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Modeling indicates efficient vaccine-based interventions for the elimination of hepatitis C virus among persons who inject drugs in metropolitan Chicago

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ABSTRACT

Background and aims: Persons who inject drugs (PWID) are at highest risk for acquiring and transmitting hepatitis C (HCV) infection. The recent availability of oral direct-acting antiviral (DAA) therapy with reported cure rates >90% can prevent HCV transmission, making HCV elimination an attainable goal among PWID. The World Health Organization (WHO) recently proposed a 90% reduction in HCV incidence as a key objective. However, given barriers to the use of DAAs in PWID, including cost, restricted access to DAAs, and risk of reinfection, combination strategies including the availability of effective vaccines are needed to eradicate HCV as a public health threat. This study aims to model the cost and efficacy of a dual modality approach using HCV vaccines combined with DAAs to reduce HCV incidence by 90% and prevalence by 50% in PWID populations.
Methods: We developed a mathematical model that represents the HCV epidemic among PWID and calibrated it to empirical data from metropolitan Chicago, Illinois. Four medical interventions were considered: vaccination of HCV naive PWID, DAA treatment, DAA treatment followed by vaccination, and, a combination of vaccination and DAA treatment.
Results: The combination of vaccination and DAAs is the lowest cost-expensive intervention for achieving the WHO target of 90% incidence reduction. The use of DAAs without a vaccine is much less cost-effective with the additional risk of reinfection after treatment. Vaccination of naïve PWID alone, even when scaled-up to all reachable PWID, cannot achieve 90% reduction of incidence in high-prevalence populations due to infections occurring before vaccination. Similarly, the lowest cost-expensive way to halve prevalence in 15 years is through the combination of vaccination and DAAs.
Conclusions: The modeling results underscore the importance of developing an effective HCV vaccine and augmenting DAAs with vaccines in HCV intervention strategies in order to achieve efficient reductions in incidence and prevalence.

1. Introduction

Approximately 180 million people worldwide have chronic hepatitis C virus (HCV) infection with approximately 500,000 HCV-related deaths per year due to liver failure or hepatocellular carcinoma [1,2]. In the United States (U.S.), an estimated 4.1 million individuals are HCV-antibody positive [3], 3.2 million of whom are chronically infected, and there are approximately 30,000 new cases of HCV infection each year [4]. The primary mode of HCV transmission in developed countries is injection drug use, with an estimated 60% of all HCV infections attributable to sharing syringes and other drug paraphernalia [5].

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HCV can be treated with direct-acting antivirals (DAAs) that provide interferon-free, all-oral treatment yielding >90% sustained virological response (SVR or cure) rates [6,7]. However, there are several barriers restricting access to treatment for persons who inject drugs (PWID) including cost [8], and limitations and requirements imposed by medical providers and insurance plans (e.g. a period of abstinence from drug use) [9,10].

Immunity to HCV infection is an important consideration with respect to the risk of reinfection, either after spontaneous clearance or successful treatment. It is well documented that 20–30% of patients spontaneously clear the infection and that a high proportion of these individuals exhibit immunity to chronic HCV infection following re-exposure to the virus [11–13]. However, among PWID attaining SVR following antiviral treatment, most remain susceptible to the development of chronic HCV infections following reinfection [14]. Indeed, while functional CD4+ and CD8+ T-cell responses have been shown in patients following early DAA treatment of acute phase HCV infections, such T-cell responses are absent or weak in patients successfully treated with DAA during the chronic phase [15,16]. Therefore, following treatment, risk reduction methods are necessary to reduce the reinfection of PWID [17,18].

Fortunately, prophylactic HCV vaccines are currently entering advanced clinical trials [19,20]. Although unlikely to induce sterilizing immunity, vaccines are expected to reduce the probability of chronic HCV infection after exposure [21]. HCV vaccines are likely to be relatively inexpensive and more accessible for PWID populations compared to DAA [22,23]. When available, a vaccine is predicted to reduce HCV transmission among PWID and their injection partners [24]. A vaccine also could reduce the risk of chronic infection after re-infections or exposures in persons who were successfully treated with DAAs [21,25]. In chimpanzees, vaccines achieved a similar rate of clearance following challenge with HCV compared to rechallenge of animals that spontaneously cleared the virus, suggesting that efficacy of 70% or higher may be attainable [26].

In light of the advances in HCV treatment, the World Health Organization (WHO) recently proposed objectives for the control of viral hepatitis as a public health threat by 2030 [27] that was deemed feasible by the U.S. National Academy of Sciences, Engineering and Medicine [28]. A key WHO objective is a 90% reduction in incidence and a 65% reduction in deaths due to viral hepatitis. In countries like the U.S., where new HCV infections (incidence) are concentrated among mostly young PWID, the WHO objectives could be achieved by an aggressive combination intervention strategy that might include scaling up of prevention (e.g., vaccine, behavioral counseling, harm-reduction) and treatment (e.g., DAA) strategies in this population [29].

We aim to examine combination strategies that would achieve rapid and efficient HCV incidence reduction with both vaccination and DAAs using a mathematical model of HCV infection in a PWID population. Guided by the WHO target, our model considers the objectives of reducing the incidence of HCV by 90% within 15 years and a supplemental objective of reducing the prevalence by at least 50% within a similar timeframe, assuming both DAAs and vaccines are available. Our model is calibrated with empirical data from the well-characterized HCV epidemic in Chicago PWID [30–33], although it is relevant to other regions with epidemiologically-similar PWID populations. In Chicago and in the rest of the State of Illinois, access to DAAs is restricted for the uninsured and for persons with Medicaid insurance [34], and antiviral treatment is estimated to be as low as 1 per 1000 PWID. Therefore, vaccines could play a significant role in controlling HCV among PWID in the future.

2. Methods

2.1. HCV prevalence estimation in metropolitan Chicago

Metropolitan Chicago, Illinois is the third largest metropolitan area in the U.S. and has a population of ~9.5 million (assessed in 2015) including an estimated 32,000 persons who inject drugs (PWID) [35] with an HCV-RNA prevalence of 47% and a calculated baseline incidence of 0.04 cases per person-year (PY) as described in the Supplementary File. To estimate the proportion of subpopulations (e.g., young, those who attend syringe services programs [SSPs]) and the prevalence of HCV antibody and HCV-RNA among the PWID, we used data from large-scale empirical studies collected on the metropolitan Chicago PWID population including: (i) the Chicago site from the CDC-sponsored 2009 National HIV Behavioral Surveillance System (NHBS) [36–38], (ii) the Third Collaborative Injection Drug Users (CIDUS III, 2002–2004) study [30,39] and (iii) the Early Natural History of HCV Infection Among Injection Drug Users (NATHCV, 2002–2006) study [40]. From these data sources, we estimate that approximately 22,000 PWID (69% of the total PWID population) attend syringe service programs (SSPs), and have an estimated HCV-RNA prevalence of 30% and calculated baseline incidence of 0.025 cases per PY. It was reported that there are 11,000 young PWID (<30 years old) [35] with an estimated HCV-RNA prevalence of 10% and baseline incidence of 0.0086 cases per PY. Of note, PWID in the SSP and young subpopulations may overlap.

2.2. Mathematical modeling

We extended a compartmental model of HCV infection [41] to include vaccination as shown in Fig. 1. Model parameters, equations and source code are shown in Table 1 and Supplemental File. Model calibration and sensitivity analysis are described in the Supplementary File and summarized in Tables 2 and 3. Numerical integration was completed with Berkeley Madonna software (Robert I. Macey & George F. Oster. www.berkeleymadonna.com) with parameter estimates (Table 1) taken from [41] and the model brought close to the desired (or estimated) experimental HCV prevalence of each PWID (sub)population by adjusting the infection rate parameter, π.

2.3. Vaccine efficacy

The vaccine effect is represented by the vaccine efficacy parameter, defined as the proportion of vaccinated PWID who, if infected, would not develop chronic HCV infection. We considered ranges of efficacy from 60% to 90% to represent the range expected based on a meta-analysis [26] of vaccinated chimpanzees, the only challenge data available to assess vaccine efficacy. As described earlier, these data showed that vaccines could achieve efficiency comparable to chimpanzees who spontaneously cleared the virus. A rigorous prior model of vaccination explored 30%, 60% and 90% vaccine efficacies [19]. A vaccine with 30% efficacy would not be significantly beneficial given that nearly 30% of PWID achieve self-clearance without a vaccine [40,42]; therefore this level of efficacy was not considered in our model.

2.4. Treatment costs

While we previously assumed [41] a DAA cost of $50,000 per subject after discounting and without other associated medical costs (e.g., monitoring HCV-RNA for response), in the current study a cost of $25,000 per patient was assumed, which reflects the lowest cost of a recent FDA approved DAA, Mavyret [43]. The cost of the hypothetical HCV vaccine was set to $200 per subject,

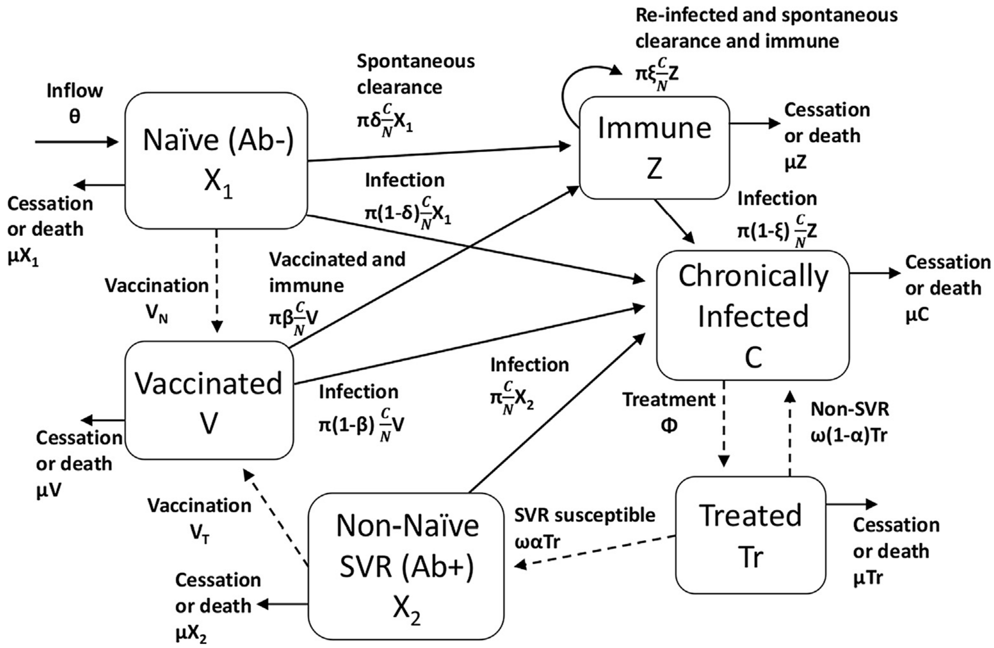

Fig. 1. Schematic description of mathematical model. Dotted lines represent the progression through treatment or vaccination. The model describes six possible states to which a given PWID may belong: (i) X_1 = naïve (Ab-) those that have not been exposed to the virus, which can move to immune, chronic, or vaccination compartments, (ii) Z = immune persons i.e., infected PWID who have spontaneously resolved the infection, (iii) C = chronically infected (viremic) PWID, (iv) V = vaccinated PWID who were previously either naïve or had received post-SVR vaccination, (v) Tr = on antiviral treatment because they are chronically infected or failed treatment and are being re-treated, and (vi) X_2 = PWID who were cured after DAA treatment and did not develop immunity to HCV. Because cured persons appear to be susceptible to HCV, PWID in compartment X_2 are assumed to be susceptible to chronic infection. N represents the total PWID population (X_1 + V + Tr + Z + C + X_2). Model equations and parameters are described in the Supplemental File and Table 1, respectively.

Table 1
Model parameters.

Model parameter definition	Formula	Value [Range]	Units	Source
Population & infection				
PWID influx rate	θ	85 [50–200]	Per 1000 PWID annually	[41]
PWID leaving rate (cessation or death)	μ	0.085 [0.05–0.2]	Per year	1000·θ
Infection rate per year	π	0.279 [0.149–0.657]	Per year	Calibrated by fitting prevalence
Proportion of infections that spontaneously clear	δ	0.26 [0.22–0.34]	Proportion of infections	[39,41]
Proportion of reinfections resulting in spontaneous clearance and immunity	ξ	0.8 [0–0.8]	Proportion of reinfections	[25,42–44]
Treatment & vaccination				
DAA treatments	Φ	0–101	Per 1000 PWID per year	Policy parameter
DAA treatment duration	1/ω	ω = 0.23	Year	[6]
Proportion of treated chronic infections achieving SVR	α	0.9 [0.5–0.9]	Proportion of treated PWID	[45]
Post-DAA vaccination	V_T	0–57	Per 1000 PWID per year	ωαTr
Naïve vaccinations	V_N	0–641	Per 1000 PWID per year	Policy parameter
Vaccine efficacy in preventing chronic HCV infection	β	0.6–0.9	Proportion of infected vaccinees	[19,25]

SVR, sustained virological response (or cure).

i.e., the upper estimated cost of vaccinating PWID for hepatitis B in the U.S. [44]. The cost of interventions was calculated as follows: We counted the total number of courses of vaccine and/or DAA treatment given from the start of the intervention (variables totV and totTr) and multiplied them by the cost of a vaccine and/or DAA treatment, respectively as described in the Supplemental File together with the source code.

2.5. Intervention strategies

We evaluated the following four interventions.

2.5.1. Intervention V: Vaccinating naïve PWID

Intervention V involves vaccination to naïve PWID at a fixed rate given by parameter V_N (Table 1) per 1000 PWID per year. Because the scale-up cannot be larger than the naïve PWID population (X_1), when required V_N is greater than X_1, the number of vaccinees was dynamically adjusted in the model (see Supplemental File) to be a maximum of X_1 per year (as in our earlier model of DAA treatment rate among PWID [41]). Furthermore, the parameter V_N was incremented until the intervention objective was achieved in 15 years, i.e. incidence was reduced by 90% or the prevalence was halved. We empirically observed that increases in the number of vaccinees have almost no effect on incidence beyond a certain threshold point when the majority of the naïve population becomes vaccinated. Therefore, if the threshold was reached, the number of vaccinees was not increased further and the duration necessary to achieve the reduction in incidence was recorded. In some subpopulations we found that, while the intervention could achieve the target objective, the required coverage

Table 2
Scale of intervention needed to reduce incidence by 90% in 15 years, if feasible.

Population				Intervention V Naïve vaccination	Intervention A DAA treatment	Intervention AV DAA with vaccination	Intervention VAV DAA with vaccination + Naïve vaccination
PWID	Initial chronic prevalence	Infection rate π	Steady State Incidence *Cases per PY*	Minimal coverage Duration Cost [$M]	Minimal annual rate per 1000 Cost [$M]	Minimal annual rate per 1000 Cost [$M]	Minimal annual rate per 1000 Cost [$M]
All	47%	0.260	0.040	100% (100–100%) 35 yrs (24–63 yrs) $18 [16–32]	45 (40–85) $461 [417–584]	39 (36–71) $407 [381–486]	29 (28–51) $313 [303–334]
SSP	30%	0.181	0.025	100% (30–100%) 22 yrs (15–33 yrs) $9 [8–13]	24 (22–43) $172 [160–195]	22 (21–40) $159 [157–176]	16 (13–27) $122 [103–130]
Young (age < 30)	10%	0.149	0.0086	100% (19–100%) 16 yrs (15–22 yrs) $4 [4–5]	7 (7–13) $25 [25–27]	7 (7–12) $25 [24–26]	5 (4–9) $22 [20–25]

[min–max] is determined from sensitivity analysis reproduced from the Supplemental File Tables S1A-S4D. Central estimate for vaccination with 90% efficacy in Intervention V, and 60% efficacy in AV and VAV. PWID, persons who inject drugs. The model was calibrated by setting the infection rate (parameter π) to match the prevalence of Chicago PWID (sub)populations.

Table 3
Scale of intervention needed to reduce the prevalence by half in 15 years using four different interventions.

Population		Intervention V Naïve vaccination	Intervention A DAA treatment	Intervention AV DAA with vaccination	Intervention VAV DAA with vaccination + Naïve vaccination
PWID	Initial chronic prevalence	Minimal coverage Cost [$M]	Minimal annual rate per 1000 Cost [$M]	Minimal annual rate per 1000 Cost [$M]	Minimal annual rate per 1000 Cost [$M]
All	47%	49% (25–49%) $9 [8–12]	28 (24–49) $291 [253–438]	23 (20–40) $243 [212–329]	11 (8–19) $125 [97–156]
SSP	30%	18% (14–100%) $6 [6–7]	14 (13–24) $99 [94–125]	13 (12–22) $94 [87–113]	5 (0–8) $43 [12–64]
Young (age < 30)	10%	15% (10–19%) $4 [3–4]	4 (4–7) $14 [13–15]	4 (4–7) $14 [14–15]	2 (0–3) $11 [6–14]

[min–max] is determined from sensitivity analysis reproduced from the Supplemental File Tables S5A-S8D. Central estimate for vaccination with 90% efficacy in Intervention V, and 60% efficacy in AV and VAV. PWID, persons who inject drugs.

rate was higher than what would be feasible for Chicago, and this was noted in intervention VAV.

2.5.2. Intervention A: DAA treatment only

Intervention A entails DAA treatment of a fixed number of HCV-chronically infected PWID, Φ, per 1000 per year, as modeled previously [41].

2.5.3. Intervention AV: DAA treatment followed by vaccination

Intervention AV involves DAA therapy of an HCV-chronically infected PWID followed by vaccination after SVR is achieved. The intervention is inspired by findings from prior studies showing that individuals remain susceptible to HCV infections following successful DAA treatment and the risk of developing a new chronic infection appears to be high for PWID [14,45]. This intervention is expected to reduce the number of new chronic infections after cure with DAA treatment, and we hypothesized that it would have a lower cost than DAAs alone.

2.5.4. Intervention VAV: Naïve vaccination coverage + DAA treatment followed by vaccination

Intervention VAV is a combination of (V) and (AV) in two different groups. Under VAV, naïve PWID receive vaccinations, while chronically HCV-infected PWID receive DAA treatment followed by vaccination immediately after SVR is achieved. We restricted the number of vaccinees of vaccination V_N so that the maximal coverage rate for the total population was 40% of the HCV-naïve PWID, which is a conservative estimate based on averaging previous studies that provided hepatitis A and/or B vaccinations to PWID under various conditions (e.g., incentives, availability at community settings convenient to PWID), including a U.S. based multi-city randomized controlled trial [46] and others in the U.S. (San Francisco) [47] and Australia [48]. We also anticipated subpopulation differences based on varying expected levels of access and readiness. The SSP population, who are connected to prevention services that improve access, are expected to have high coverage rates (90% of the HCV-naïve PWID), while young PWID who are likely to be in the early stages of their injection career and not as connected to health services are expected to low coverage rates (30%). Because vaccination has a relatively lower cost, we hypothesized that intervention VAV would be the lowest cost intervention for reducing HCV prevalence among PWID.

3. Results

Our model forecasts the effect of four interventions on the HCV epidemic among PWID using a timeframe of 15 years with a target of either reducing incidence by 90% or reducing prevalence by at least 50%.

3.1. Reducing incidence by 90%

With intervention A (DAA only), we found that 90% reduction in 15 years is feasible, but would require treatment of 45, 24, and

7 per 1000 PWID with a total cost of $461, $172, and $25 (millions), for the total, SSP, and young populations, respectively. With intervention V (vaccinating naïve PWID), we found that, if a 90% effective HCV vaccine was available for 15 years, the maximal feasible reduction in incidence would be 77% for all PWID, 84% for SSP attendees, and 87% for young PWID, with costs (millions) $9, $7, and $4, respectively. To achieve the 90% reduction in incidence would require 35 years, 22 years, and 16 years, respectively, for the 3 subpopulations (Table 2). These durations are required because in populations with high prevalence of chronic HCV and with limited access to care, many persons who newly-initiate injecting would become infected before they could receive vaccines. With intervention AV (DAA followed by post-treatment vaccination) treatment needs to be 39, 22, and 7 per 1000 PWID for the total, SSP, and young populations, respectively, (Table 2) to reduce incidence by 90% in 15 years. The costs (millions) are $402, $159, and $25, respectively.

Intervention VAV entails vaccination of naïve PWID and DAA treatment of chronically infected PWID followed by vaccination (post DAA treatment vaccination). Fig. 2 shows the relationship between the numbers of DAA treatment followed by vaccination and the coverage of the naïve population needed to reduce the baseline incidence by 90%. Assuming vaccine efficacy of 60%, intervention VAV would require number of PWID treated with DAA and cost (million) of 29 ($313), 16 ($122), and 5 ($22) per 1000 PWID for the total, SSP, and young PWID populations, respectively (Table 2). Using the most effective vaccine efficacy (90%), the number of PWID treated with DAA followed by vaccination, and the cost (million) would be 15 ($166), 5 ($43), and <0.5 ($4) per 1000 PWID for the total, SSP, and young PWID populations, respectively (data not show). These costs are the lowest possible among the four interventions that achieve the WHO objectives.

3.2. Halving the prevalence of HCV in chronically-infected PWID

We examined the DAA treatment rate and/or vaccine coverage and cost needed to halve the Chicago subpopulation chronic prevalence in 15 years (Table 3). Vaccination of the naïve PWID population with 90% efficacy would be able to reduce the HCV prevalence by 50% in 15 years among total, SSP, and young PWID by coverage (cost in millions) of 49% ($9), 18% ($6) and 15% ($4), respectively (Table 3). Vaccines with 60% efficacy cannot achieve halving the prevalence in 15 years at realistic coverage rates. Intervention A (DAA alone) after 15 years of treatment at a rate of 28 per 1000 PWID, achieved a 50% reduction in the prevalence and a 17% reduction in the incidence of HCV for the total population (Table 3).

Intervention VAV involves combining naïve vaccination and DAA treatment followed by vaccination (post DAA treatment vaccination). Fig. 3 shows the relationship between the number of PWID treated with DAA followed by vaccination and the coverage of the naïve population needed to halve the chronic prevalence in 15 years. Based on our proposed vaccination rates for the total (40%), SSP (90%), and young (30%) naïve PWID populations and assuming VAV intervention vaccine efficacy of 60%, the projected numbers of PWID and costs (million) are 11 ($125), 5 ($43), and 2 ($11) per 1000 PWID, respectively (Table 3).

4. Discussion

We applied mathematical modeling to consider the use of vaccines, DAAs, and their combination to reduce the incidence and prevalence of HCV among PWID from large metropolitan area. Our study suggests that combination intervention strategies may best facilitate achieving the goal of reducing the incidence of HCV by 90% among PWID in 15 years. Examination of interventions using DAAs without vaccines shows this may be the most expensive intervention overall and among all subpopulations. The cost could be significantly reduced by using a vaccine in combination with DAA therapy – a finding that underscores the important role vaccines could play in reaching HCV elimination goals.

We found a naïve vaccination intervention alone would not achieve the 90% incidence reduction objective in 15 years even if all accessible PWID were vaccinated with a vaccine of 90% efficacy. The suboptimal efficacy of vaccination alone may arise from difficulty in achieving sufficient vaccine coverage among recently-initiated PWID, who are at highest risk for new (incident) HCV infection and who would be susceptible to infection until they are vaccinated (see Methods). Indeed, a recent meta-analysis examining the time from onset of injection to incidence of HCV infection found a cumulative incidence of 28% (95% confidence interval = 17%, 42%) at 1 year of drug injection [49]. However, when the risk of infection is low, vaccination alone achieves the incidence reduction objective. This scenario is feasible in metropolitan Chicago among young, suburban PWID who are less likely to have HCV-infected partners than their urban counterparts [30]. We also considered a naïve vaccination-only intervention for halving HCV prevalence. In populations with low prevalence and low risk of infection, such as the SSP population in select cities (e.g. Chicago) [30], naïve vaccination alone can halve the prevalence in 15 years without DAA treatment. Namely, if only 20% of the SSP naïve population is vaccinated with a 90% efficacious vaccine, the SSP population's chronic prevalence can be halved in 15 years without DAA treatment or post-treatment vaccinations (Table 3). However, in populations with high prevalence or with vaccines of lower efficacy, the 50% reduction cannot be achieved with naïve vaccination alone (Fig. 3) because it would require a coverage rate of 49% (Table 3) that might be difficult to achieve for the entire PWID population, and indeed much of it (47%) is already infected with HCV. Among all PWID subpopulations, combination intervention such as AV or VAV are the only strategies capable of achieving 50% reduction in HCV prevalence. Vaccine efficacy is another significant parameter when considering the total cost for halving HCV prevalence. The use of a vaccine that is 90% effective would halve the prevalence of HCV in PWID without DAAs, and it is the lowest cost intervention, but with lesser vaccine efficacy (e.g. 60%) and in situations with high chronic prevalence, intervention VAV has the lowest cost.

According to a previous modeling study of vaccination of PWID [19], vaccinating everyone not chronically infected was the most effective and financially feasible intervention. Our findings align with this result but, as noted earlier, we find that this approach would *not* achieve the WHO-based objective of reducing the incidence by 90% in 15 years. In agreement with previous modeling efforts in San Francisco [50], we found that if a vaccine was available a vaccine-only approach would require a longer duration of intervention (16–31 years), but interventions such as AV and VAV that combine vaccination and treatment can achieve this objective in 15 years. Our model accounts for spontaneous development of immunity, an important factor that explains the divergent finding. As shown in our previous work [41], the immunity process means that the true risk of transmission is considerably higher than supposed in [19], and consequently, the scale of interventions must be greater to achieve the WHO objective.

Although DAA treatment is now considered a promising strategy to reduce HCV prevalence, we observe that post-DAA vaccination can significantly reduce the needed level of DAA treatment rates. For instance, when considering all PWID (47% chronic prevalence), DAA treatment followed by vaccination reduces treatment rate and cost by 21% (Table 3). Therefore, the simple DAA strategy should be enhanced by a vaccine, as soon as a vaccine becomes

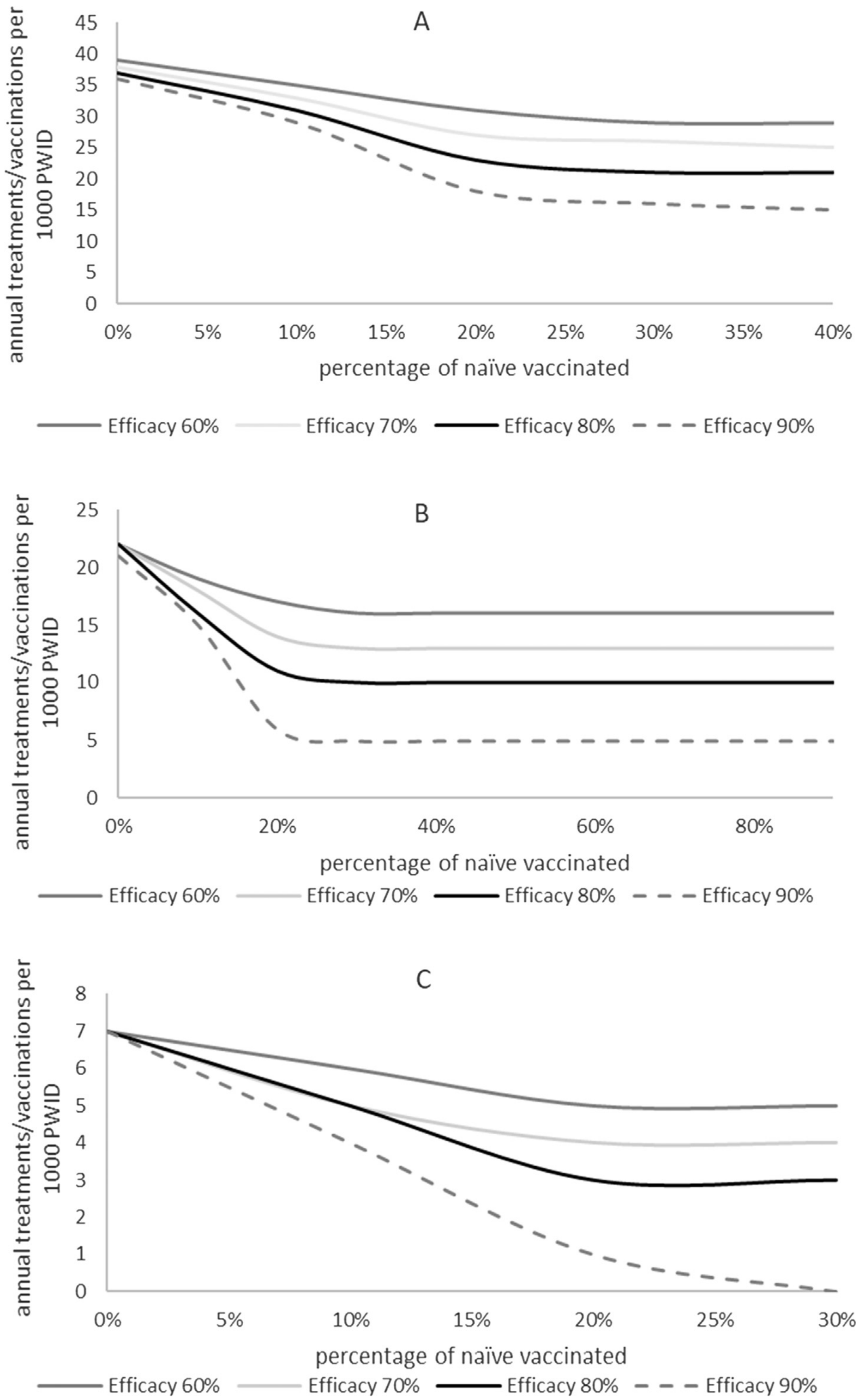

Fig. 2. Modeling VAV (i.e., combinations of AV (DAA treatment followed by vaccination) rates and V (naive vaccination) coverage) intervention to reduce HCV incidence by 90% in 15 years. Initial incidence of 0.040 cases per PY (A) for the total PWID population, 0.025 cases per PY (B) for the SSP population, and 0.0086 cases per PY (C) for the young population. Note that even high efficacy vaccines are projected not to achieve the WHO incidence reduction objective without combination of DAA therapy.

available. Non-medical prevention strategies could also play a role in controlling transmission.

Our study has several limitations. First, the cost of a HCV vaccine was set to $200 based on hepatitis B vaccine cost among in the U.S. [44] which is within the range used (or noted) in previous modeling efforts [51–53] and thus could be considered as a conservative assumption. In particular, we assume a single scenario — rapid uptake of a one dose vaccine that confers long-term protection. This assumption is based on the partial protection from chronic infection that is observed in recovered patients and chimpanzees who are re-exposed to HCV [12,26]. Second, vaccine efficacy is unknown; to minimize the impact of this uncertainty, we used a range of efficacies and feasible coverage rates for the total PWID population and subpopulations. Third, similar to a recent

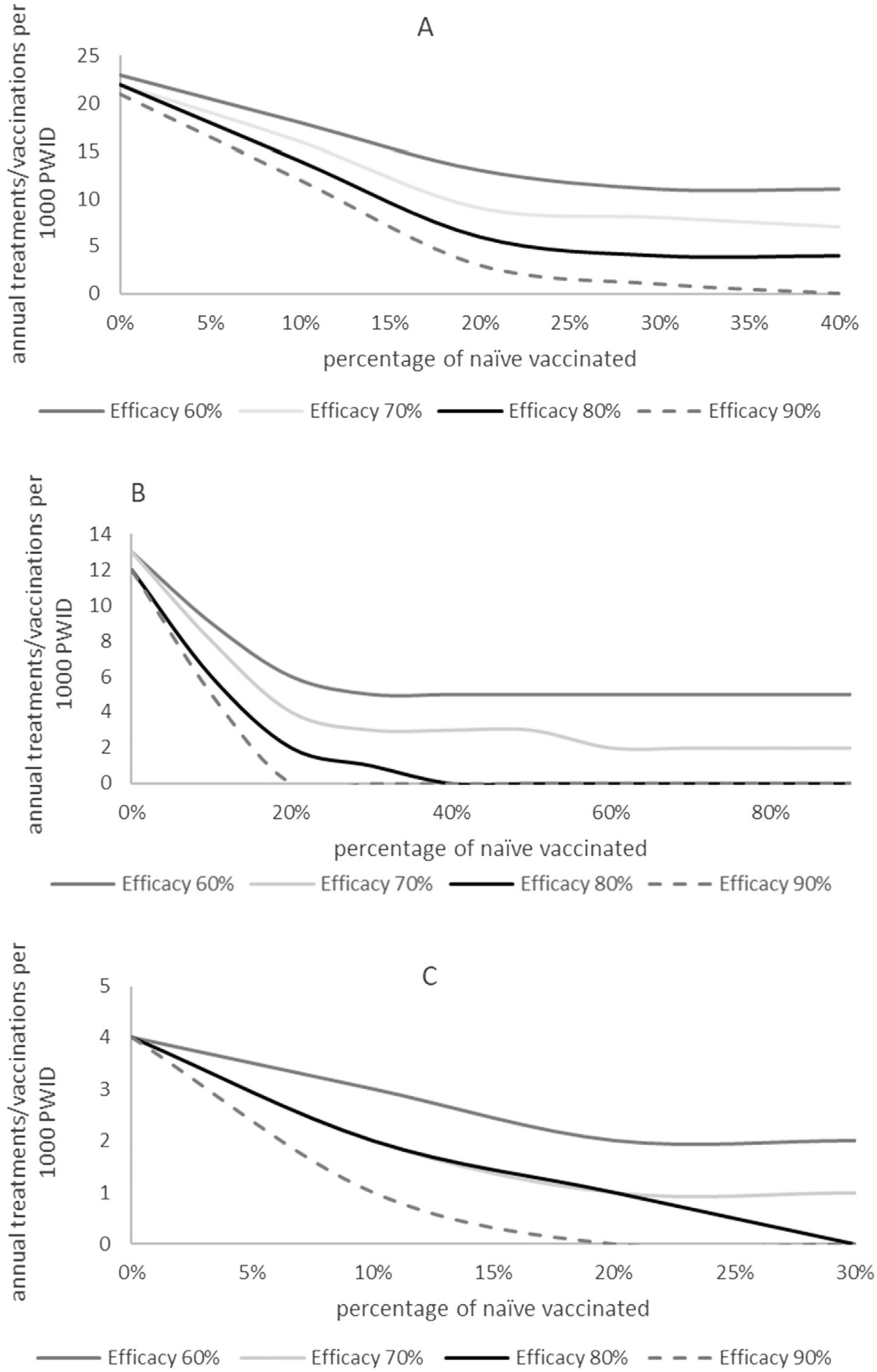

Fig. 3. Modeling VAV (i.e., combinations of AV (DAA treatment followed by vaccination) and V (naive vaccination) coverage) intervention to halve HCV prevalence in 15 years. HCV prevalence of 47% (A) for the total PWID population, 30% (B) for the SSP population, and 10% (C) for the young population.

DAA/vaccine PWID modeling study for PWID in the United Kingdom by Stone et al. [51], our model assumes rapid DAA treatment uptake rates. The model does not account for the entire HCV cascade of care (i.e., diagnosis, linkage to care and treatment initiation) that is driven mainly by cost and limited access in the U.S., particularly among PWID [9,10]. Fourth, our model does not account for the overall Chicago PWID population that is entering and leaving SSPs as well as the levels of access to SSPs by subgroups to minimize the model's complexity. Moreover, since most of the total PWID population is estimated to be in SSPs (69%), the projected results of our model represent a conservative estimate for the number of treatments needed to reduce new HCV incidences within 15 years. Fifth, we stratified the PWID population to understand the effect of intervention on two subpopulation: young PWID and those in SSPs. However, we do not suggest that these subpopulations are mutually exclusive (i.e., a young PWID could also be an SSP enrollee). Rather, subpopulations may have differing roles in the epidemiology of HCV (e.g., young PWID are more likely to contribute to incidence) and thereby are expected to have differing trajectories through the HCV care cascade that would require specific types and combinations of strategies to eliminate HCV. One could extend our work by constructing a group-level model in which the PWID populations are stratified by intervention status [54]. However, given the large number of parameters needed in such a stratified model (e.g. mixing and transition rates) and the lack of data on these parameters, our current model is better suited for analyzing the benefit of vaccines and combining them with DAAs in Chicago. Despite the above limitations, the results provide new and important insight into how DAA treatment and vaccination can be used together to address the problem of HCV in PWID. Future studies using agent-based models (e.g. [55–57]), will be needed to more fully simulate the complexity of HCV transmission among PWID and HCV cascade of care in the U.S. [58], to further refine estimated rates of vaccination and DAA treatment needed to achieve elimination of HCV.

5. Conclusion

Despite the current availability of effective antivirals for HCV, the development of vaccines would significantly reduce the cost of controlling HCV within a 15-year horizon. In PWID populations infected with HCV, a combination of vaccination and antivirals is the most efficient intervention for bringing HCV incidence in PWID to the cusp of elimination.

Competing interests

All authors declare that they do not have any financial and/or conflict of interest related to this research.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.081.

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