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Prognosis of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort

H.-H. Thein,[1,2] Q. Yi,[3] E. J. Heathcote[4] and M. D. Krahn[1,2,5] [1]*Toronto General Research Institute, University Health Network, Toronto;* [2]*Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto, Toronto;* [3]*National Epidemiology and Surveillance, Canadian Blood Service, Ottawa;* [4]*Toronto Western Hospital, University Health Network, University of Toronto, Toronto; and* [5]*Departments of Medicine and Health Policy, Management and Evaluation and Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada*

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SUMMARY. Accurate prognostic estimates were required to ensure the sufficiency of the $1.1 billion compensation fund established in 1998 to compensate Canadians who acquired hepatitis C virus (HCV) infection through blood transfusion between 1986 and 1990. This article reports the application of Markov modelling and epidemiological methods to estimate the prognosis of individuals who have claimed compensation. Clinical characteristics of the claimant cohort (n = 5004) were used to define the starting distribution. Annual stage-specific transition probabilities (F0 → F1, . . ., F3 → F4) were derived from the claimants, using the Markov maximum likelihood estimation method. HCV treatment efficacy was derived from the literature and practice patterns were estimated from a national survey. The estimated stage-specific transition probabilities of the cohort between F0 → F1, F1 → F2, F2 → F3 and F3 → F4 were 0.032, 0.137, 0.150 and 0.097 respectively. At 20 years after the index transfusion, approximately 10% of all living claimants (n = 3773) had cirrhosis and 0.5% developed hepatocellular carcinoma (HCC). For nonhaemophilic patients, the predicted 20-year (2030) risk of HCV-related cirrhosis was 23%, and the risk of HCC and liver-related death was 7% and 11% respectively. Haemophilic patients who are younger and are frequently co-infected with human immunodeficiency virus would have higher 20-year risks of cirrhosis (37%), HCC (12%) and liver-related death (19%). Our results indicate that rates of progression to advanced liver disease in post-transfusion cohorts may be lower than previously reported. The Canadian post-transfusion cohort offers new and relevant prognostic information for post-transfusion HCV patients in Canada and is an invaluable resource to study the natural history and resource utilization of HCV-infected individuals in future studies.

Keywords: cirrhosis, decision making, hepatitis C, Markov model, natural history, transfusion-acquired.

INTRODUCTION

Although there is a clear association between chronic hepatitis C virus (HCV) infection and progression to cirrhosis, liver failure and hepatocellular carcinoma (HCC) [1–3], considerable uncertainty remains regarding the rate of liver disease progression and the overall proportion of people who will develop these complications. Progression to cirrhosis is highly variable and dependent on several host- and virus-related and external factors that modify the rate at which fibrosis progression occurs in an individual. HCV was first identified in 1989 [4] and was subsequently established as the causative agent of more than 90% of non-A, non-B post-transfusion hepatitis [5]. Blood transfusion and blood product use were a major source of HCV infection prior to 1990, when serological screening of donated blood for HCV was first instituted [6]. Between 1986 and 1990, surrogate marker testing (i.e. alanine aminotransferase and anti-hepatitis B virus core antigen) for residual non-A, non-B hepatitis was employed to screen blood donors in the United States to reduce the risk of HCV infection in the general population [7]. However, in Canada, surrogate marker testing was not implemented in most jurisdictions [8,9]. Consequently, an estimated 10 000–16 000 Canadians

Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; PTCC, post-transfusion claimant cohort; RNA, ribonucleic acid; CI, confidence intervals; MMLE, Markov maximum likelihood estimation.

Correspondence: Murray Krahn, The Toronto General Hospital, EN14-207, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada.
E-mail: murray.krahn@theta.utoronto.ca

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became infected with HCV through blood and blood product transfusions between January 1, 1986 and July 1, 1990 [8,9].

The federal, provincial and territorial governments of Canada agreed to compensate claimants, including haemophilic patients, individuals with human immunodeficiency virus (HIV) who became co-infected with HCV and those secondarily infected individuals in the 1986 to 1990 Hepatitis C Compensation Agreement [8]. The Canadian compensation program was unique in that it linked compensation levels to stage of liver disease [10]. Hence, accurate prognostic estimates were required to ensure the sufficiency of the compensation fund over the lifetime of potential claimants.

This article reports the application of a previously validated HCV Markov model [11] and comprehensive epidemiological methods to estimate the prognosis of individuals who have claimed compensation [post-transfusion compensation claimant (PTCC) cohort] and to guide allocation of the $1.1 billion compensation fund. This study incorporates updated information regarding both the characteristics of a large Canadian PTCC cohort (e.g. HCV-related liver disease stage distribution and size of claimant cohort) and the best evidence regarding HCV outcomes (e.g. natural history prognostic data, treatment patterns and treatment intensity) relevant to this unique cohort of HCV-infected individuals.

METHODS

Data sources

The model used input data from three data sources: data directly collected from the PTCC cohort; a national survey of Canadian hepatologists determining their antiviral therapy practice; and published HCV natural history data, treatment efficacy, general population and post-transfusion mortality rates, and the effect of HIV and haemophilia on long-term prognosis.

Post-transfusion compensation claimant cohort

As part of the claims process, demographic and clinical data were collected from claimants with transfusion-related HCV infection. Demographic information included year of birth, gender, place of residence and date of death for deceased individuals; haemophilic history and/or the underlying medical condition necessitating blood transfusion; blood transfusion history (for nonhaemophilic patients only), date of first transfusion and number of transfusions; serological testing results and dates for HCV antibody and HCV ribonucleic acid (RNA) status at the time of claim being made; severity of HCV infection based on a six-level compensation scale and supporting diagnostic information. History of co-infection with HIV and HCV treatment information was also collected.

National survey of Canadian hepatologists' practice patterns

The national survey of Canadian hepatologists provided data regarding current treatment patterns in their practice. In 2002 and 2004, practice surveys were conducted among Canadian hepatologists to establish which patients were likely to receive HCV treatment [12]. We used the 2002 survey data in the model for future projections, as the sample size was larger and practice patterns had not changed by 2004. Clinicians with a specialty in hepatology were identified through the Canadian Medical Directory. Clinicians were surveyed regarding the likelihood of antiviral treatment as a function of age, co-morbidity and disease stage. Thirty-eight of 44 clinicians responded to the survey with an overall response rate of 86.4%.

Model structure

The current natural history model (Fig. 1) consists of mutually exclusive HCV health states defined by serological status (nonviraemic/viraemic), liver fibrosis stage (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis) [13–16] and clinical status (decompensated cirrhosis, HCC, death). These health states closely reflect the six-level compensation scale defined in the compensation agreement (Table 1). The model was implemented in DATA PRO [17].

Model assumptions

We assume that transition rate from F0 to F1 for a nonviraemic patient is zero and that future prognosis after F0 is

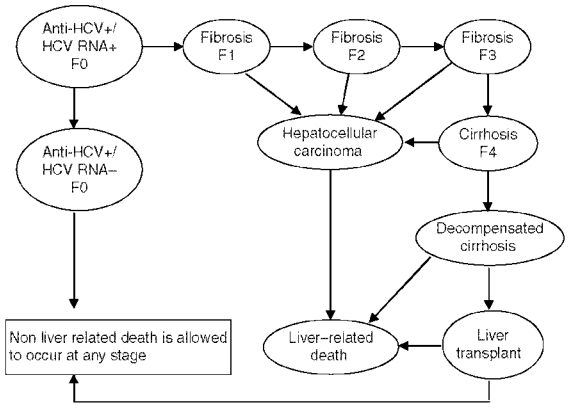

Fig. 1 Simplified schematic Markov model of natural history of hepatitis C virus infection. Each circle represents a health state for the individuals infected because of blood transfusion in Canada between 1986 and 1990. Each solid arrow represents possible transitions between health states that may occur each year. HCV, hepatitis C virus; RNA, ribonucleic acid.

Table 1 Baseline clinical data of post-transfusion compensation claimant cohort by haemophilic status, 2007

	Total	Haemophiliacs		NonHaemophiliacs		
	N = 5004	*N* = 1305		*N* = 3699		
Characteristics	*N*	*N*	%*	*N*	%*	*P*-value
Gender						
Male	3112	1157	88.7	1955	52.9	<0.0001
Female	1892	148	11.3	1744	47.1	
Survival status at 2007						
Alive	3773	904	69.3	2869	77.6	<0.0001
Deceased	1231	401	30.7	830	22.4	
Biopsy evidence						
Yes	1082	225	17.2	857	23.2	<0.0001
No	3922	1080	82.8	2842	76.8	
Level of compensation†						
Level 1	807	145	14.1	662	18.7	<0.0001
Level 2	1526	251	24.5	1275	36.1	
Level 3	1198	358	34.9	840	23.8	
Level 4	261	68	6.6	193	5.5	
Level 5	319	104	10.1	215	6.1	
Level 6	446	100	9.7	346	9.8	
Missing	447	279	–	168		
HCV-antibody test						
Positive	3395	773	93.9	2622	93.6	0.718
Negative	230	50	6.1	180	6.4	
Unknown	1379	482	–	897	–	
HCV-RNA test						
Positive	2491	609	92.8	1882	93.2	0.770
Negative	185	47	7.2	138	6.8	
Unknown	2328	649		1679		
HCV therapy						
Yes	1080	315	24.1	765	20.7	0.009
No	3924	990	75.9	2934	79.3	
HIV Positive						
Yes	536	523	41.0	13	0.4	<0.0001
No	4115	754	59.0	3361	99.6	
Missing	353	28	–	325		
Gender (among alive)						
Male	2181	770	85.2	1411	49.2	<0.0001
Female	1592	134	14.8	1458	50.8	
Current Age (among alive) (mean ± SD) years	54.0 (18.2)	44.3 (13.8)	57.1 (18.4)	<0.0001		
HIV Positive (among alive)						
Yes	218	210	23.8	8	0.3	<0.0001
No	3289	674	76.2	2615	99.7	
Missing	266	20	–	246	–	

*Percentages were calculated based on available observations excluding missing and unknown categories. †Level 1, HCV antibody positivity; Level 2, HCV RNA positivity; Level 3, Nonbridging fibrosis; Level 4, Bridging fibrosis; Level 5, Cirrhosis or unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia; Level 6, Liver transplant, decompensated cirrhosis, hepatocellular carcinoma, B-cell lymphoma, symptomatic mixed cryoglobulinema, glomerulonephritis, renal failure.
HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid; SD, standard deviation.

determined by fibrosis stage alone. We also assume that regression from a later to an earlier stage (e.g. F1–F0, F3–F2) does not occur, although there is recent evidence to suggest that this may occur in some individuals with successful treatment or may occur because of sampling error [18–21]. In addition, the disease progresses one stage at a time. Thus, skipping stages within a single cycle (1 year) is not allowed in the model (e.g. F1 directly to F3). We further assume that there is no excess mortality attributable to transfusion based on the survival experience of the cohort reported by Vamvakas [22,23]. According to Vamvakas, the mortality rate of patients after 10 years of receiving a blood transfusion would be the same as that of the general population. In the model, there is no excess HCV-related mortality in individuals whose liver disease has not yet progressed to F4. The sole exception to this is HCC. Individuals are allowed to develop and die from HCC at earlier stages. The probability of progressing to HCC for a nonviraemic person is zero.

The effects of covariates such as gender, age, and HCV treatment on disease progression are incorporated within the model structure. Disease progression rates are very low or zero in those who respond to treatment [24,25]. We employed a very conservative assumption that treatment-induced sustained response decreases the progression rate of liver fibrosis to 10% of that in untreated patients. We also assume that haemophilic status does not affect HCV disease progression [26–28].

Model input parameters

Demographic and clinical data

Data from the PTCC were used to estimate age, gender and the proportion of individuals with haemophilia and HIV infection. In addition, it was used to derive the starting distribution of cases across fibrosis stages (F0–F4) and clinical states (e.g. decompensated cirrhosis, post-transplant) for the cohort simulation, and to estimate stage-specific transition probabilities (F0 → F1, . . ., F3 → F4) (see below). Determining the true fibrosis stage distribution among claimants posed challenges, as only 20% of cases included had liver biopsy data (Tables 1 and 2). To address this problem, we used a propensity score approach [29,30] to estimate the true stage distribution of the cohort for 2007. The propensity score approach is a means of adjusting for differences between two groups (i.e. patients with and without liver biopsy) in multiple covariates (i.e. age, gender, HCV treatment, haemophilic status, compensation level/stage and survival status) by collapsing all covariates into a single variable, which in this case is the probability of having received a liver biopsy. Propensity score method has been used to reduce selection bias in observational studies including heart disease [30], hepatitis C [31] and prostate cancer [32] by balancing groups based on the known covariates [33,34].

Propensity score for biopsy was derived by fitting a logistic model with liver biopsy status as dependent variable and the above covariates as independent variables. Alanine aminotransferase level and platelet count were not available for inclusion in the model. Based on the propensity score (predicted probability of having a biopsy, from 0 to 1), patients were classified into three groups: ≤0.4; 0.4–0.6; and ≥0.6. In each group, stage distributions were compared between patients with and without biopsy records. The patients without biopsy but with the closest propensity score were assumed to have the same stage distribution as the patients with biopsy records. For individuals in the F1–F3 stages, those who had not been biopsied were assigned a 'true' stage distribution based on their propensity score. No adjustments were made for individuals in the F0 stage assuming that these individuals did not have liver fibrosis. We also assumed that patients in the late stages could be diagnosed using clinical information only. Thus, no further adjustments were made for these stages.

HCV natural history

We assumed that 20% of individuals who acquire HCV would clear the virus within the first 6 months of their infection [35,36]. Estimation of the subsequent annual rate of viral clearance in published studies was based on the cumulative clearance rate and the mean duration of follow up in the study. The weighted annual HCV clearance rate estimated from available 21 published studies including the PTCC cohort data (2005) was 0.020 (95% confidence intervals (CI), 0.013–0.027) (Table 3) [37].

Stage-specific transition probabilities were derived from the available PTCC cohort data, using the Markov Maximum Likelihood Method (MMLE) method. We used data from the nonhaemophilic population because the time of HCV infection for haemophilic patients was unknown. The PTCC cohort-derived annual mean (95% CI) transition probabilities are as follows: F0 → F1 0.032 (0.027–0.036); F1 → F2 0.137 (0.091–0.184); F2 → F3 0.150 (0.085–0.215); and F3 → F4 0.097 (0.040–0.154) units/year (Table 3).

Transition probabilities from F4 to decompensated cirrhosis and HCC were obtained from a meta-analysis [37,38]. Although most patients who progress to HCC have a background of cirrhosis, there are some who develop HCC with no or minimal liver fibrosis [39,40]. Transition probabilities for these and for advanced liver disease (e.g. from decompensated cirrhosis → liver transplant → liver-related death) were obtained from our previous models [11,41] (Table 3).

Competing risk

Some of the apparent acceleration of disease progression seen in circumstances that decrease the life expectancy of the underlying population may be accounted for by competing risks [42]. We obtained our baseline estimate of excess transfusion-associated mortality from the study of Vamvakas and Taswell [22]. This study reported a 10-year overall death rate of 52% among a population-based cohort

Table 2 Observed and estimated HCV disease stage distribution of living post-transfusion compensation claimant cohort by haemophilic status, August 2007

	Total living claimants (%)				Haemophiliacs (%)				Nonhaemophiliacs (%)			
	Observed			Adjusted*	Observed			Adjusted*	Observed			Adjusted*
	No Biopsy	Biopsy	Total	Total	No Biopsy	Biopsy	Total	Total	No Biopsy	Biopsy	Total	Total
Stage	*N* = 2899	*N* = 874	*N* = 3773	*N* = 3773	*N* = 723	*N* = 181	*N* = 904	*N* = 904	*N* = 2176	*N* = 693	*N* = 2869	*N* = 2869
HCV RNA− F0	29.3	0.1	22.6	22.6	20.2	0.0	16.2	16.2	32.4	0.1	24.6	24.6
HCV RNA+ F0	35.1	0.5	27.1	27.1	28.6	0.0	22.9	22.9	37.3	0.6	28.4	28.4
F1/2	28.2	46.5	32.4	24.0	41.5	30.9	39.4	22.8	23.7	50.5	30.2	24.4
F3	0.0	28.0	6.5	14.9	0.0	37.6	7.5	24.1	0.0	25.5	6.2	12.0
Cirrhosis	2.7	21.9	7.1	7.1	4.7	31.5	10.1	10.1	2.0	19.3	6.2	6.2
Decompensated Cirrhosis	2.0	1.8	1.9	1.9	3.5	0.0	2.8	2.8	1.5	2.3	1.7	1.7
HCC	0.4	0.9	0.5	0.5	0.6	0.0	0.4	0.4	0.3	1.2	0.5	0.5
Liver transplant	0.8	0.1	0.6	0.6	0.4	0.0	0.3	0.3	0.9	0.1	0.7	0.7
Other liver disease	1.6	0.2	1.3	1.3	0.6	0.0	0.4	0.4	1.9	0.3	1.5	1.5

*The propensity adjustment was made for haemophiliacs and nonhaemophiliacs separately, and overall adjustment was combined from both.
HCV, hepatitis C virus; RNA, ribonucleic acid; F, stage of liver fibrosis; HCC, hepatocellular carcinoma.

Table 3 Summary of transition probabilities used in the current HCV Markov prediction model

Type of transition probability	Baseline probability	Low	High	Source
Proportion of whole cohort with RNA− in F0, 6 months post-infection	0.20			[1,10,79–86]
Proportion of whole cohort with RNA+ in F0, 6 months post-infection	0.80			
Proportion of whole cohort with RNA− in F0, year 2007	0.226			Table 2
Transition from RNA+ to RNA− (without treatment)	0.020	0.013	0.027	[35,37]
Transition from RNA− to recover	0.002	0.001	0.004	[74]
Transition from F0 RNA− to F1	0.000	0.000	0.000	
Transition from F0 RNA+ to F1	0.032	0.027	0.036	PTCC cohort data
Transition from F1 to F2	0.137	0.091	0.184	PTCC cohort data
Transition from F2 to F3	0.150	0.085	0.215	PTCC cohort data
Transition from F3 to F4	0.097	0.040	0.154	PTCC cohort data
Transition from F4 (cirrhosis) to decompensated cirrhosis	0.055	0.040	0.092	[38,87]
Transition from decompensated cirrhosis to liver transplantation	0.033	0.017	0.049	[11]
Transition from F0 directly to HCC	0.000	0.000	0.000	[11]
Transition from F1 directly to HCC	0.0001	0.000	0.0020	[11]
Transition from F2 directly to HCC	0.0001	0.000	0.0020	[11]
Transition from F3 directly to HCC	0.001	0.0001	0.020	[11]
Transition from F4 directly to HCC	0.031	0.024	0.038	[38,87]
HCC to death	0.605	0.545	0.676	[38,87]
Liver transplantation to death (first year)	0.169	0.127	0.210	[88,89]
Liver transplantation to death (after first year)	0.034	0.024	0.043	[88,89]
Decompensated cirrhosis to HCV-related death	0.138	0.074	0.202	[90]
HCV treatment efficacy				
Proportion eligible for HCV treatment <65 years:				[10,12]
0.14 × 0.60 (95% CI, 0.52–0.68)* (F0 RNA+ to F1)	0.084	0.073	0.095	Pooled [54,60,65]
0.80 × 0.49 (95% CI, 0.42–0.56)* (F1 to F4)	0.392	0.336	0.448	Pooled [51,52,54,56–61,63–65]
0.75 × 0.25* (F4 to decompensated cirrhosis)	0.188	0.038	0.334	[10]
Excess mortality attributable to transfusion	0.520	0.323	0.575	[11,22,23]
Effect of HIV status on fibrosis progression rates (relative risk)	2.122	1.518	2.967	[67]
Excess mortality associated with HIV infection (relative risk)	6.24	5.43	7.18	[26,27,43–47]

*Product of the proportion of patients eligible for HCV treatment and the response rate. Treatment rates are based on the survey of hepatologists in 2002. The response rates are based on the 2008 literature review.
HCV, hepatitis C virus; RNA, ribonucleic acid; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis; HCC, hepatocellular carcinoma; CI, confidence intervals.

of 802 individuals transfused in Olmsted County, Minnesota, in 1981.

We also used our pooled mortality relative risk of 6.24 [26,27,43–47] to adjust upward the risk of non-HCV-related death in HIV/HCV co-infected patients (Table 3).

HCV treatment efficacy and treatment rate

Hepatitis C virus treatment-induced sustained viral clearance has been shown to halt fibrosis progression or may lead to fibrosis regression [21,48–50]. Estimates of treatment efficacy were derived from a meta-analysis of 15 randomized controlled trials [51–65] evaluating pegylated interferon and ribavirin combination therapy in treatment naïve HCV-infected individuals. Based on these 15 studies, the sustained virological response rates were as follows: for F0–F1 (n = 3 studies), 60%; and for F1–F4 (n = 14 studies), 49% (Table 3). We did not consider genotype-specific treatment response as the PTCC cohort data lack information about genotype.

We estimated the proportion of post-transfusion recipients who had been treated. Based on the 2002 Canadian hepatologists' practice patterns survey data [10,12], the median

treatment rate for patients with and without liver fibrosis is 80% and 14% respectively. In our survey, patients with decompensated cirrhosis were not offered treatment.

Covariates

Studies have shown that HIV/HCV co-infection may accelerate progression of HCV-related liver disease [27,45,47,66]. We took into account the fact that prognostic studies often do not report HIV status. However, for haemophilic patients, HIV status usually is reported. Although HIV testing information is not available in nonhaemophilic patients, we assumed that HIV positivity was more common in haemophilic patients. In our model for haemophilic patients, therefore, we incorporated the effect of HIV status by assuming that fibrosis transition rates between F0 and F4 were increased, on average by a factor of 2.12 among the co-infected individuals [67]. We obtained these data from our recent meta-analysis of 27 reports of HCV natural history studies involving 7666 individuals with HCV mono-infection (n = 4970) and HIV/HCV co-infection (n = 2636).

Analysis

For the baseline analyses, observed age, gender, age at first blood transfusion and distributions of compensation level in the PTCC cohort were used. Based on the results from HCV testing, liver biopsy data and reported compensation level, we grouped claimants into five fibrosis stages from F0 to F4. With the starting fibrosis stage, age and gender distributions in 2007, in conjunction with the estimated stage-specific transition probabilities, we predicted prognosis of the individuals using a Markov state-transition model. Cumulative proportions of individuals entering each health state in the predicted year were tabulated using the baseline estimates for each parameter.

Model calibration

Our model was calibrated using data from nonhaemophilic patients who have data on the dates of the first blood transfusion. We allowed baseline natural history parameters to vary over plausible ranges. We identified unique sets of parameter values that achieved close fit to the observed data and proceeded with the long-term prediction using a sample of good-fitting parameter sets.

Sensitivity analysis

The effects of overall uncertainty in our prognostic model were explored using second order Monte Carlo simulation. This includes variables such as treatment efficacy, HIV status and transition probabilities. In this approach, probability estimates for the model are represented by probability distributions rather than by fixed point estimates. Random variables were generated from beta distribution (transition from F0 to F1, . . . , F3 to F4), from triangular distribution (transition from fibrosis stages to HCC), from binary distribution for individual characteristics (gender, treatment, treatment response) and from imported tables (age, mortality). The 'baseline' value was assumed to represent the mean of the distribution. For each randomly sampled set of transition probabilities, 50 000 repeated patients with different age, gender, or treatment were simulated. Overall, 500 sets of transition rates were sampled with 10 000 simulations per set. From the model outcomes, we calculated standard deviation and constructed 95% CI of predicted rates.

RESULTS

Characteristics of the post-transfusion compensation claimant cohort

A total of 5004 post-transfusion patients with valid claims for compensation as of August 2007 were included in this study. Overall, the majority of the claimants were HCV antibody/HCV RNA positive (93%), males (62%), and were compensated at Level 3 or below (78%). Males were more likely to be in a higher compensation category compared with females (Level 3+, 52% *vs* 44%). More than one-fifth (22%) had received prior HCV therapy (Table 1). Over a quarter of claimants (26%) were haemophiliacs, of which 69% were alive. Haemophilic patients were significantly younger (44 *vs* 57 years, $P < 0.0001$), were more likely to be males (89% *vs* 53%, $P < 0.0001$) and had a higher rate of co-infection with HIV (41% *vs* 0.4%, $P < 0.0001$) compared with nonhaemophiliacs. The mean ± SD age at the time of first blood transfusion and duration of follow up among the nonhaemophilic patients was 42 ± 18 years and 19 ± 6 years, respectively. The median year of transfusion was 1986.

Among the 3773 living claimants, only 23% had received a liver biopsy. The observed-adjusted starting distribution of disease severity based on the propensity score among the living claimants were: 50% F0, 24% F1/2, 15% F3, 7% cirrhosis, 2% decompensated cirrhosis, 0.5% HCC and 0.6% who had received a liver transplant (Table 2). The proportion of patients in F4 stage was much higher in individuals who had a liver biopsy than those who did not have a liver biopsy (22% *vs* 3%).

Predicted long-term hepatitis C prognosis

Table 4 shows the cumulative proportion of HCV outcomes among PTCC cohort. At 20 years (2007) after the index transfusion, an estimated 10% of all living patients had cirrhosis, and 0.5% had developed HCC. It was also estimated that 9% of nonhaemophilic patients alive in 2007 had cirrhosis, and that 29% of patients will ultimately develop cirrhosis and 17% will ultimately die of liver disease. Haemophilic patients who are younger and are frequently

Table 4 Cumulative proportion of hepatitis C outcomes, 2007–2060

	2007	2010	2020	2030	2040	2050	2060
All living claimants							
Cirrhosis	9.8	11.8	20.3	26.5	30.2	32.2	33.0
HCC	0.5	2.9	5.9	8.0	9.2	9.9	10.0
Liver transplant	0.6	0.7	1.2	1.7	2.1	2.3	2.4
Nonliver related death	–	4.1	22.5	38.8	53.2	65.6	73.4
Liver-related death	–	1.2	6.9	12.4	16.7	19.1	20.2
All cause death	–	5.4	29.5	51.2	69.8	84.6	93.7
Haemophilic patients							
Cirrhosis	13.2	16.6	28.9	36.8	41.5	44.1	45.4
HCC	0.4	4.3	8.6	11.7	13.5	14.4	14.6
Liver transplant	0.3	0.5	1.4	2.2	2.8	3.1	3.2
Non-liver-related death	–	2.4	13.5	26.0	40.0	53.2	62.8
Liver-related death	–	1.4	10.1	18.5	24.6	28.1	29.8
All cause death	–	3.8	23.6	44.5	64.6	81.3	92.6
Nonhaemophilic patients							
Cirrhosis	8.7	10.3	17.6	23.2	26.7	28.4	29.1
HCC	0.5	2.5	5.0	6.8	7.9	8.5	8.6
Liver transplant	0.7	0.8	1.2	1.6	1.9	2.1	2.2
Non-liver-related death	–	4.7	25.4	42.8	57.4	69.5	76.8
Liver-related death	–	1.2	5.9	10.5	14.2	16.2	17.2
All cause death	–	5.9	31.4	53.3	71.5	85.7	94.0

HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

co-infected with HIV would have a higher cumulative lifetime risk of cirrhosis (45%) and liver-related death (30%). The all cause mortality rate was higher in nonhaemophilic patients than in haemophilic patients in the next 10–30 years, even though the cumulative mortality would be similar by the year 2060.

Sensitivity analysis

Monte Carlo simulations (Table 5) showed that by 2030, 27% of living PTCC cohort are predicted to develop cirrhosis, with the 95% CI extending from 13% to 40%. The error in lifetime risk of HCV-related cirrhosis is approximately ±14% in absolute terms and ±43% in relative terms. Similarly, the error in lifetime risk of liver-related death is approximately ±9% in absolute terms and ±46% in relative terms. These values reflect the overall uncertainty in our prediction model.

DISCUSSION

Our study contributes to the existing literature on HCV outcomes in several ways. First, it offers the virtually complete description of a large (n = 5004) and unique clinical cohort, the Canadian 1986 1990 PTCC cohort. Second, we report updated estimates of stage-specific transition probabilities for the PTCC cohort itself using a new method (MMLE), which does not assume constant rate of

Table 5 Monte Carlo simulation describing overall uncertainty in the prediction model: Predicted cumulative rates of hepatitis C-related major events among living post-transfusion claimants at August 2007

	2010	2020	2030	2040	2050	2060
Event	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cirrhosis (%)	11.8 (8.3–15.3)	20.3 (9.5–31.1)	26.5 (13.2–39.8)	30.2 (14.4–46.0)	32.2 (16.9–47.5)	33.0 (18.8–47.2)
Hepatocellular carcinoma (%)	2.9 (2.0 3.8)	5.9 (2.2 9.6)	8.0 (3.0 13.0)	9.2 (3.7 14.7)	9.9 (4.2 15.6)	10.0 (3.0 17.0)
Liver-related death (%)	1.2 (0.6–1.8)	6.9 (3.4–10.4)	12.4 (6.8–18.0)	16.7 (10.0–23.4)	19.1 (12.3–25.9)	20.2 (11.0–29.4)

Variables including treatment efficacy, HIV status and transition probabilities were included in the second order Monte Carlo simulation.

fibrosis progression. Finally, our study offers predictions of the very long-term prognosis of a post-transfusion hepatitis C cohort based on clinical characteristics, existing practice patterns, HCV treatment efficacy and best estimates of HCV natural history data.

Our current model has unique strengths: incorporation of meaningful clinical data to estimate stage distribution, separate estimates for haemophilic patients and nonhaemophilic patients, use of patient-derived stage-specific transition probabilities, estimates of the overall model uncertainty generated by Monte Carlo simulations, the direct estimation of current practice patterns among Canadian hepatologists and the use of updated pooled treatment efficacy.

Our model estimated that 10% of the PTCC cohort had developed cirrhosis 20 years after the index transfusion, and that less than 1% had developed HCC. Furthermore, our model estimated that 33% of the cohort will ultimately develop cirrhosis, 10% will develop HCC and 20% will die of liver disease. Thus, about 20–25% of the PTCC cohort, who are currently living but do not yet have cirrhosis, are predicted to develop cirrhosis over the course of their lifetime. The current predicted estimates are higher than those in our previous model [11]. The key difference is the source of transition probabilities, where previous estimates were derived solely from a selection of published literature.

Based on the PTCC cohort-derived transition probabilities, the estimated number of years (55.5 years) required to progress from F0 to cirrhosis in our study are substantially longer than the 30 years reported by Poynard *et al.* [13]. Our PTCC cohort-derived transition probabilities are, however, higher than the estimates of a recent UK post-transfusion cohort [68]. Among PTCC patients with viraemia who had a biopsy, 22% had cirrhosis, which is lower than the outcomes among transfusion-acquired HCV-infected cohorts reported by Seeff *et al.* (35%) [69], Hamada *et al.* (31%) [70] and Tong *et al.* (51%) [71], but is higher than those observed in community-acquired hepatitis C among injecting drug users (8%) [72] and in our recent meta-analysis [73] estimates among liver clinic series (16%). The predicted liver-related mortality attributable to chronic hepatitis C at 2010 approximately 25 years after the index transfusion among our PTCC, is 1%. This estimate is lower than the outcomes among transfusion-acquired hepatitis C cases reported by Seeff *et al.* (2–4%) [69], but comparable with those observed in community-acquired hepatitis C among injecting drug users (1%) [72]. The likely explanations for these varying estimates may relate to the differences in the method of cohort recruitment, age at the initial infection/age at transfusion and the underlying chronic condition necessitating blood transfusions, which may influence disease progression.

Furthermore, our predicted lifetime cumulative risk of cirrhosis (45% *vs* 29%), HCC (15% *vs* 9%) and liver-related death (30% *vs* 17%) attributable to chronic hepatitis C were higher in haemophilic patients than nonhaemophilic patients. Haemophilic patients are more commonly co-infected with HIV, but nonhaemophilic patients are older. In the medium term, the effect of age on mortality is greater than the effect of HIV infection. Although haemophilia *per se* is not associated with a significant increase in excess mortality, when taking HIV infection into account, the modelled excess mortality for haemophilic patients was approximately twice that of the general population for the entire lifespan.

There are several potential biases and limitations in the current model. One key limitation is the lack of liver biopsy data for many members of the post-transfusion cohort. A number of fairly strong assumptions were required to derive reasonably plausible estimates of the true stage distribution. However, we believe that incorporating this assumption to estimate the 'propensity-adjusted' stage distribution is a less biased approach than using the unadjusted data, which would incorporate the implicit assumption that all patients without a liver biopsy have no liver fibrosis. Another key limitation is that the size of the full PTCC cohort remains unknown. We believe that as of August 2007, most claimants have come forward, but some uncertainty remains regarding the final size of the potential claimant cohort. Finally, we assumed that there is no regression between stages, and that progression continues at 10% of the baseline rate in treatment-induced sustained virological responders. It is possible that each of these factors can result in an upward bias (small-moderate) in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops, particularly if the estimates of treatment rates are inaccurate.

Somewhat different models have been used for HCV natural history. Compared with Bennett *et al.* [74] and Wong *et al.* [75] models, our model employed more comprehensive data and used a method (MMLE) of estimating transition probabilities for progression between fibrosis stages. Our data confirm that transition between fibrosis stages is not constant and that stage 0–1 is relatively slow, whereas transitions occur more rapidly from stages 1–4. Deuffic *et al.* [76] and Law *et al.* [77] used mathematical models, and combined modelled HCV incidence with estimates of progression rates from the literature. Salomon *et al.* [78] used a mathematical model, incorporating published data to estimate transition probabilities by randomly selecting parameters to fit population-based epidemiological data. It is reassuring that our 20-year prognostic estimates are similar to Salamon *et al.* estimates [10,37], however, the key difference in these models is the estimates of transition probabilities.

Our model predicted that approximately one in three of living PTCC cohort will ultimately develop cirrhosis and one in five will die of liver disease. Future studies will be useful in updating and revising model projections. Comparison of accepted and rejected claims will be useful in estimating the clinical and demographic characteristics of transfusion-acquired and non-transfusion-acquired HCV infection, and provide some information on the generalizability of our

model's projections to HCV infected patients as a whole. Finally, this cohort provides an invaluable resource to study the natural history and resource utilization of HCV-infected patients in future studies.

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REFERENCES

1 Seeff LB. Natural history of hepatitis C. *Hepatology* 1997; 26: 21S–28S.
2 Seeff LB. Natural history of hepatitis C. *Am J Med* 1999; 107: 10S–15S.
3 Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36: S35–S46.
4 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; 244: 359–362.
5 Tobler LH, Busch MP. History of posttransfusion hepatitis. *Clin Chem* 1997; 43: 1487–1493.
6 Kuo G, Choo QL, Alter HJ *et al.* An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science* 1989; 244: 362–364.
7 Stevens CE, Taylor PE, Pindyck J *et al.* Epidemiology of hepatitis C virus. A preliminary study in volunteer blood donors. *JAMA* 1990; 263: 49–53.
8 Comeau P. Hepatitis C compensation may be extended. *CMAJ* 2005; 172: 25.
9 Witkos M, Yi Q, Heathcote J, Kapral MK, Krahn M. Predictors of antiviral therapy in a post-transfusion cohort of hepatitis C patients. *Can J Gastroenterol* 2006; 20: 107–111.
10 Krahn M, Wang P, Yi Q, Scully L, Sherman M, Heathcote EJ. Estimating the Prognosis of Canadians Infected with the Hepatitis C Virus Through the Blood Supply, 1986–1990 – Second Revision of Prognostic Model Incorporating Data from the Compensation Claimant Cohort. Toronto: University Health Network, 2005.
11 Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. *Med Decis Making* 2004; 24: 20–29.
12 Wang P, Yi Q, Scully L, Heathcote J, Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. *Can J Gastroenterol* 2003; 17: 183–186.
13 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; 349: 825–832.
14 Poynard T, Ratziu V, Benmanov Y, Di Martino V, Bedossa P, Opolon P. Fibrosis in patients with chronic hepatitis C: detection and significance. *Semin Liver Dis* 2000; 20: 47–55.
15 The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994; 20: 15–20.
16 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; 24: 289–293.
17 TreeAge Software I. Data Pro for Health Care User's Manual. Williamstown, MA: TreeAge Software, INC., 2001.
18 Desmet VJ, Roskams T. Cirrhosis reversal: a duel between dogma and myth. *J Hepatol* 2004; 40: 860–867.
19 Friedman SL. Liver fibrosis – from bench to bedside. *J Hepatol* 2003; 38(Suppl. 1): S38–S53.
20 Friedman SL, Bansal MB. Reversal of hepatic fibrosis – fact or fantasy? *Hepatology* 2006; 43: S82–S88.
21 Poynard T, McHutchison J, Manns M *et al.* Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; 122: 1303–1313.
22 Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. *Transfusion* 1994; 34: 471–477.
23 Vamvakas EC, Moore SB. Length of survival after perioperative transfusion. *Transfus Med* 1997; 7: 115–121.
24 Poynard T, McHutchison J, Davis GL *et al.* Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000; 32: 1131–1137.
25 Sobesky R, Mathurin P, Charlotte F *et al.* Modeling the impact of interferon alfa treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. The Multivirc Group. *Gastroenterology* 1999; 116: 378–386.
26 Goedert JJ, Eyster ME, Lederman MM *et al.* End-stage liver disease in persons with hemophilia and transfusion-associated infections. *Blood* 2002; 100: 1584–1589.
27 Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. *J Infect Dis* 2001; 183: 1112–1115.
28 Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. *Br J Haematol* 1994; 87: 555–561.
29 D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; 17: 2265–2281.
30 Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. *Am J Cardiol* 2003; 92: 1447–1451.
31 Chen W, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. *J Hepatol* 2008; 49: 711–717.

32 Potosky AL, Legler J, Albertsen PC *et al.* Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 2000; 92: 1582–1592.

33 Rosenbaum PR. Discussing hidden bias in observational studies. *Ann Intern Med* 1991; 115: 901–905.

34 Rosenbaum PR, Rubin DB. Reducing Bias in Observational Studies Using Subclassification on the Propensity Score. *J Am Stat Assoc* 1984; 79: 516–524.

35 Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; 13: 34–41.

36 Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997; 26: 15S–20S.

37 Krahn M, Thein HH, Yi Q. Estimating the Prognosis of Canadians Infected with the Hepatitis C Virus Through the Blood Supply, 1986–1990 – Third Revision of Hepatitis C Prognostic Model Incorporating Data from the Compensation Claimant Cohort. Toronto: University Health Network, 2008.

38 Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology* 2005; 42: 711–723.

39 Bralet MP, Regimbeau JM, Pineau P *et al.* Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000; 32: 200–204.

40 Yatsuhashi H, Yano M. Natural history of chronic hepatitis C. *J Gastroenterol Hepatol* 2000; 15: E111–E116.

41 Krahn M, Heathcote J, Scully L, Seeff L, Wong J. Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada Between 1986 and 1990. Toronto: University Health Network, 1999.

42 Kim WR, Poterucha JJ, Benson JT, Therneau TM. The impact of competing risks on the observed rate of chronic hepatitis C progression. *Gastroenterology* 2004; 127: 749–755.

43 Arnold DM, Julian JA, Walker IR. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. *Blood* 2006; 108: 460–464.

44 Darby SC, Kan SW, Spooner RJ *et al.* The impact of HIV on mortality rates in the complete UK haemophilia population. *AIDS* 2004; 18: 525–533.

45 Darby SC, Ewart DW, Giangrande PL *et al.* Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet* 1997; 350: 1425–1431.

46 Soucie JM, Nuss R, Evatt B *et al.* Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood* 2000; 96: 437–442.

47 Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. *Gut* 2000; 47: 845–851.

48 Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003; 362: 2095–2100.

49 Shiratori Y, Imazeki F, Moriyama M *et al.* Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000; 132: 517–524.

50 Nishiguchi S, Shiomi S, Nakatani S *et al.* Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2001; 357: 196–197.

51 Carrat F, Bani-Sadr F, Pol S *et al.* Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004; 292: 2839–2848.

52 Chung RT, Andersen J, Volberding P *et al.* Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; 351: 451–459.

53 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–982.

54 Hadziyannis SJ, Sette H Jr, Morgan TR *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346–355.

55 Laguno M, Murillas J, Blanco JL *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 2004; 18: F27–F36.

56 Torriani FJ, Rodriguez-Torres M, Rockstroh JK *et al.* Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351: 438–450.

57 Alfaleh FZ, Hadad Q, Khuroo MS *et al.* Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4. *Liver Int* 2004; 24: 568–574.

58 Bosques-Padilla F, Trejo-Estrada R, Campollo-Rivas O *et al.* Peginterferon alfa-2a plus ribavirin for treating chronic hepatitis C virus infection: analysis of Mexican patients included in a multicenter international clinical trial. *Ann Hepatol* 2003; 2: 135–139.

59 Gish RG, Arora S, Rajender Reddy K *et al.* Virological response and safety outcomes in therapy-nai ve patients treated for chronic hepatitis C with taribavirin or ribavirin in combination with pegylated interferon alfa-2a: a randomized, phase 2 study. *J Hepatol* 2007; 47: 51–59.

60 Krawitt EL, Gordon SR, Grace ND *et al.* A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. *Am J Gastroenterol* 2006; 101: 1268–1273.

61 Crespo M, Sauleda S, Esteban JI *et al.* Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-coinfected patients. *J Viral Hepat* 2007; 14: 228–238.

62 Helbling B, Jochum W, Stamenic I *et al.* HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *J Viral Hepat* 2006; 13: 762–769.

63 Lee SD, Yu ML, Cheng PN *et al.* Comparison of a 6-month course peginterferon alpha-2b plus ribavirin and interferon alpha-2b plus ribavirin in treating Chinese patients with

chronic hepatitis C in Taiwan. *J Viral Hepat* 2005; 12: 283–291.

64 Mimidis K, Papadopoulos VP, Elefsiniotis I *et al.* Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. *J Gastrointestin Liver Dis* 2006; 15: 213–219.

65 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958–965.

66 Benhamou Y, Bochet M, Di Martino V *et al.* Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology* 1999; 30: 1054–1058.

67 Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008; 22: 1979–1991.

68 Sweeting MJ, De Angelis D, Neal KR *et al.* Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *J Clin Epidemiol* 2006; 59: 144–152.

69 Seeff LB, Hollinger FB, Alter HJ *et al.* Long-term mortality and morbidity of transfusion-associated non-A, non-B, and type C hepatitis: a National Heart, Lung, and Blood Institute collaborative study. *Hepatology* 2001; 33: 455–463.

70 Hamada H, Yatsuhashi H, Yano K *et al.* Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. *Cancer* 2002; 95: 331–339.

71 Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995; 332: 1463–1466.

72 Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. *Hepatology* 2000; 32: 582–587.

73 Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008; 48: 418–431.

74 Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997; 127: 855–865.

75 Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000; 90: 1562–1569.

76 Deuffic S, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. *Hepatology* 1999; 29: 1596–1601.

77 Law MG, Dore GJ, Bath N *et al.* Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *Int J Epidemiol* 2003; 32: 717–724.

78 Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol* 2002; 156: 761–773.

79 Mattsson L, Sonnerborg A, Weiland O. Outcome of acute symptomatic non-A, non-B hepatitis: a 13-year follow-up study of hepatitis C virus markers. *Liver* 1993; 13: 274–278.

80 Vogt M, Lang T, Frosner G *et al.* Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999; 341: 866–870.

81 Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *N Engl J Med* 1999; 340: 1228–1233.

82 Alter MJ, Margolis HS, Krawczynski K *et al.* The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med* 1992; 327: 1899–1905.

83 Barrera JM, Bruguera M, Ercilla MG *et al.* Persistent hepatitis C viremia after acute self-limiting posttransfusion hepatitis C. *Hepatology* 1995; 21: 639–644.

84 Thomas DL, Astemborski J, Rai RM *et al.* The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000; 284: 450–456.

85 Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999; 29: 908–914.

86 Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. *Hepatology* 2000; 32: 91–96.

87 Sweeting MJ, De Angelis D, Brant LJ, Harris HE, Mann AG, Ramsay ME. The burden of hepatitis C in England. *J Viral Hepat* 2007; 14: 570–576.

88 Charlton M, Seaberg E, Wiesner R *et al.* Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998; 28: 823–830.

89 Gane EJ, Portmann BC, Naoumov NV *et al.* Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; 334: 815–820.

90 Fattovich G, Giustina G, Degos F *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112: 463–472.