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Potential impact of vaccination on the hepatitis C virus epidemic in injection drug users

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ABSTRACT

Background: Hepatitis C virus (HCV) causes significant morbidity and mortality in injecting drug users (IDU) worldwide. HCV vaccine candidates have shown promise for reducing the infectivity of acute infection and averting chronic infection, yet the impact of varying levels of vaccine efficacy and vaccine delivery strategies on the HCV epidemic in IDU has not been explored.

Methods: We utilized extensive data on injecting behavior collected in the UFO study of young IDU in San Francisco to construct a stochastic individual-based model that reflects heterogeneous injecting risk behavior, historical HCV trends, and existing information on viral dynamics and vaccine characteristics.

Results: Our modeled HCV rate closely paralleled observed HCV incidence in San Francisco, with estimated incidence of 59% per person year (ppy) early in the epidemic, and 27% ppy after risk reduction was introduced. Chronic HCV infection, the clinically relevant state of HCV infection that leads to liver disease and hepatocellular cancer, was estimated at 22% ppy (±3%) early in the epidemic and 14% ppy (±2%) after risk reduction was introduced. We considered several scenarios, and highlight that a vaccine with 50% to 80% efficacy targeted to high-risk or sero-negative IDU at a high vaccination rate could further reduce chronic HCV incidence in IDU to 2–7% ppy 30 years after its introduction.

Conclusions: Our results underscore the importance of further efforts to develop both HCV vaccines and optimal systems of delivery to IDU populations.

Introduction

Hepatitis C virus (HCV) infects an estimated 130–170 million people worldwide, and chronic HCV infection is the leading cause of liver-related morbidity and mortality in the United States (Perz et al., 2006). HCV is primarily spread through sharing of contaminated needles and syringes used to inject drugs, as well as sharing of ancillary equipment used in drug preparation (reviewed in De et al., 2008). Approximately 65–90% of injection drug users (IDU) in the US, Western Europe, and Australia were HCV antibody positive in the 1980s and early 1990s (reviewed in Hagan et al., 2007). There is evidence that the prevalence of HCV in IDU has declined in several cities in recent years (Des et al., 2005; van de et al., 2005; Burt et al., 2007; Tseng et al., 2007; Amon et al., 2008). This trend is generally attributed to the declines in injecting risk behavior that occurred after the initiation of HIV prevention education programs, and the provision of new needles/syringes and other injecting equipment that began in the late 1980s.

However, the incidence of new HCV infection remains unacceptably high, at 25% to 40% per person year (ppy) in IDU in San Francisco (Hahn et al., 2002; Page-Shafer et al., 2007), and 9% to 38% ppy in IDU elsewhere (Hagan and Des Jarlais, 2000). New interventions are urgently needed. A recent behavioral intervention trial to reduce injecting-related HCV acquisition (Garfein et al., 2007) and transmission (Kapadia et al., 2007) had little success in reducing the HCV incidence from 18% ppy in young IDU (Garfein et al., 2007). HCV vaccines are currently in development, based on the findings in both human and chimpanzee studies that early cell-mediated immune responses (multi-specific $CD4^+$ T_H-1 and $CD8^+$ T-cell activation) and possibly humoral responses are associated with clearance of acute HCV infection (Houghton and Abrignani, 2005). While all vaccine candidates to date have failed to induce sterilizing immunity (Lauer and Chung, 2007), they have been very successful in preventing chronic infection in chimpanzees (Houghton and Abrignani, 2005)

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and in a human liver/chimeric mouse model (Law et al., 2008), and in one study led to reduced levels of viremia in chimpanzees (Folgori et al., 2006).

Simulation models of infectious disease dynamics are powerful tools for understanding disease transmission and for evaluating the potential population-level benefits of various public-health interventions. While randomized clinical trials can establish the efficacy of a vaccine, they cannot predict the effect of introducing a vaccine into a population, due to the added indirect benefit of preventing transmission by those who became immune. Dynamic models have provided insights into the level of injecting behavior change needed to have an impact on the HCV epidemic in IDU (Mather and Crofts, 1999; Pollack, 2001; Murray et al., 2003; Esposito and Rossi, 2004; Hutchinson et al., 2006; Vickerman et al., 2007). However, of the two studies that explored the potential effect of an HCV vaccine (Mather and Crofts, 1999; Krahn et al., 2005), neither examined a vaccine that decreases infectivity (rather than protects against infection in the first place) nor incorporated the risk of transmission due to sharing ancillary injecting equipment.

We constructed a mathematical model incorporating these factors to gain insight into the likely short- and long-term effects of the introduction of a vaccine under several scenarios of vaccine efficacy, vaccination rate, and targeting strategies. We based our model and parameter estimates on extensive data collected in the UFO study of young IDU (under age 30) in San Francisco from 2000 to 2001 (data collection methods described in Hahn et al., 2001; Hahn et al., 2002) and analyzed specifically for this purpose, together with published data on HCV in older IDU in San Francisco (Page-Shafer et al., 2007; Tseng et al., 2007).

Methods

Overview

We developed a three-phase model of the HCV epidemic in San Francisco, using a stochastic individual-based model with structure depicted schematically in Fig. 1 and with parameters defined in Table 1. For Phase 1 we assumed that all active IDU engaged in receptive needle sharing (RNS), consistent with historic data of high rates of RNS (Tseng et al., 2007). We constructed Phase 2 to reflect reductions in risk behavior starting in the late 1980s, by altering the model so that new IDU entered the population into one of three risk groups (low, medium, or high-risk, defined below). We estimated the HCV sero-prevalence and incidence of acute infection in Phases 1 and 2 and present these results for comparison with the historical data. We modeled Phase 3 to represent the introduction of an HCV vaccine 40 years after the beginning of Phase 2. We examined several vaccine efficacies, introduction rates, and introduction strategies. We tracked the estimated incidence of chronic HCV infections following vaccine introduction, focusing on chronic HCV because it can lead to more significant morbidity and potential mortality compared to acute HCV. Incidence was calculated on a yearly basis. The numerator for incidence of acute HCV infection was the number of new first-time infections in each year, and the denominator was the number of individuals in the population at any point in that year (including migration and emigration) who were HCV uninfected (HCV RNA negative) at the beginning of the year. The numerator for the incidence of chronic infection was the number of new infections occurring in that year that progressed to chronic infection. The denominator was the same as for acute infection.

We conducted simulations with an IDU population size of 1000 to obtain a population large enough to avoid overly large stochastic fluctuations, but small enough to be computationally feasible. We ran 100 realizations of each parameter set, using a one-day time step because a substantial proportion of IDU inject on a daily basis. In each time step, IDU were randomly selected, based on their risk group membership, to engage in RNS and/or ancillary equipment sharing (AES). Modeled HCV infections then occurred with the probability based on each person's susceptibility to infection (described below), the transmission probability associated with the HCV state of their injecting partner, and the infectivity associated with the risk activity (RNS versus AES). We examined the robustness of our conclusions to alternative values of key parameters. All simulations were conducted using MATLAB©. The procedures for the UFO study, from which many of the parameter estimates arose, were approved by the Institutional Review Board of the University of California, San Francisco.

HCV transmission probability by phase of HCV infection

The early phases of acute HCV infection are associated with very high viral replication in the absence of detectable antibody (Busch, 2001; Glynn et al., 2005; Page-Shafer et al., 2007). As with other bloodborne infections, it has been hypothesized that infectivity of an HCV carrier is highest during the early seronegative viremic period

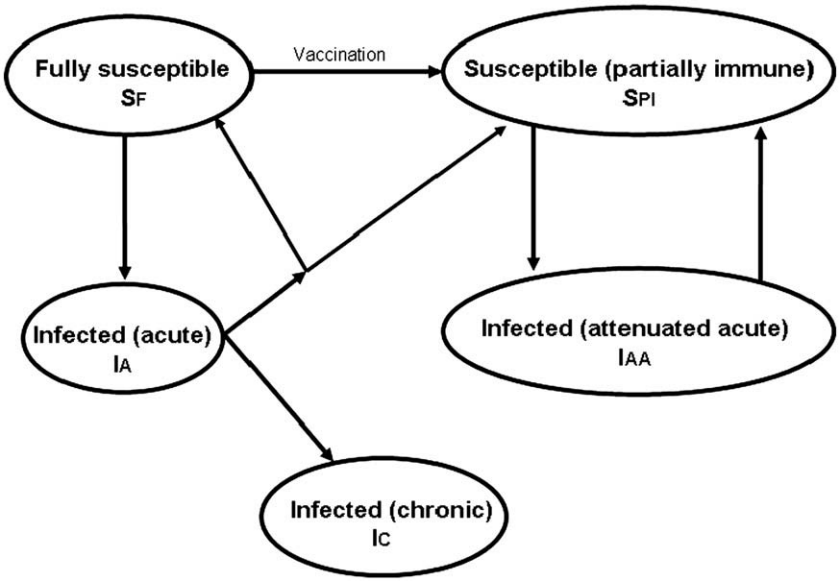

Fig. 1. HCV transmission diagram.

Table 1
Simulation parameter definitions and values

Parameter	Interpretation	Value	Source
$p_{RNS,HR}$ $p_{RNS,MR}$ $p_{RNS,lR}$	Probability of RNS per day; high, medium, low risk IDU	0.3, 0, 0	Data collected in studies of young IDU; see Table A1
$p_{AES,HR}$ $p_{AES,MR}$ $p_{AES,LR}$	Probability of AES per day; high, medium, low risk IDU	0.5, 0.5, 0.2	Data collected in studies of young IDU; see Table A1 for high and medium risk. Probability for low risk estimated from model
μ	Probability per day of leaving the IDU cohort (due to ceasing to inject, emigration, death)	0.00029	10% probability of leaving injecting per year [49]. We assumed no excess mortality due to HCV during injecting career.
θ	Probability per day of joining the IDU cohort (due to initiating injection)	0.00029	Set equal to the rate of leaving the cohort and completely dependent on random leaving such that each IDU leaving is replaced immediately by one new IDU entering state S_F.
C	Probability of spontaneous clearance of acute HCV infection (one-time event, 180 days after infection)	0.25	Micallef et al. (2006)
c_{PI}	Probability of entering partially protected susceptible state after spontaneous clearance of initial acute infection	0.50	Approximation of assumptions used by Hutchinson et al. (2006)
c_{AAs}	Probability of entering partially protected susceptible state after 180 days of attenuated acute infection	1.0	See text
$\beta_{C,j}$	HCV transmission probability where source IDU is chronically infected (I_C); $j=\{$RNS, AES$\}$	0.0073, 0.0023	Estimated by fitting observed behavioral data to observed HCV incidence (see Appendix)
$\beta_{A,j}$	HCV transmission probability where source IDU is acutely infected (I_A); $j=\{$RNS, AES$\}$	$10\beta_{C,j}$	
$\beta_{AA,j}$	HCV transmission probability where source IDU is in infected attenuated acute state, (I_{AA}); $j=\{$RNS, AES$\}$	$\beta_{C,j}$	
$\beta_{\cdot,j}$	HCV transmission probability averaged over the three states of infection (I_C, I_A, I_{AA}); $j=\{$RNS, AES$\}$	0.0098, 0.0031	

(Alter, 1994; Operskalski et al., 2003; Logvinoff et al., 2004). While empirical support for this hypothesis is lacking, two recent modeling studies incorporated increased infectivity in the acute phase (Hutchinson et al., 2006; Vickerman et al., 2007). Accordingly, we assumed that the transmission probability β associated with the acute phase of HCV (denoted by I_A in Fig. 1), was ten times that of the chronic phase (denoted by I_C).

Spontaneous HCV clearance and re-infection

Based on the median value of previous studies of spontaneous clearance of HCV infection (Micallef et al., 2006), and following earlier work (Hutchinson et al., 2006), we assumed a 25% probability for clearing infection after 180 days in the acute phase, with the remaining individuals progressing to the chronic phase.

Current data on re-infection after spontaneous clearance are conflicting, with reports of no protection against re-infection in untreated (Micallef et al., 2007) and treated (Dalgard et al., 2002; Backmund et al., 2004; Dalgard, 2005) individuals as well as reports of reduced rates of re-infection or progression to chronic infection that suggest partial immunity to re-infection after spontaneous HCV clearance (Mehta et al., 2002; Grebely et al., 2006; Currie et al., 2008). We modeled partial immunity such that those who clear initial HCV infection have a 50% probability of becoming partially immune to subsequent HCV infection, with the remainder returning to the fully susceptible state (denoted by S_F in Fig. 1). We assumed that those who are partially immune experience attenuated viremia in acute infection (denoted by I_{AA}), with complete lack of progression to chronic infection upon re-exposure to HCV, and return to the susceptible state with partial immunity (denoted by S_{PI}) after clearance of viremia. We assumed that those in state I_{AA} were 10% as infectious as those in state I_A (i.e. those acutely infected with HCV from the fully susceptible state). In our model, once an IDU gains partial immunity this protection is permanent and they can only experience attenuated infection upon re-exposure to HCV. This depiction of partial immunity is consistent with assumptions of one recent HCV modeling study (Hutchinson et al., 2006) and the observed 10-fold decrease in level of viremia in vaccinated chimpanzees (Folgori et al., 2006), but differs from another modeling study that assumed complete immunity from re-infection after spontaneous clearance (Vickerman et al., 2007).

Vaccine-induced immune protection

We modeled a prophylactic HCV vaccine to provide partial immunity (denoted by state S_{PI} in Fig. 1) to individuals in the fully susceptible state (denoted by S_F), based on recent vaccine studies (Houghton and Abrignani, 2005; Folgori et al., 2006) that reduced the risk of chronic infection in chimpanzees. We assumed that immunity due to vaccination will be epidemiologically equivalent to partial immunity achieved by spontaneous clearance, which is consistent with the vaccine trials that showed attenuated levels of viremia and high rates of clearance after HCV challenges given to vaccinated chimpanzees (Houghton and Abrignani, 2005; Folgori et al., 2006; Lauer and Chung, 2007).

Vaccine efficacy and effectiveness

Prior studies of hepatitis B virus (HBV) multi-dose vaccine adherence in IDU have shown low rates of completion (Lum et al., 2003; McGregor et al., 2003; Altice et al., 2005). We modeled HCV vaccine completion based on our experience in San Francisco, in which 25%, 50% and 25% of young IDU stopped at one, two, and three vaccine doses, respectively (Lum et al., 2003). We assumed that vaccination confers immunity to all HCV exposures to 31%, 78% and 99% of subjects 30 days after the first, second, and third doses respectively, as stated in the package insert for HBV vaccine (GlaxoSmithKline). With 25%, 50%, and 25% of those vaccinated completing 1, 2, and 3 vaccine doses respectively, the average modeled effectiveness was 71.5% of the 50%, 65%, and 80% efficacy used in the model.

IDU risk behavior groups

We defined "low-risk" IDU as those who never engage in receptive needle sharing (RNS) and rarely or never engage in AES, "medium-risk" IDU as those who engage in AES but never engage in RNS, and "high-risk" IDU as those who engage in RNS whether or not they

engage in AES. We assumed that at the beginning of the epidemic (Phase 1) all IDU were high-risk, and that following the introduction of risk reduction measures (Phase 2), 40%, 20% and 40% of new IDU entered in the high-, medium-, and low-risk categories respectively. These proportions were based on three-month frequencies of risk behavior reported in the UFO study baseline screening sample (see Appendix).

RNS and AES frequency

We utilized self reported behavioral data from baseline interviews from 2000 to 2001 from the UFO study to determine the frequency of engaging in RNS and AES (Table A1). Using data from recent risk behavior, we estimated that the rate of RNS was approximately 0.3 per day in the high-risk group, and was zero by definition in the medium and low-risk groups. We estimated that the rate of AES was approximately 0.5 per day for the high- and medium-risk groups and approximately 0.2 for the low-risk group.

Selection of injecting partners

Injecting partners with whom to engage in RNS were selected at random from the pool of all active IDU for each RNS event. AES partners were chosen with probability proportional to the relative frequency of AES in each risk group. All sharing events were selected independently from each other, therefore it was possible that an individual would engage in both RNS and AES with different partners in the same time step.

HCV transmission probability for RNS and AES

Previous dynamic models of HCV in IDU have employed a range of HCV transmission probabilities for RNS ranging from 1–3% per event, based on infection rates of health care workers who suffered accidental needle-sticks (Mather and Crofts, 1999; Murray et al., 2003; Hutchinson et al., 2006; Vickerman et al., 2007). However, the probability of transmission of HCV in the RNS setting may differ from health care exposures due to the use of different gauge needles and rinsing needles/syringes with water or bleach between uses. In addition, no estimates of the probability of transmission of HCV from AES exist. For these reasons, rather than using transmission probabilities derived from needle-stick injuries in health care settings, we estimated transmission probabilities for RNS and AES utilizing risk behaviors and HCV incidence rates observed in the UFO study (described in Appendix A), and report the estimates in Table 1.

Vaccine introduction scenarios

We simulated intervention scenarios to investigate the potential impact of different vaccine efficacies, vaccination rates and targeting strategies. Targeting strategies were: no targeting, in which IDU were selected for vaccination at random from all IDU who had not yet received HCV vaccine, regardless of their infection status; risk targeting, in which high-risk IDU who had not yet received vaccine were prioritized for vaccination over medium-risk and then low-risk IDU; and sero-targeting, in which HCV antibody negatives were prioritized to receive vaccine. We considered vaccine efficacies of 50%,

Table 2
Analysis of robustness of the estimates of the incidence of chronic HCV after the introduction of a vaccination program to several alternate parameter values

			Incidence of chronic HCV (ppy) (SD)				
			No vaccine	50% efficacy		80% efficacy	
Domain	Assumption/parameter	Parameter estimates or assumptions	Prior to vaccine program initiation	10 years after vaccine program introduction	30 years after vaccine program introduction	10 years after vaccine program introduction	30 years after vaccine program introduction
Base case		See Table 1	13.6 (1.8)	A. 10.7 (1.9)	5.3 (1.1)	9.1 (1.5)	2.6 (0.65)
				B. 8.0 (1.5)	5.3 (1.1)	4.8 (0.85)	2.4 (0.59)
				C. 6.2 (1.2)	5.1 (1.1)	3.2 (0.87)	2.3 (0.65)
Acute versus chronic infectivity	$\beta_{A,RNS}$:$\beta_{C,RNS}$ Ratio of acute versus chronic infectivity (base case is 0.073:0.0073 [10:1])	0.0098:0.0098 (1:1)	12.6 (1.4)	A. 9.8 (1.2)	5.2 (0.90)	8.5 (1.2)	2.5 (0.55)
				B. 7.5 (1.1)	4.8 (0.70)	5.3 (0.95)	2.3 (0.52)
				C. 6.0 (1.0)	4.8 (0.81)	3.3 (0.66)	2.3 (0.53)
AES infectivity (per-event)	$\beta_{C,AES}$(base case is 0.0023)	0.0006	6.3 (1.1)	A. 4.6 (0.93)	2.7 (0.75)	3.9 (0.94)	1.2 (0.45)
				B. 3.3 (0.86)	2.5 (0.76)	2.0 (0.59)	1.1 (0.39)
				C. 3.2 (0.82)	2.5 (0.73)	1.7 (0.52)	1.0 (0.41)
		0	2.9 (0.78)	A. 2.1 (0.61)	1.3 (0.45)	1.7 (0.58)	0.62 (0.29)
				B. 1.4 (0.46)	1.2 (0.42)	0.75 (0.33)	0.47 (0.25)
				C. 1.8 (0.51)	1.2 (0.42)	1.2 (0.41)	0.50 (0.27)
RNS infectivity (per-event)	$\beta_{C,RNS}$(base case is 0.0073)	0.02	14.7 (2.0)	A. 11.8 (1.6)	6.0 (1.1)	10.3 (1.6)	3.2 (0.74)
				B. 9.0 (1.4)	5.8 (1.0)	6.0 (1.2)	2.9 (0.58)
				C. 6.8 (1.2)	5.8 (1.0)	3.8 (0.76)	2.9 (0.71)
Vaccine series completion of those initiating	(Base case: 25%, 50%, and 25% receive 1, 2, and 3 doses respectively)	100% receive 3 vaccinations	14.0 (2.1)[a]	A. 9.9 (1.7)	3.9 (0.91)	8.0 (1.4)	0.96 (0.37)
				B. 6.4 (1.2)	3.6 (0.81)	3.4 (0.78)	0.92 (0.37)
				C. 4.6 (1.0)	3.6 (0.84)	1.5 (0.50)	0.86 (0.42)
Behavior change at the start of Phase 2	% enter population in low-, medium-, and high-risk groups (base case is 40, 20, 40)	0, 0, 100	21.9 (2.5)	A. 19.3 (2.4)	8.6 (1.6)	17.2 (2.2)	4.7 (0.88)
				B. 19.8 (2.4)	9.0 (1.5)	17.9 (2.1)	4.2 (0.82)
				C. 9.6 (1.6)	7.9 (1.3)	5.2 (1.2)	3.9 (0.88)
		60, 20, 20	11.4 (1.8)	A. 8.0 (1.4)	4.0 (0.82)	6.3 (1.1)	1.9 (0.55)
				B. 6.2 (1.3)	4.0 (0.86)	3.8 (0.89)	1.7 (0.47)
				C. 4.8 (0.99)	3.8 (0.79)	2.4 (0.59)	1.6 (0.54)
HCV re-infection	c_{PI} Probability of entering partially protected susceptible state after spontaneous clearance of initial acute infection (base case $c_{PI}=0.50$)	0.0 (Everyone who clears becomes fully susceptible to re-infection)	19.5 (2.5)	A. 15.0 (2.2)	6.5 (1.3)	12.1 (1.8)	3.1 (0.60)
				B. 10.6 (1.7)	6.4 (1.2)	6.6 (1.3)	2.8 (0.67)
				C. 7.7 (1.2)	6.1 (1.1)	4.2 (0.96)	2.8 (0.70)
		1.0 (Everyone who clears becomes partially immune to re-infection)	10.6 (1.7)	A. 8.6 (1.3)	4.2 (0.96)	7.0 (1.3)	2.1 (0.65)
				B. 6.1 (1.1)	4.0 (0.91)	4.0 (0.91)	2.0 (0.61)
				C. 4.8 (0.93)	4.3 (0.77)	2.8 (0.73)	2.0 (0.60)

We examined three targeting strategies, A. no targeting, B. risk targeting, and C. sero-targeting and a high vaccination rate (1% of the population per month).
[a] Differs from base case due only to stochastic fluctuation.

65% and 80%, and 0.2%, 0.6%, and 1% of the IDU population vaccinated per month.

Robustness of findings to assumptions

We conducted analyses to examine the robustness of our main findings to alternative assumptions about several key parameters, including the relative infectivity of acute versus chronic infection, transmission probabilities for RNS and AES, vaccine completion rates, behavior change at the end of Phase I, and immunity to re-infection after spontaneous clearance of HCV (Table 2). We felt that our assumptions about the proportion of IDU at high risk in Phase I and the timing of vaccine introduction after reaching equilibrium in Phase 2 would not substantially affect our conclusions about potential HCV vaccine strategies. We determined the effect of alternative assumptions on (1) HCV sero-prevalence and incidence of new infections in the pre-vaccine era (Phase 1 and Phase 2), (2) incidence of chronic HCV infections in an optimistic Phase 3 scenario in which there is high vaccine efficacy (80%) and high vaccination rate (1% of IDU per month), and (3) incidence of chronic HCV infections in a less optimistic Phase 3 scenario where there is low efficacy (50%) but strong public health efforts leading to a high vaccination rate (1% of IDU per month).

Results

HCV epidemic before vaccination

Fig. 2 depicts modeled trends in HCV sero-prevalence and incidence in Phases 1 and 2, overall and stratified by injecting risk group. In Phase 1, the overall HCV sero-prevalence rose rapidly and then leveled off at an average of 94% (standard deviation of 100 realizations, ±0.8%) 10 years after the start of the epidemic, with an average modeled incidence of acute infection of 59% ppy (±0.4%) (Fig. 2). These estimates compare well with the observed 95% HCV sero-prevalence in IDU in San Francisco in 1987 (Lorvick et al., 2001), and 65% HCV sero-prevalence in IDU injecting for one year or less in 1988–1989 in Baltimore (Garfein et al., 1996). Behavior change caused the modeled HCV sero-prevalence to decline to 79% (±1.3%) 30 years after the start of Phase 2. This estimate is between the 91% prevalence observed for older IDU (median age 45, IQR: 38–49) in San Francisco in the years 1998–2000 (Tseng et al., 2007) and 45% for younger IDU (median age 22, IQR: 20–25) in San Francisco studied from 1997 to 1999 (Hahn et al., 2001). The estimated incidence of acute HCV infection declined to 27% ppy (±4%) 30 years after the start of Phase 2, similar to observed HCV incidence of 25–40% ppy in IDU in San Francisco (Hahn et al., 2002; Page-Shafer et al., 2007). The modeled incidence of chronic HCV infection was 22% ppy (±3%) 10 years after the start of the epidemic and 14% ppy (±2%) and 30 years after the start of Phase 2.

The impact of introduction of HCV vaccine

Fig. 3 illustrates the simulated effects of the introduction of a hypothetical HCV vaccine. We made the conservative assumption that the vaccine will be ready to be introduced 40 years after the start of Phase 2, essentially around the year 2025; note that because the dynamics in Phase 2 are already near steady state 20 years earlier than this, the results would be very similar for an earlier vaccine introduction date. The best case scenario was a sero-targeted, high vaccination rate (1% per month), 80% efficacious vaccine, which caused a drop in the incidence of chronic HCV from an average of 13.5% (±2%) to 4.3% (±1%), 3.2% (±0.9%), and 2.3% (±0.6%) ppy at 5, 10, and 30 years, respectively, after the initiation of the vaccination program (Fig. 3C). The risk-targeting strategy approached a similar long-term outcome, but the rate of decrease was much slower (Fig. 3B) because many vaccine doses were wasted on previously-infected IDU. Vaccine delivered at a moderate rate (0.6% per month) resulted in a slightly higher (0.1% to 0.7% at 30 years) incidence of chronic HCV in the risk-targeting strategy compared to the sero-targeting strategy, but this difference was within the range of error of the simulations. An untargeted approach (Fig. 3A) had little impact on the predicted incidence of chronic HCV, regardless of vaccine efficacy, except when vaccine coverage is very high (1% per month). The topmost curves in Figs. 3A–C additionally highlight that low vaccine coverage is unlikely to have substantial impact on the estimated incidence of chronic HCV, regardless of vaccine efficacy. Similar qualitative effects were seen on the prevalence of chronic HCV infection (Appendix, Fig. A1), though the decrease is more gradual. The prevalence of chronic HCV 60 years after the introduction of vaccine ranged from 20% to 35% for a risk-targeted or sero-targeted vaccine strategy with very high vaccine coverage (1% per month) and ranged from 29% to 44% for the same strategies with moderate coverage (0.6% per month).

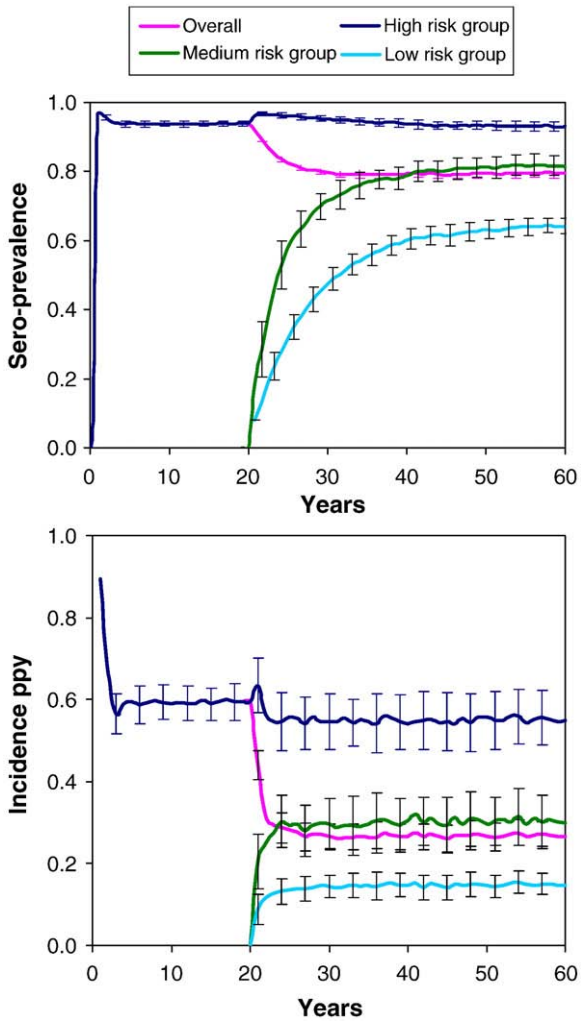

Fig. 2. HCV sero-prevalence and incidence of acute infection for Phases 1 and 2, overall and by risk group. Behavior change is modeled to begin 20 years after the start of the epidemic. Lines show the average over 100 realizations of the model, and error bars delineate one standard deviation in either direction.

Robustness to alternative parameter estimates

With few exceptions, the dynamics of Phase 1 and Phase 2 HCV sero-prevalence and incidence of acute infection were very robust to alternative values of key parameters (Figs. 4 and 5). A striking exception was the dramatic impact of reducing the transmission

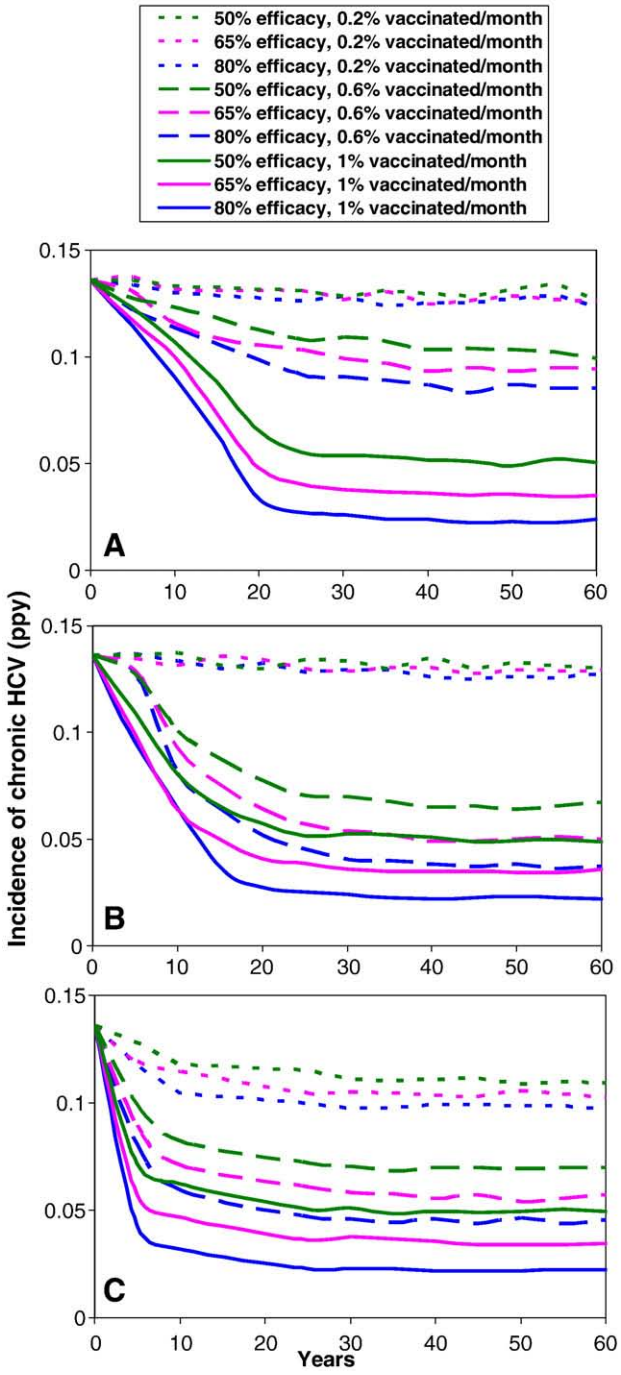

Fig. 3. Incidence of chronic HCV infection (ppy) after the introduction of a hypothetical HCV vaccine, by targeting strategy: (A) no targeting, (B) risk targeting, and (C) sero-targeting, efficacy, and vaccination rate over time. Figures show the mean of 100 realizations. Standard deviations 30 years after vaccine introduction range from 0.006 (for lower incidence) to 0.019 (for higher incidence).

probability of AES: the estimated incidence of acute HCV infection 30 years after the start of Phase 2 fell from 27% (±4%) ppy in the base case to 10% (±2%) ppy and 4% (±1%) ppy when we reduced the transmission probability of AES to 25% of the value used in the base model and to zero, respectively. Also, when the levels of infectivity of chronic and acute infection were set equal, it took longer to reach equilibrium in Phase 1, but the equilibrium values were similar to the base case parameter estimates. When we assumed greater behavior change in Phase 2, the estimated Phase 2 equilibrium sero-prevalence and incidence decreased from the base case, but not substantially. The assumptions about protective immunity after spontaneous clearance of HCV had minimal effect on sero-prevalence (Fig. 4C) and acute incidence (Fig. 5C) because these measures detect first time infections and not re-infection. There was, however, an effect on the estimated incidence of chronic HCV infection in Phases 1 and 2, with incidence of chronic infection reduced if we assume that all persons who spontaneously clear HCV gain partial protective immunity to future infection (15.7% ± 2.2% ppy 10 years after the start of the epidemic and 10.5% ± 1.5% 30 years after the start of Phase 2) and higher if we assume full susceptibility to re-infection after spontaneous clearance of infection (38.5% ± 3.9% ppy 10 years after the start of the epidemic, and 19.7% ± 2.5% ppy 30 years after the start of Phase 2, data not shown).

The qualitative results of the vaccination scenarios were robust to alternative parameter estimates, in that the sero-targeting strategy always provided the most rapid reduction of chronic incidence and high vaccine coverage rates were essential for significant declines in HCV (Table 2). Our results did not differ markedly when we assumed that 100% of vaccinees complete the three-dose vaccine series, presumably because in the base case most complete two doses which yield significant protection. We note that the incidence of chronic HCV infection was substantially reduced after the introduction of a vaccination program when we assumed no reductions in risk behavior in Phase 2, which is of relevance to areas where other programs designed to reduce bloodborne infections are not being implemented.

Conclusions

Our investigations suggest that the introduction of an HCV vaccine to an IDU population can have substantial impact on the incidence of chronic HCV, and the effect of such a program will be optimized through targeting strategies and high vaccination rates. However, we found that an untargeted vaccination strategy (as might be considered to maximize vaccination coverage) will be effective in reducing population incidence of chronic HCV only at very high rates of vaccination, and such an approach will take longer to reduce chronic HCV compared to targeted approaches. Though even the most aggressive vaccine scenario still leaves about 20% HCV prevalence of chronic infection after several years, such vaccination can bring the system to a state where other interventions may drive HCV to extinction.

We designed our model to reflect both our direct experience with IDU populations in San Francisco and the reports of researchers elsewhere. Crucial model parameters were estimated by analysis of extensive data we have collected in IDU, and we investigated the robustness of our results to a range of values for those biological and behavioral parameters for which there is the most uncertainty. With a few exceptions, our results were robust to changes in most of the parameter values. There were no substantial changes in epidemic dynamics under alternative assumptions regarding vaccine series completion, behavior change, infectivity of RNS, and immunity to re-infection after spontaneous clearance. Rather than using transmission probabilities derived from infection rates of health care workers sustaining occupationally-acquired needle-sticks, we estimated the transmission probability for RNS based on rates of infection and frequency of RNS in the UFO study. Our estimate, when averaged over the acute and chronic phase of HCV infection, was 0.98%, only slightly lower than the range (1–3%) used in other models of HCV in IDU (Mather and Crofts, 1999; Murray et al., 2003; Hutchinson et al., 2006; Vickerman et al., 2007). Our estimates of Phase 1 and Phase 2 HCV sero-prevalence and incidence were highly sensitive to the assumed per-event transmission probability of AES: this arose because low- and medium-risk IDU do not practice RNS (by definition), so AES is the only route by which they can be infected. When we reduced the transmission probability of

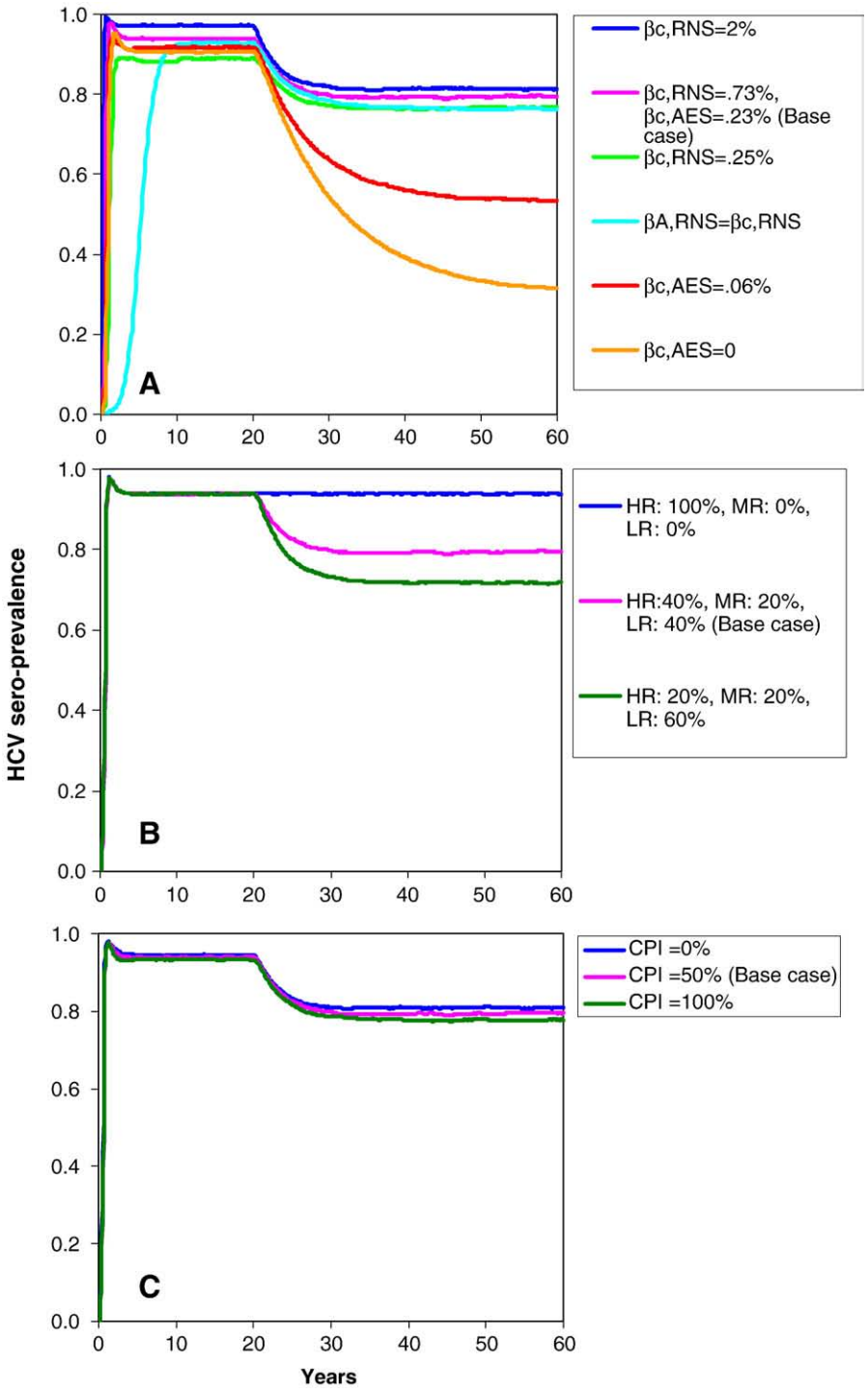

Fig. 4. HCV sero-prevalence in Phases 1 and 2 of the HCV epidemic under alternative parameter values for (A) the infectivity of receptive needle sharing (RNS), ancillary equipment sharing (AES), acute HCV, and chronic HCV; (B) the behavior of IDU entering the population at the start of Phase 2; and (C) immunity to re-infection after spontaneous clearance of HCV. Parameters are defined in Table 1.

AES in our model, estimates of Phase 2 HCV incidence fell below the range of published values for IDU. We feel that this reinforces the evidence that AES is a significant factor in the HCV epidemic in IDU (Mathei et al., 2006), especially in populations such as San Francisco in which AES is the only risk behavior for a substantial fraction of the IDU. This finding suggests further emphasis should be placed on interventions to reduce the rate of sharing ancillary injecting equipment. However, we do caution that it is possible that RNS is under-reported relative to AES, thereby causing us to overstate the importance of AES. In any case, other studies have reported that AES is quite common (Thiede et al., 2007) and is on the rise (Burt et al., 2007). Because our study is the first to estimate the per-event transmission probability of AES we suggest that further estimates of this quantity be pursued.

For simplicity, we modeled constant risk behavior for each IDU over their injecting career, rather than allowing for within-person variability, and introduced behavior change at the population level rather than modeling within-person changes. This assumption may

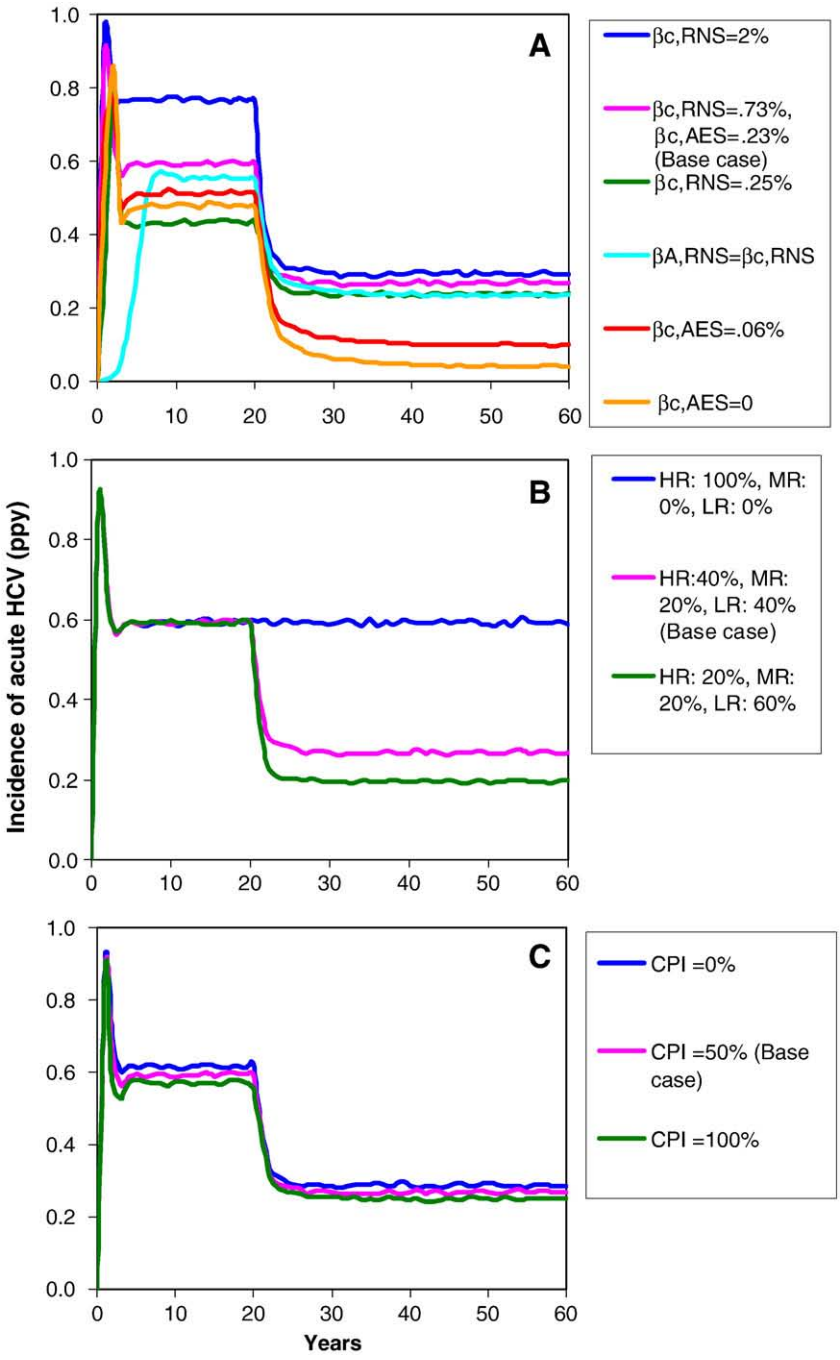

Fig. 5. Incidence of acute HCV infection in Phases 1 and 2 when varying parameters related to (A) the infectivity of receptive needle sharing (RNS), ancillary equipment sharing (AES), acute HCV, and chronic HCV; (B) behavior of IDU entering the population at the start of Phase 2; and (C) immunity to re-infection after spontaneous clearance of HCV. Parameters are defined in Table 1.

have delayed the dynamical impact of reduced risk behavior at the outset of Phase 2, but will not affect average long-term dynamics. Immigration of HCV-positive individuals was not incorporated into our model, consistent with our finding that HCV prevalence was higher in young IDU who had lived in San Francisco for a longer period (Hahn et al., 2001). This assumption would not qualitatively influence our results, since the infection is endemic in the population and has a negligible chance of extinction. We did not consider sexual transmission of HCV due to the low risk of transmission by this route relative to injecting (Hahn, 2007).

We considered a network-based model to reflect non-randomness in choice of injecting partners, as have been constructed in models of HIV transmission in IDU (Kretzschmar and Wiessing, 1998). However, our data indicated that partner turnover is likely to be quite high because the IDU we surveyed reported large number of partners for buying and presumably sharing drugs (Table A1). We decided not to pursue a network approach because as the number of partners and the rate of partner turnover increases relative to the rate of disease transmission, network models may approach random mixing models (Volz and Meyers, 2007). Further data on the structure of IDU networks, such as degree distribution, partnership duration, mixing patterns by age or years injecting, and clustering, are needed to determine whether a network-based model will lead to significantly different results. We suggest that further studies also consider the implications of differential injecting risk by sex or mixing patterns based on age.

Our analysis extends previous work in two important ways. First, we estimated the overall effects of vaccination on an IDU population and compared several strategies for vaccine delivery. We used data-based estimates of vaccine series completion and risk behavior in this population. Second, our models were the first to include the likely substantial effect of ancillary equipment sharing on HCV transmission. Our robustness analyses indicated that these behaviors may account for a large number of HCV infections, particularly in lower-risk groups, and should be considered in future prevention programs and epidemiological and modeling studies.

These results carry significant messages for public health planning. There is clearly a need to reduce the incidence of HCV in IDU, and previous work showed that very large reductions in risk behavior are needed to have a substantial impact on HCV prevalence (Vickerman et al., 2007). Our findings are encouraging because they illustrate that a vaccine with efficacy even as low as 50% can substantially reduce the incidence of chronic HCV in an IDU population given a high rate of delivery, although further reductions in risk behavior would also be needed to eradicate HCV in IDU. However, history has shown that vaccinating IDU is not an easy task. Recent studies reported that only 3–22% of IDU had been vaccinated against HBV (Campbell et al., 2007; Lum et al., 2008), although immediate vaccination, without waiting for serologic results, resulted in higher rates (Campbell et al., 2007). The latter observation, combined with our finding that sero-targeted vaccine strategies are significantly more effective, emphasizes that rapid HCV testing such as a recently developed antibody test (Desbois et al., 2008) may be a crucial tool in reducing the public health burden of HCV in IDU populations. Our broader results underscore the importance of further research in HCV vaccine development and methods of vaccine delivery.

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Conflict of interest

The authors do not have commercial or other associations that might pose a conflict of interest.

Author contributions

JH wrote the first draft of the manuscript. All authors contributed to conception and design of the study, critically edited the manuscript, and approved the final draft. DW and JD conducted the model coding. KPS and JH collected and analyzed the data in the young IDU.

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Appendix A

Methods for estimation of per-event transmission probabilities

We sought to estimate three unknown quantities: (1) the per-event transmission probability due to RNS in the acute phase (denoted $\beta_{A,RNS}$), which was set equal to 10 times the probabilities in the chronic and attenuated acute phases (denoted $\beta_{C,RNS}$ and $\beta_{AA,RNS}$ respectively), (2) the per-event transmission probability due to AES in the acute phase (denoted $\beta_{A,AES}$), set equal to 10 times the probabilities in the

Table A1
Self-reported recent injecting risk behaviors in young IDU in San Francisco, 2000–2001

	High-risk IDU ($n=360$)	Medium-risk IDU ($n=162$)	Low-risk IDU ($n=322$)
Median number of days injected, prior 30 (inter-quartile range)	25 (14–30)	20 (9–30)	20 (8–30)
Median typical number of injections per day injecting, prior 30 days (inter-quartile range)	3 (2–4)	2.5 (2–4)	2.5 (1.5–4)
Median # of injecting events, prior 30 days (number of days injected times usual number of injections per day injecting) (inter-quartile range)	69 (30–105)	45 (16–40)	42 (15–90)
Frequency of RNS[a] (prior 3 months)			
Always	5%	–	–
Usually	7%	–	–
Sometimes	22%	–	–
Rarely	66%	–	–
Never	0%	100%	100%
Median imputed number RNS[a] events, prior 30 days (inter-quartile range)[b]	9 (4–15)	0	0
Median number of persons with whom engaged in RNS, prior 3 months (inter-quartile range)	1 (1–2)	0	0
Frequency of AES[c] (prior 3 months)			
Always	18%	22%	–
Usually	17%	19%	–
Sometimes	27%	60%	–
Rarely	21%	–	28%
Never	17%	–	72%
Median imputed number of AES[c] events, prior 30 days (inter-quartile range)[b]	12 (3–38)	17 (6–34)	0 (0–.7)
Median number of partners with whom pooled money to buy drugs, prior 3 months (inter-quartile range)[d]	3 (1–4)	2 (1–5)	2 (0–4)

[a] RNS, receptive needle sharing.
[b] Imputations multiplied the total number of injections per month by the proportion of injecting events in which risk behavior occurred in the prior 3 months, where always = 1; usually = .75, sometimes = .25, rarely = .1, never = 0.
[c] AES, ancillary equipment sharing.
[d] This variable is used as a proxy for number of persons with whom the IDU engaged in AES.

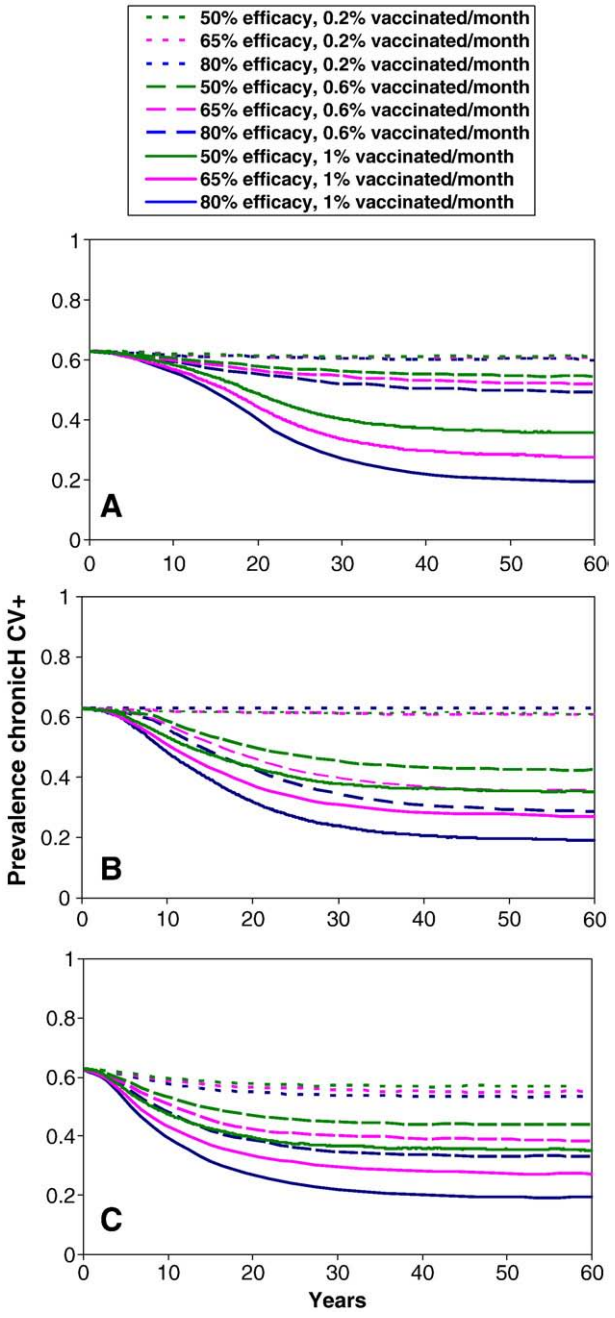

Fig. A1. Prevalence of RNA positive HCV after the introduction of a hypothetical HCV vaccine, by targeting strategy: A. no targeting, B. risk targeting, and C. sero-targeting, efficacy, and vaccination rate over time. Figures show the mean of 100 realizations.

chronic and attenuated acute phases (denoted $\beta_{C,AES}$ and $\beta_{AA,AES}$ respectively), and (3) the per-day probability of AES events in the low-risk group. We estimated these by requiring that the average incidence values at Phase 2 equilibrium equaled (to within 1%) the values measured in the UFO study for the three risk groups. The incidence rates we observed in 213 young IDU studied prospectively from 2000 to 2001 were 55% ppy (95% confidence interval [CI]: 36.2–79.7% ppy), 30% ppy (95% CI: 11.9–61.5% ppy), and 15% ppy (95% CI: 9.5–22.6% ppy) for high-, medium-, and low-risk IDU respectively. We allowed the estimated rate of AES per day in the low-risk group to be greater than zero to allow for some HCV transmission because we observed an HCV incidence of 15% ppy in this group. We estimated the infectivity parameters manually, by running the model 100 years past phase II equilibrium (60 years after the start of the epidemic) and adjusting the transmission probabilities one at a time, using time-averaged results over 100 years. We first estimated the transmission probability for AES by fitting to the incidence in the low risk users who only engaged in AES.

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