original scale of measurement. Note that the coefficient for the intercept cannot be interpreted as HCV prevalence at onset of drug injection because, according to the definition of the HCV Synthesis Project sample, there were no subjects for whom time at risk equaled 0.

Table 3 presents mean fitted values for selected categories of time at risk and other covariates. Fitted values were calculated by using results from models of the data in the original scale of measurement. The fitted values also show that prevalence was expected to be higher at each time-at-risk interval in developing/transitional countries. For example, post-1995, at 1 year of drug injection, mean fitted prevalence was 59.13% (95% confidence interval (CI): 30.39, 82.74) in developing/transitional countries versus 32.02% (95% CI: 25.31, 39.58) in developed countries. In developed

Table 1. Studies of Injection Drug Users Reporting HCV Prevalence in Relation to Categories of Time Since Onset of Drug Injection, HCV Synthesis Project, 1989–2006

First Author, Year (Reference No.)	Location	Study Period	Recruitment Setting	Time at Risk, years[a]	No. Tested	HCV Prevalence, %
Alizadeh, 2005 (27)	Hamedan, Iran	2002	Correctional	2.2	149	31.5
Backmund, 2003 (28)	Muchen, Germany	1991–1997	Drug treatment	8.9	1,049	61.3
Bell, 1990 (29)	Westmead, Australia	1986–1989	Medical	5.8	172	86.0
Bradshaw, 2005 (30)	Melbourne, Australia	1999–2002	Needle exchange; street locations	5.8	314	74.0
Budd, 2002 (31)	Edinburgh, United Kingdom	1985–2000	Medical	13.4	237	65.4
Butler, 1999 (32)	New South Wales, Australia	1996	Correctional	10.6	328	72.6
Butler, 2005 (33)	Multiple, Australia	2004	Correctional	10.2	265	56.2
Chang, 1999 (34)	Kaohsiung, Taiwan	1994–1996	Drug treatment; correctional	1.4	247	67.2
Chetwynd, 1995 (35)	Christchurch, New Zealand	1993	Drug treatment	9.4	114	84.2
Christensen, 2000 (36)	Nyborg, Denmark	1996–1997	Correctional	3.3	140	87.1
Coppola, 1996 (37)	Cagliari and Sardinia, Italy	1992–1993	Drug treatment	6.4	137	81.0
Craine, 2004 (38)	Northwest Wales, United Kingdom	2001–2002	Drug treatment; needle exchange	5.8	153	23.0
Crofts, 1994 (39)	Unspecified, Australia	1990–1991	Multiple	8.8	303	68.0
Denis, 2000 (40)	Unspecified, Belgium	1995–1998	Drug treatment; medical	2.9	244	78.3
Des Jarlais, 2005, study 1 (15)	New York	1990–1991	Drug treatment	8.6	69	92.8
Des Jarlais, 2005, study 2 (15)	New York	2000–2001	Drug treatment	8.8	411	62.8
Diaz, 2001, study 1 (41)	New York	1997–1998	Street locations	5.8	357	42.0
Diaz, 2001, study 2 (41)	New York	1997–1998	Street locations	6.1	200	52.0
Edlin, unpublished study	San Francisco, California	1987–2000	Street locations	5.2	969	73.0
Egeland, unpublished study	Oslo, Norway	2002	Needle exchange	11.7	327	81.0
Eicher, 2000 (42)	Churachandpur, India	1996	Street locations	4.1	191	97.9
Galeazzi, 1995 (43)	Veneto region, Italy	1992–1993	Drug treatment	8.6	227	75.0
Garfein, 1996 (9)	Baltimore, Maryland	1988–1992	Multiple	2.4	312	76.9
Garfein, 1998 (44)	Baltimore, Maryland	1994–1996	Multiple	4.5	229	37.6
Garten, 2004 (45)	Pingxiang and Binyang, China	1999–2000	Street locations	4.2	485	82.9
Girardi, 1990 (46)	Rome, Italy	1989	Drug treatment	10.5	80	67.5
Gore, 1999 (47)	Unspecified, United Kingdom	1994–1996	Correctional	9.0	536	49.0
Guadagnino, 1995 (48)	Catanzaro, Italy	1991	Drug treatment	8.8	146	68.0
Gyarmathy, 2002 (49)	New York	1996–2001	Street locations	9.7	146	58.2
Hahn, 2001 (50)	San Francisco, California	1997–1999	Street locations; community organizations	6.0	308	45.0
Haley, 2001 (51)	Dallas, Texas	1991–1992	Medical	3.5	40	37.5
Harder, 2004 (52)	Freiburg, Germany	1997–1998	Drug treatment	5.4	91	75.8
Hernandez-Aguado, 2001 (53)	Multiple, Spain	1990–1996	Public health clinic	6.9	3,238	85.0
Hope, 2001 (54)	Unspecified, England and Wales	1997–1998	Drug treatment; street locations	8.3	2,943	30.4
Judd, 2005, study 1 (55)	London, United Kingdom	2001–2002	Multiple	5.4	354	34.5
Judd, 2005, study 2 (55)	Glasgow, United Kingdom	2001–2002	Multiple	4.9	366	57.0
Kemp, 1998 (56)	Unspecified, New Zealand	1994	Drug treatment; community	10.2	241	64.0
Kuo, 2006, study 1 (57)	Lahore, Pakistan	2003	Drug treatment	6.3	255	92.9

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Location	Study Period	Recruitment Setting	Time at Risk, years[a]	No. Tested	HCV Prevalence, %
Kuo, 2006, study 2 (57)	Quetta, Pakistan	2003	Drug treatment	4.6	96	75.0
Lamden, 1998 (58)	Liverpool, United Kingdom	1992–1996	Drug treatment; medical	7.3	530	68.0
Lamothe, 1997 (59)	Montreal, Canada	1992	Drug treatment; street locations	9.5	281	70.1
Luksamijarulkul, 1996 (60)	Bangkok, Thailand	1992	Medical	6.7	150	95.3
MacDonald, 2000, study 1 (61)	Multiple, Australia	1995	Needle exchange	10.2	979	63.0
MacDonald, 2000, study 2 (61)	Multiple, Australia	1996	Needle exchange	9.3	1,463	51.0
MacDonald, 2000, study 3 (61)	Multiple, Australia	1997	Needle exchange	9.0	1,699	50.0
Maher, 2004 (62)	Sydney, Australia	1999–2002	Multiple	5.1	377	36.6
Malliori, 1998 (63)	Athens and Patra, Greece	1994–1995	Correctional	11.7	365	80.6
Mathei, 2005 (64)	Antwerp and Limburg, Belgium	1999–2000	Drug treatment	7.7	225	79.1
Mathei, 2006 (65)	Multiple, Belgium	1995; 1999–2000	Drug treatment	0.7	421	77.2
Miller, 2002 (66)	Vancouver, Canada	1996	Street locations	4.1	234	46.0
Patti, 1993 (67)	Rome, Italy	1990–1991	Drug treatment	8.3	645	63.4
Plasschaert, 2005 (68)	Multiple, Belgium	2004–2005	Drug treatment	9.8	569	50.3
Quaglio, 2003 (69)	Veneto region, Italy	2001	Drug treatment; public health center	12.8	965	81.6
Reyes, 2006 (70)	San Juan, Puerto Rico	Unspecified	Street locations	10.3	372	89.0
Rhodes, 2005 (71)	Togliatti, Russia	2001	Street locations	7.2	411	86.7
Rhodes, 2006, study 1 (72)	Moscow, Russia	2003	Street locations	8.0	434	68.2
Rhodes, 2006, study 2 (72)	Volograd, Russia	2003	Street locations	5.9	507	69.6
Rhodes, 2006, study 3 (72)	Barnaul, Russia	2003	Street locations	6.7	491	54.0
Samuel, 2005 (73)	Albuquerque, New Mexico	1998	Street locations	13.1	445	86.7
Shirin, 2000 (74)	Dhaka, Bangladesh	1996–1997	Drug treatment	3.7	129	24.8
Smyth, 1998 (75)	Dublin, Ireland	1992–1997	Drug treatment	2.4	733	61.8
Stark, 1997 (76)	Berlin, Germany	1993–1994	Drug treatment/ storefront	9.7	575	84.0
Taylor, 2000 (77)	Glasgow, Scotland	1990–1996	Multiple	7.6	1,949	61.0
Thorpe, 2000 (78)	Chicago, Illinois	1997–1999	Street locations	2.9	698	27.0
Turci, 2006 (79)	Unspecified, Italy	1986–2004	Medical	23.3	13	84.6
van Beek, 1994 (80)	Sydney, Australia	1991–1992	Medical	6.8	201	59.0
van de Laar, 2005, study 1 (81)	Amsterdam, the Netherlands	1985–1989	Multiple	6.2	189	90.5
van de Laar, 2005, study 2 (81)	Amsterdam, the Netherlands	2000–2004	Drug treatment; street locations	5.1	61	44.3
Weild, 2000 (82)	Unspecified, United Kingdom	1997–1998	Correctional	10.0	659	30.3
Wylie, 2006 (83)	Winnipeg, Canada	2003–2004	Medical; street locations	14.7	365	54.2
Zeldis, 1992 (84)	Sacramento, California	1987–1989	Drug treatment	10.7	585	72.0
Zocratto, 2006 (85)	Multiple, Brazil	1998	Needle exchange	11.3	272	53.0

Abbreviation: HCV, hepatitis C virus.

[a] Refers to the study mean of the time-at-risk category interval midpoint weighted by the number of participants included in the analysis from each time-at-risk category.

Table 2. Relation Between Time at Risk (Number of Years Since Onset of Drug Injection) and HCV Prevalence in Injection Drug Users in 72 Studies and 293 Categories of Time at Risk, HCV Synthesis Project, 1989–2006

Parameter	Estimate	SE	95% CI	
			Lower Bound	Upper Bound
Intercept	−0.82	0.17	−1.16	−0.47
Time at risk**	0.18	0.01	0.16	0.20
Centered quadratic time at risk**	−0.20	0.02	−0.23	−0.16
Recruitment before 1995**	0.72	0.22	0.28	1.16
Developing/transitional country*	1.10	0.38	0.35	1.84

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; SE, standard error.

* $P < 0.05$; ** $P < 0.01$; type III tests of fixed effects as estimated by generalized mixed-effects meta-regression.

countries, mean fitted HCV prevalence was higher in earlier studies, for example, 52.04% (95% CI: 36.38, 67.30) at 2 years of injection in studies carried out in 1985–1995 versus 37.32% (95% CI: 29.15, 46.28) in later studies. Fitted values for 1985–1995 data from developing/transitional countries are not shown in this paper because only 1 such study was represented in the data.

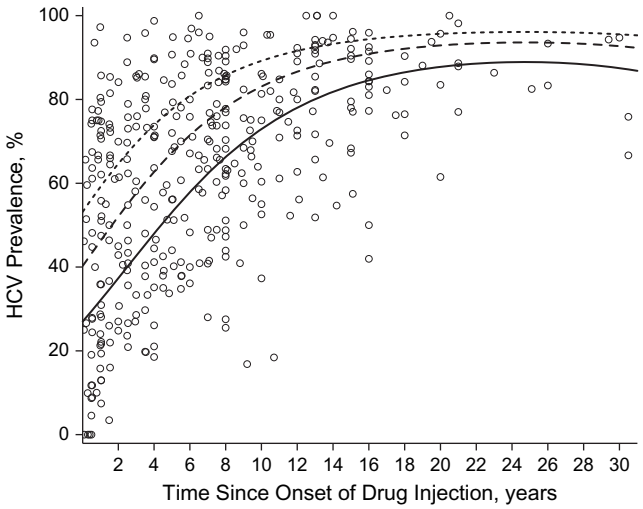

Figure 1. Hepatitis C virus (HCV) prevalence in relation to time at risk (number of years since onset of drug injection), with fitted regression lines (72 studies and 293 categories of time at risk), HCV Synthesis Project, 1989–2006. Data points (circles): reported HCV prevalence for midpoints of the time-at-risk categories; solid line: model-predicted prevalence in relation to time since onset of drug injecting for studies in developed countries after 1995; dashed line: predicted prevalence for developed countries before 1995; dotted line: predicted prevalence for developing/transitional countries. Initial HCV prevalence cannot be interpreted as prevalence at onset of drug injecting because, according to the definition of the HCV Synthesis Project sample, from which the study data were drawn, there were no subjects for whom time at risk = 0.

HCV incidence in relation to time at risk

Ten studies (3, 4, 45, 86–91; B. R. Edlin, unpublished study) reported HCV seroconversion rates in relation to categories of time since onset of drug injection (Table 4; $n = 29$ categories). Median time at risk across categories was 5.29 years (minimum: 2.37; maximum: 9.34; interquartile range: 4.06, 6.52), and median cumulative HCV incidence was 20.69% (minimum: 8.22; maximum: 67.0; interquartile range: 11.57, 29.81).

The final model of HCV incidence indicated a statistically significant linear effect of time at risk (parameter estimate = −0.05 (standard error, 0.02), $P < 0.05$, type III test of fixed effect). The small sample size limited our ability to assess other covariates. Because these studies were primarily recent and based in the United States, study time and place could not be examined as covariates in the models. Addition of the squared time-at-risk variable or the time-at-risk interval-width variable did not improve model fit. The test for heterogeneity using the random-effect variance parameter estimate was significant ($P < 0.01$). The mean fitted value for cumulative HCV incidence after 1 year at risk was 27.63% (95% CI: 16.92, 41.70).

DISCUSSION

Previous studies have noted extremely high HCV incidence and prevalence in IDUs sampled throughout the world, particularly in the early years following onset of drug injection. This quantitative meta-analysis contributes several new insights into the relation between time since onset of drug injection and HCV infection. First, the linear and quadratic effects of this relation were quantified in our models, with the meta-analysis providing a sample of sufficient size to test multivariable associations in prevalence studies. We also showed that calendar time and place explained a significant proportion of variability in HCV prevalence, with more rapid acquisition characterizing studies conducted in 1985–1995 and in countries where public health resources are likely to be limited. Although similar associations have been reported in individual studies (13–15), this meta-analysis is the first known to quantify them across both calendar time and place.

The results of our analysis are also consistent with those of recent papers—using different methodology—showing that date of onset of drug injection should not be used to estimate when HCV infection occurred (92). These estimates are typically used in conjunction with degree of hepatic fibrosis to gauge the rate of progression of HCV disease. Our results suggest that this method of estimating the time that HCV infection occurred is clearly misleading and will tend to estimate a much slower rate of progression. Moreover, although our analysis of incidence studies was limited by the small sample size, the mean fitted value for incidence after the first year of injecting was similar to the mean fitted values for prevalence after the first year of injecting for post-1995 studies in developed countries, and it supports our

Table 3. Mean Fitted Values[a] of HCV Prevalence in Relation to Time at Risk and Selected Covariates, HCV Synthesis Project, 1989–2006

No. of Years Since Onset of Drug Injection	Post-1995 Developed Countries		Pre-1995 Developed Countries		Post-1995 Developing/ Transitional Countries	
	%	95% CI	%	95% CI	%	95% CI
1	32.02	25.31, 39.58	46.19	32.02, 61.01	59.13	30.39, 82.74
2	37.32	29.15, 46.28	52.04	36.38, 67.30	64.64	34.64, 86.31
3	42.69	33.06, 52.91	57.58	40.70, 72.86	69.58	38.88, 89.16
5	53.08	40.69, 65.09	67.33	48.82, 81.66	77.64	46.92, 93.17
10	72.93	55.91, 85.12	83.08	63.80, 93.18	89.22	62.03, 97.67
15	83.30	63.51, 93.45	90.09	70.76, 97.15	93.87	69.16, 99.05

Abbreviations: CI, confidence interval; HCV, hepatitis C virus.
[a] Fitted values were calculated by using results from models of the data in the original scale of measurement.

conclusion that many IDUs remain free of HCV infection after the first year of drug injection.

Several limitations need to be acknowledged. As in any meta-analysis, we were restricted to the data as presented. Thus, it was necessary to manipulate data to permit calculation of pooled estimates, and this manipulation may have led to misclassification. For example, assignment of the HCV infection rates to the midpoint of a time-at-risk category assumed that the data were not skewed within categories. Although we included measures of the width of the intervals in our time-at-risk measure, information regarding the distribution of time at risk within intervals was not available. Both prevalence and incidence models exhibited substantial unexplained heterogeneity.

Differences in mean time since onset of drug injection across studies would principally be a consequence of sampling approach and study purpose (e.g., if a study intended to sample new injectors). We did classify studies according to recruitment method and recruitment location and examined whether these variables were confounders in the observed association. However, in most cases, there was little detail on recruitment method and location; thus, poor measurement of this confounding factor may have led to bias in the direction of the confounding. Geography may also explain differences in mean time since onset of injection (93). It is unlikely that these sources of misclassification led to systematic bias toward detecting an association but rather that they biased our associations toward the null.

In addition, recruitment crossed the 1995 cutoff in 11 studies in the sample; all of these studies were classified as having completed recruitment post-1995. Recruitment in preceding years would have included higher-prevalence samples attributed to a later period when, according to our model, HCV prevalence declined. Thus, this misclassification

Table 4. Studies of Injection Drug Users Reporting HCV Incidence in Relation to Categories of Time Since Onset of Drug Injection in 10 Studies and 29 Categories of Time at Risk, HCV Synthesis Project, 1989–2006

First Author, Year (Reference No.)	Location	Study Period	Recruitment Setting	Time at Risk, years[a]	No. Tested	No. of Seroconverters	Cumulative HCV Incidence, %
Edlin, unpublished study	San Francisco, California	1987–2001	Street locations	9.3	204	62	22.7
Garten, 2004 (45)	Pingxiang and Binyang, China	1999–2000	Street locations	4.0	112	52	53.4
Hagan, 2001 (3)	Seattle, Washington	1994–1997	Multiple	6.5	317	53	20.9
Hahn, 2002 (91)	San Francisco, California	2000–2001	Street locations	3.9	195	48	26.5
Lucidarme, 2004 (86)	Unspecified, France	1999–2000	Drug treatment	5.6	165	16	9.0
Maher, 2006 (87)	New South Wales, Australia	1999–2002	Multiple	6.0	368	68	30.6
Rezza, 1996 (88)	Naples, Italy	1991–1993	Drug treatment	5.5	106	21	34.0
Smyth, 2003 (89)	Dublin, Ireland	1992–1998	Drug treatment	2.4	100	67	66.1
Thorpe, 2002 (4)	Chicago, Illinois	1997–1999	Street locations	2.8	353	29	16.4
van Beek, 1998 (90)	Sydney, Australia	1992–1995	Primary care facility for IDUs	5.1	152	31	21.0

Abbreviations: HCV, hepatitis C virus; IDU, injection drug users.
[a] Refers to the study mean of the time-at-risk category interval midpoint weighted by the number of participants included in the analysis from each time-at-risk category.

would also have led to underestimating the calendar-time effect.

Our analysis of effect modification may have been affected by an imperfect correlation between the availability of HIV/HCV prevention programs and our a priori classification of calendar time and place. Indeed, we cannot rule out the possibility that other secular changes (e.g., shifts in IDU demographics, drug purity or availability, policing activities, or underlying changes caused by a maturing HIV epidemic) may have led to the observed declines in HCV prevalence. It is also possible we missed key reports in our search (although standard search methods were rigorously used), and not all important geographic areas were well represented in the data (e.g., Africa and Latin America). Clearly, there are regions of the world in which time to acquisition of HCV in injectors has not been characterized. We were not able to explain the frequently observed high prevalence and incidence among IDUs with a short time-at-risk interval (13–15). A high-risk subgroup of injectors has been hypothesized (94), but specific biologic, behavioral, or environmental factors that contribute to this high risk is the subject of future research.

We showed that more rapid onset of HCV infection in drug injectors in developing/transitional countries resembles an earlier era of the HCV epidemic in other regions. In developed countries, HCV prevalence in new injectors (<2 years) has declined from an estimated 53% in 1985–1995 to 38% in more recent years. Although consistent with the hypothesis that efforts to promote safe injection may have affected HCV transmission, the data do not lead to the interpretation that present programming will control HCV transmission in this population. Indeed, for a substantial proportion of these new injectors, the interval before acquiring HCV remains extremely brief. A heavy investment in public health resources will likely be required to make further gains in HCV prevention. However, doing so may allow more individuals to emerge from injection drug use free of HCV disease. There is also the prospect of reducing the very large reservoir of HCV infection that overlays the drug injection environment, a goal that will require sustained effort.

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