

## **AN AGENT-BASED MODEL OF HEPATITIS C VIRUS TRANSMISSION DYNAMICS IN INDIA**

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### **ABSTRACT**

In this study, we develop a model of hepatitis C virus (HCV) transmission dynamics capable of analyzing the health, economic and epidemiological impact of treatment and large-scale screening in the Indian context. The model simulates the interaction of infected and uninfected agents in environments wherein key risk factors of HCV transmission operate. The natural history of disease is simulated using a previously published and validated Markov model. The agent interaction/transmission environments simulated by the model include a home environment for transmission via unprotected sex, a medical environment for transmission via unsafe medical practices, educational and social interaction environments for conversion of non-injecting drug user (IDU) agents to IDUs and transmission via sharing of injecting equipment among IDUs. The model is calibrated to current HCV and IDU prevalence targets. We present model calibration results and preliminary results for the impact of treatment uptake rates on HCV and IDU prevalence.

### **1 INTRODUCTION**

Hepatitis C, a blood-borne disease, has become the leading cause of liver cirrhosis and hepatocellular carcinoma (WHO 2017). The hepatitis C virus (HCV), of which six genotypes exist (genotypes 1 through 6), is typically spread through unscreened blood transfusions, unsafe medical procedures, injection drug abuse, tattooing, unprotected sex, and from mother to child (Dhiman et al. 2016). In India, HCV is estimated to affect 0.5-1.5% of the population (Dhiman et al. 2016), with a recent epidemiological meta-analysis estimating a prevalence of 0.85% (Goel et al. 2019). This yields a burden of approximately 10.7 million persons, with most of those infected thought to be unaware of the infection.

HCV is now treated with directly acting antivirals (DAAs), replacing the previous standard of care, an antiviral agent known as interferon (IFN) and its variants in combination with ribavirin (RBV) (Sood et al. 2014). DAAs have significantly improved efficacies ( $> 90\%$ , Sood et al. 2014) and tolerability in achieving sustained virologic response (SVR, the equivalent to an HCV cure) when compared to IFN-based therapies (50-80% depending upon HCV genotype, Rao et al. 2014; Sood et al. 2014). India also has adopted a DAA based approach to HCV treatment (Sood et al. 2018). However, uptake rates for treatment have remained low even though DAAs have been introduced in India at compassionate prices. This is partly because of low awareness among patients and medical practitioners, and also because the 300 US dollar price point remains out of reach for a significant proportion of the Indian population. Low uptake rates thus add to the economic burden of HCV (He et al. 2016).

Treatment uptake rates can improve with HCV screening programs; however, HCV screening programs in India are inadequate (Pandey and Singh 2016). Before a screening and public health education program

is implemented on a large scale, it would be prudent to evaluate the cost-effectiveness of such a program using decision-analytic modelling.

In this study, we develop an agent-based model of HCV transmission dynamics capable of assessing the health, economic and epidemiological impact of HCV treatment, screening and public health education programs. Agent-based simulation is an appropriate methodology for modeling HCV transmission dynamics, as the disease spreads through interactions between disease-carrying persons or ‘agents.’ While deterministic compartmental models also facilitate such analysis, the stochastic nature of the spread of HCV – for example, through chance contamination by an infected patient of equipment used by a doctor engaging in unsafe medical practices – make stochastic simulation a natural modeling choice (Cousien et al. 2015).

Our model simulates interaction of agents in multiple environments wherein key factors of HCV transmission in the Indian context operate: a home environment; social interaction and educational environments wherein both injecting drug users (IDUs) and non-IDUs can interact; and a medical environment wherein HCV can spread via unsafe medical practices. Our literature survey did not yield this type of comprehensive model of HCV transmission dynamics in either Indian or international settings, and hence we attempt to address this gap in the literature. Specifically, in this paper, we describe the key features of this simulation model, including model parameterization and calibration, and present preliminary results regarding the impact of DAAs and changes in treatment uptake rates on HCV prevalence.

## **2 LITERATURE REVIEW**

We begin by discussing state transition models (STMs), many of which have been developed to assess the cost-effectiveness of HCV treatments. We limit our discussion to STMs used in cost-effectiveness analyses of DAAs, given that treatment with DAAs has been the standard of care since 2011 (Chhatwal et al. 2016). A discussion of all such STMs is beyond our scope here; hence we refer the reader to a systematic review by Chhatwal et al. (2016) for a comprehensive discussion.

Chhatwal et al. (2016) found that a majority of the models (94%) have been developed for analyses conducted in the Western hemisphere, and only found one conducted in Asia (Singapore). They also found that none of these studies considered HCV transmission dynamics, and only considered persons already infected. However, since this review was published, we identified three published agent-based simulations investigating the cost-effectiveness of HCV interventions for IDUs, which we discuss in the context of transmission models. Two cost-effectiveness analyses of DAAs in the Indian context have also been published (Aggarwal et al. 2017; Goel et al. 2018).

In both studies in the Indian context (Aggarwal et al. 2017; Goel et al. 2018), the authors used a Markov STM to assess the cost-effectiveness of DAAs in chronically infected individuals (G1, G3 and G4 HCV genotypes) in the Indian context. However, this study did not consider disease transmission dynamics, and therefore did not consider the effect of treatment on HCV prevalence. Also, because treatment of those infected may prevent further transmission, the cost-effectiveness of treatment is likely to be underestimated if the number of cases averted is not taken into account along with gains in health outcomes for individual patients. More importantly, given that treatment uptake rates in the Indian context are low, evaluating the effect of increased treatment uptake rates achieved via screening on HCV prevalences becomes imperative. We attempt to develop a model of HCV transmission dynamics that addresses these gaps, among others, in this study. However, we use a modified version of the Markov STM used in these studies to simulate the natural history of HCV for infected agents.

A large number of HCV transmission dynamics models have been published, and hence we refer to a review of these models by Pitcher et al. (2018). A majority of transmission models have been developed in a developed economy setting, where the dominant mode of transmission of HCV is via injecting drug use. Hence the review focuses on models developed for IDUs alone. Pitcher et al. (2018) found that transmission models were developed to estimate the effect of harm reduction programs (e.g., syringe/needle substitution programs) and/or ‘treatment as prevention’ programs. The authors reported that most studies determined that a combination of harm reduction and treatment as prevention (i.e., screening and treatment

of IDUs) is most likely to achieve the WHO incidence target of a reduction of  $> 90\%$  in new infections by 2030.

We identified three agent-based models used in cost-effectiveness analyses (He et al. 2016; van Santen et al. 2016; Cousien et al. 2018). All were targeted to IDUs, and all were conducted in Western developed settings. Only one study (He et al. 2016) attempted modelling HCV transmission in the general community; however, IDUs remained the key transmission mode.

Overall, our survey of transmission models yielded a few gaps: (a) given that all the models focus primarily on HCV transmission via IDUs, and a majority of infections in India occur due to unsafe medical and dental procedures, a transmission model that accounts for unsafe medical care is required in this context; (b) we found no work in comprehensively modeling the transmission dynamics of HCV in the Indian or South Asian contexts and on assessing the impact of screening on HCV prevalence and incidence. We attempt to address these gaps via our agent-based model that includes transmission via unsafe medical practices, injecting drug use and unsafe sexual practices. Planned uses of the model include estimating the cost-effectiveness of treatment-as-prevention strategies with DAAs in the Indian context, and also to model the effect of a public awareness program on HCV epidemiology. Finally, unsafe medical care is likely to be a substantial contributor to the HCV burden in other developing countries, and hence our model could provide a roadmap for conducting such studies in other developing countries.

### 3 MODEL DEVELOPMENT

We started model development by constructing agents representing individuals in society with two principal characteristics relevant to the spread of HCV: infected or uninfected individuals (may or may not be IDUs), IDU or non-IDU (may or may not be infected). HCV is spread in the model by interactions between these agents in environments constructed to reflect the contribution of key HCV transmission modalities. Once an agent in the model acquires an infection, his/her disease progression is simulated via a Markov model adapted from previously published cost-effectiveness studies (Aggarwal et al. 2017; Goel et al. 2018). The cohort of agents in the model is dynamic, with demographics, birth and death processes calibrated to Indian census data. The model thus consists of two components: (a) disease transmission in key environments; and (b) natural history and treatment model. Figure 1 provides an overview of the model. We now provide

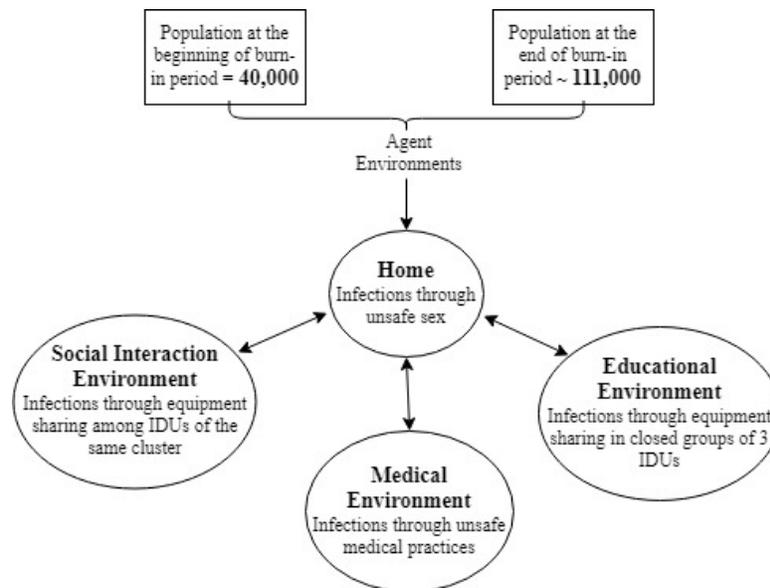


Figure 1: HCV transmission model: overview.

a brief overview of the birth and death processes in the simulation. The model has a burn-in period of

50 years (a year consisting of 12 30-day months). The model was initialized for the burn-in period with 10,000 homes, each consisting of a ‘family’ of 4 agents. Each ‘family’ consisted of two male-female pairs, with one younger pair between the ages of 23 and 27 capable of birthing new agents and one older pair between the ages of 48 and 52, assuming a generation change every 25 years. This particular configuration was chosen to initialize the simulation so as to arrive at the demographics of the Indian population in 2011, when the last decadal census was conducted in India. Children are not included in this initial configuration as a matter of convenience; however, given that birth of new agents begins immediately upon start of the burn-in period, a reasonable distribution of agents of all ages is achieved within the first 25 years.

Daily probabilities of death were generated by using publicly available census data, using which the average annual number of deaths per 1000 people between 1960 and 2014 was estimated as 14.85 (Ministry of Home Affairs 2016). For births we used the demographic distribution of India where the distribution of people within each 5 year age group from 0-50 (e.g., 0-5, 5-10) was used (Ministry of Home Affairs 2016). This yielded a daily birth rate of 4.94.

New families are formed in the following manner: when two persons belonging to different families cross the age of 23 - the average age of marriage in India (Ministry of Home Affairs 2016) - they are paired and moved to a new family. When births occur, they are randomly allocated to these new families with the limit that each pair cannot have more than five children.

Finally, we choose the district of Ludhiana in the Punjab province in India to provide a geographical basis for our model, because the HCV prevalence in this district is similar to that in India as a whole: 1.8% in Ludhiana compared to 0.5-1.5% in India (Sood et al. 2018). Further, HCV is prevalent at high levels in Punjab (3.6%, from Sood et al. 2018), and hence many prominent cross-sectional studies of HCV and IDU prevalence were conducted here, leading to the availability of more data for this province. We now describe key features of the model.

### **3.1 Disease Transmission in Key Environments**

We construct environments wherein key risk factors for transmission of HCV operate. In the Indian context, the majority of infected persons have reported medical procedures in their history of risky interactions: 80% as reported by Chakravarti et al. (2013). Hence, we model a “medical environment” as a catch-all environment for all types of medical procedures capable of HCV transmissions.

Injecting drug use is the next most important mode of HCV transmission in the Indian context - 9.2% as reported by Chakravarti et al. (2013). However, inputs from our clinical expert indicate that there is likely to be significant underreporting of injecting drug use in cross-sectional surveys, and its contribution to HCV prevalence is likely to be larger than current estimates. Thus to model interactions within the IDU cohort and between IDUs and non-IDUs (wherein non-IDUs may be influenced to become IDUs), we incorporate a “social interaction” environment. Further, given that younger agents are likely to attend educational institutions, and most IDUs have been found to be between the ages of 18-30 (Ambekar and Tripathi 2008), we also incorporate an “educational environment” wherein IDU and non-IDU agents between the ages 18-25 years can interact in the same manner as in the social interaction area, with some differences which we will describe in the following sections.

In addition to injecting drug use, tattooing also appears to contribute to HCV prevalence, with 4.7% of HCV patients reporting having received a tattoo (Chakravarti et al. 2013). We do not explicitly include tattooing in our model due to a paucity of data regarding the prevalence of tattooing among the general population in the country.

In addition to the above environments, we also incorporate a ‘home’ environment from which agents and families of agents originate. HCV transmission in the home environment occurs only through unprotected sex between paired agents. We now describe the details of agent movement and interactions through each of the above environments.

### 3.1.1 Home Environment

The home environment serves as a repository for agents and the ‘families’ they are part of. Agents interact within the home environment and move from the home environment to all other environments considered in the model.

Within this environment the only mode of HCV transmission is unsafe sex. While the contribution of unsafe sex to HCV prevalence is very low in the Indian context, we included it in the model mainly to accommodate future adaptations of the model to HCV/HIV comorbidity as well as to model hepatitis B transmission, which can be spread due to unsafe sex. The per-event probability of transmission of HCV via unprotected sex was estimated as  $3.57 \times 10^{-6}$  from a study of heterosexual partners in long-term relationships known as the HCV Partners Study (Osmond et al. 1993). This estimate is consistent with the fact that the contribution of unprotected sex to HCV prevalence is very low. We do not go into further detail regarding this environment due to space limitations, and mention only the key assumption involving this environment: we consider the unprotected sex that occurs in the home environment to be a proxy for all unsafe sexual interactions; hence we assume that the per-event probability estimated for heterosexual partners applies to all types of unsafe sexual activity. This may underestimate the contribution of unsafe sexual practices to HCV burden; hence we assume that paired agents engage in unprotected sex daily to include all sexual interactions that may occur external to the familial setting.

### 3.1.2 Medical Environment

This environment is modelled to encompass all medical procedures capable of transmitting HCV. These interactions include procedures such as injections, dental procedures, blood transfusions, surgeries, wound care, and renal dialysis. The model of infection transmission and agent interactions within the medical environment is depicted in Figure 2 below. The daily probability of visiting the medical environment was

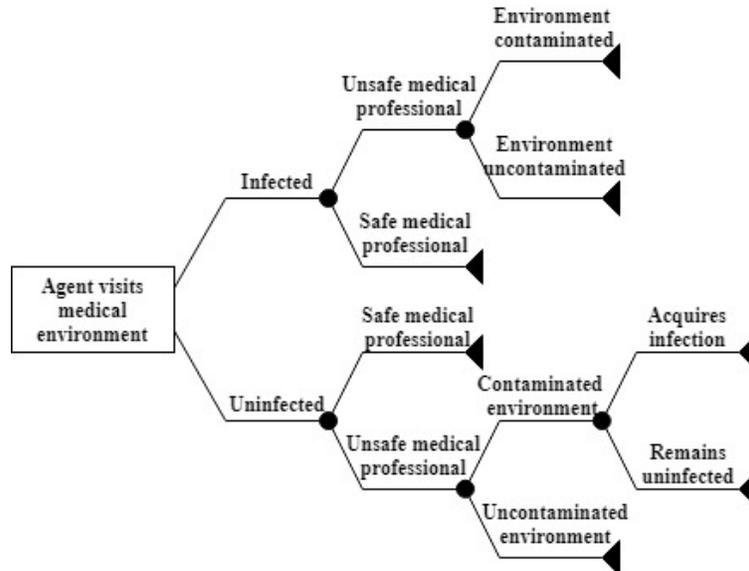


Figure 2: Medical environment interaction model.

estimated by considering the annual rates at which persons received injections, underwent dental procedures, surgeries and received blood transfusions, as these are the key procedures implicated in HCV transmission within the healthcare setting (Chakravarti et al. 2013). In India a person receives on average 5.1 injections per year (Atul et al. 2004), and visits a dentist approximately 0.982 times a year (Statista 2018). We estimate the per capita rate of receiving a blood transfusion per year to be 0.023 (NACO, 2014), and the annual per capita probability of undergoing a surgery is estimated to be 0.009 (Weiser et al. 2016). These

are unlikely to have a significant impact on the daily probability of visiting the medical environment, and hence we assume that an agent visits the medical environment 6 times a year, yielding a daily probability of approximately 0.017.

The number of medical professionals (40) was estimated using the 1:1800 doctor:patient ratio in India (Deo 2013). Note that our use of the term ‘medical professional’ reflects the fact that we are considering all personnel – doctors, nurses, phlebotomists, etc. – engaging in activities capable of transmitting HCV to a patient. The proportion of medical professionals engaging in unsafe medical practices was estimated as 50%, based on a survey of sterilization and disinfection practices in 791 dental clinics in India (Pala et al. 2016). We used this estimate instead of the estimates of unsafe injections in India - nearly 77.5% (Atul et al. 2004) - to reflect potential improvement in sterilization practice since publication of this study. We assume that the infection from the contaminated setting can be acquired only on the day of the contamination itself.

The per-event probability of acquiring an HCV infection from a contaminated medical environment was estimated by considering the probabilities of acquiring HCV infection from contaminated injections, surgical procedures, blood transfusions, and dental procedures. The probability of acquiring an HCV infection from unsafe surgical procedures was estimated as 33.3% from a small study in an Australian setting (Chant et al. 1994). This study was chosen due to the lack of larger studies for this infection mechanism in Indian or international contexts.

The per-event probability of acquiring HCV through contaminated injections was estimated as 0.018 by the Centers for Disease Control and Prevention, USA (CDC 2003). We could not identify literature that reported the risk of acquiring an HCV infection from a contaminated blood transfusion. Hence, we used the probability of acquiring an HIV infection from a contaminated blood transfusion as a proxy. This estimate was 0.925 (Patel et al. 2014) and given that HCV is a blood-borne disease, the use of HIV as a proxy, yielding the high probability of acquiring HCV from a blood transfusion appears reasonable.

We were unable to obtain reliable information in the literature regarding acquiring an HCV infection in a contaminated dental care setting. Therefore, we assumed that the per-event risk of acquiring an HCV infection in a contaminated dental care setting would be greater than that of a needle-stick injury and less than that in the surgical care setting, and hence we assumed a probability of 10%. We find the overall probability of acquiring an HCV infection in a contaminated medical care setting (estimated as 0.0317) by weighting the above probabilities with the annual probabilities of visiting the medical environment for each procedure type. Note that while we are able to use this estimate directly in the model, a degree of calibration of this parameter may be required when adapting the model for settings with markedly different HCV epidemiology.

### **3.1.3 Social Interaction Environment**

The social interaction environment was created primarily to enable interactions among IDUs and between IDUs and non-IDUs. IDUs (both infected and uninfected) can engage in drug use either solitarily or in groups, where injecting equipment sharing may occur, by which uninfected IDUs can acquire HCV. Interactions of IDUs with non-IDUs may also involve the conversion of a non-IDU into an IDU via an influence factor. Figure 3 depicts the agent interaction model in this environment. Only agents between the ages of 18 and 32 are assumed to interact in this environment. We believe this assumption is reasonable since this environment primarily serves as an area where IDUs can interact and convert non-IDUs into IDUs, and because we allow only agents between ages 18-32 to be IDUs, based on the report by Ambekar and Tripathi (2008) who find that more than 90% of IDUs are aged between 18-30 years. Non-IDU agents are assumed to visit the social interaction area once a week, and hence the daily probability of a non-IDU visiting this environment is approximately 0.142. Agents remain IDUs only for a three-year period (Ambekar and Tripathi 2008).

The per-encounter probability of an IDU effecting conversion of a non-IDU into an IDU (the influence factor) was estimated by calibrating an initial estimate to reach the IDU prevalence calibration target of 0.1% (Sood et al. 2018), and then using differential rates of employment among IDUs (26%) and non-IDUs

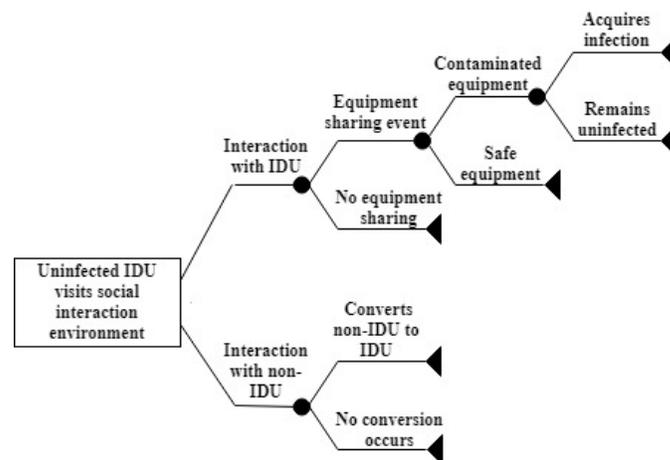


Figure 3: Social interaction environment model.

(16%) (Ambekar and Tripathi 2008) to arrive at estimates of  $3.58 \times 10^{-5}$  and  $2.29 \times 10^{-5}$  for interactions with unemployed and employed non-IDUs, respectively. The daily probability of an IDU visiting the social interaction environment was estimated as 0.744 by weighting together drug use frequencies obtained from Ambekar and Tripathi (2008).

We restrict interactions to only agents residing in the same geographical cluster, under the assumption that agents will engage in social interaction in nearby geographical areas. These clusters are determined using (geographical) distance-based K-means clustering of the population in Ludhiana, yielding three distinct geographical clusters. The cohort of agents in the model was distributed geographically such it matched the actual population distribution across the sub-districts of Ludhiana.

We then assumed that if IDUs engage in equipment-sharing, they do so in groups of 3. This is based on a study of IDU characteristics by Azim et al. (2008) who reported IDU network sizes of 1-2.8 in Bangladesh. We chose to use the data from study due to lack of Indian sources and because of its South Asian context.

Ambekar and Tripathi (2008) reported that 53% of IDUs reported sharing needles or injecting equipment at least once in the past (and hence not that they share during every injecting event). Therefore, we estimate via calibration (by initializing the parameter at 53% and adjusting downwards) that 20% of IDU interactions involve an equipment-sharing event.

The probability of acquiring HCV via sharing a needle with an infected IDU was estimated as 0.02, based on the probability of acquiring an HCV infection from a contaminated needle (Rolls et al. 2012). Finally, we note that we do not explicitly model the contribution of tattooing to HCV prevalence due to the paucity of data regarding tattooing practice in India. However, given that we use the upper limit of the IDU network size estimated by Azim et al. (2008), we are likely modeling more IDU interactions than is realistic. We made this modeling decision to account for tattooing interactions in addition to IDU interactions, assuming that the probability of acquiring HCV from a contaminated tattooing environment is similar to that from sharing needles.

### 3.1.4 Educational Environment

We incorporate the educational environment into the model for two reasons: (a) we assume that agents from all geographical clusters can attend the educational facility, thus permitting agent interactions from across clusters; and (b) to introduce the capability of modelling the impact of screening and public education programs aimed at increasing awareness about HCV among youth attending higher educational institutions.

We estimate that 20% of agents aged between 18 and 25 years visit the educational facility, based on government higher-education statistics (Ministry of Home Affairs 2016). Interactions between agents

(IDUs/no-IDUs) within the educational environment occur in the the same manner as they do in the social interaction environment.

### 3.2 Natural History and Treatment Model

We use a Markov model to simulate the natural history of HCV. We use a modified version of a previously validated model of HCV progression called the MATCH model, which was used by Aggarwal et al. (2017) and Goel et al. (2018) to assess the cost-effectiveness of DAAs in the Indian context. We modified the MATCH model to include the acute infection state, to incorporate SVR states explicitly within the model, and to consider relapse of HCV among patients who achieve SVR. Due to space limitations, and because the model is largely based upon a previously published model, we do not provide further details regarding the Markov model in this paper, and refer readers to Aggarwal et al. (2017) for more details.

We incorporate two types of treatment: (a) the previous standard of care (PSoC), a combination of pegylated interferon with ribavirin, and (b) DAAs. Patients with all genotypes can be treated with the PSoC, whereas DAAs are genotype-specific. We considered genotypes 1, 3 and 4 in the model, as they make up more than 99% of the HCV infections in India. The proportions of HCV patients with genotypes 1, 3 and 4 were estimated as 22%, 72% and 6% in accordance with the literature (Mehta et al. 2018). The PSoC was introduced into the model for infected patients 35 years into the burn-in period, as this treatment was introduced in India in the late nineties. A primary objective of the model is to evaluate the impact of HCV treatment with DAAs on population health. Therefore, we introduce DAAs for newly infected HCV patients at the end of the burn-in period (at 50 years), when we meet our calibration targets. Based on inputs from our clinical expert, we no longer consider the PSoC as a treatment option after the end of the burn-in period. We also assume that once an infected agent starts treatment, the agent no longer engages in interactions capable of transmitting infection since they are aware of the disease and have been educated about HCV transmission modes.

The treatment uptake rate for the PSoC is estimated to be 27% of all chronically infected patients (Gupta et al. 2015). Because DAAs are significantly more tolerable than the PSoC, we run analyses in the following section that involve studying the impact on epidemiological outcomes when the treatment uptake rate is increased.

The SVR rates for the PSoC and the DAAs considered in our analysis are provided in the tables below. We consider the combination DAA treatments of sofosbuvir plus ledipasvir (SOF + LED) and sofosbuvir plus daclatasvir (SOF + DAC). Note that SOF + LED is indicated only for G1 and G4 patients, whereas SOF + DAC is indicated only for G3 patients.

Table 1: Probabilities of achieving SVR by genotype with PSoC.

Transition	G1	G3	G4	Source/Notes
Non-cirrhotic chronic HCV→SVR	0.663	0.839	0.529	G1, G3: Sood et al. (2014); G4: Rao et al. (2014). Treatment duration: 48 weeks for G1 and G4, 24 weeks for G3
Compensated cirrhosis→SVR	0.286	0.492	0.529	

Before describing model calibration, we note that nearly all model parameters were estimated using data from disparate sources, many of which do not specify the degree of uncertainty around their data. Most estimates of uncertainty around model parameter estimates therefore are assumed (e.g.,  $\pm 50\%$ , or beta distribution parameters estimated from ratios). Therefore, for this preliminary version of the model, we have refrained from specifying uncertainty (e.g., confidence intervals) around our parameter estimates. However, for all final analyses, we will conduct sensitivity analyses to quantify the robustness of model outcomes to the (assumed) uncertainty around model parameter estimates.

Table 2: Probabilities of achieving SVR by genotype with SOF + LED and SOF + DAC.

Transition	G1, G4	G3	Source/Notes
Non-cirrhotic chronic HCV→SVR	1.000	0.985	Mehta et al. (2018). SOF + LED (G1, G4): 12 weeks, with RBV for decompensated cirrhosis patients; SOF + DAC (G3): 12 weeks
Compensated cirrhosis→SVR	1.000	0.967	
Decompensated cirrhosis→SVR	1.000	0.950	

#### 4 MODEL CALIBRATION AND SIMULATION EXPERIMENTS

The simulation is programmed on the Matlab computing platform (R2017b). The simulation is run on an Intel Xeon workstation with 4 cores and 32 gigabytes of memory.

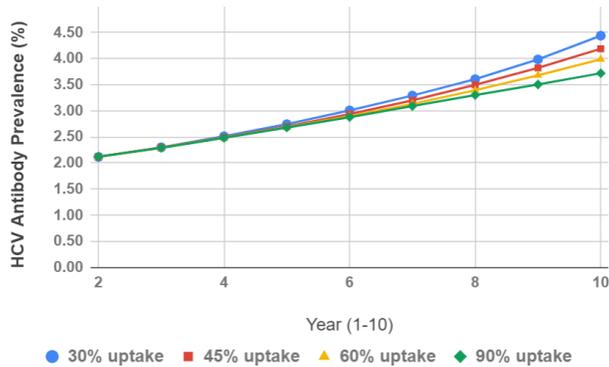
We calibrate the model to the following population-level outcomes reported for Ludhiana: (a) HCV antibody prevalence (number of persons in the population under consideration with antibodies to the HCV in their blood serum, including those with an active HCV infection and those who achieved SVR); (b) HCV RNA prevalence (number of persons with active HCV infection); and (c) IDU prevalence. The rationale for the choice of the Ludhiana district for calibration remains the same as that for its use as a geographical basis for the model.

The HCV antibody prevalence in Ludhiana in 2014 was reported in a recent study by Sood et al. (2018) as 1.8% (95% CIs were not provided). This study did not report HCV RNA prevalence for Ludhiana. However, the HCV RNA prevalence for the state of Punjab as a whole was reported as 2.6% (95% CI: 2.0-3.1%), and the HCV antibody prevalence was reported as 3.6% (95% CI: 3.0-4.2%) in the same study. Hence the HCV RNA prevalence target for Ludhiana was obtained as 1.30% using the ratio of RNA to antibody HCV prevalence for the state of Punjab. Finally, we obtained the IDU prevalence also from the study by Sood et al. (2018) as approximately 0.1% in the same year.

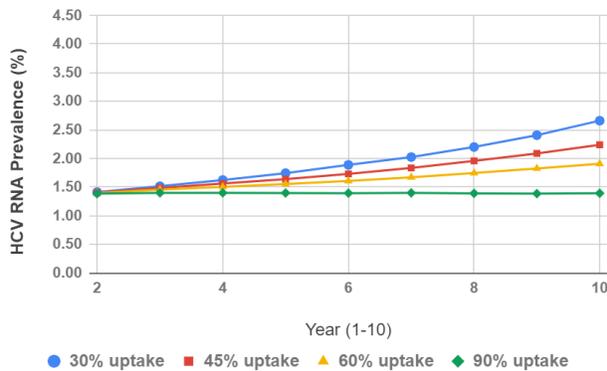
The probability of an IDU influencing conversion of a non-IDU into an IDU and the per-event probability of equipment sharing during an IDU injecting event are varied during model calibration. For these preliminary experiments, our calibration criteria were as follows: calibration targets within 95% CIs of estimated values; HCV RNA and IDU prevalences within 10% of targets; and HCV antibody prevalence within 15% of its target. Our model estimates HCV antibody prevalence in 2014 at 2.03% (95% CI: 1.78-2.28), and the HCV RNA prevalence at 1.37% (95% CI: 1.21-1.53). IDU prevalence from our model was also estimated at 0.104% (95% CI: 0.098-0.110). In all cases, the 95% CIs for our prevalence values encompass the calibration targets. The prevalences estimated by our model steadily increase with time over the burn-in period. While we do not have a longitudinal study of HCV prevalence in the Indian context that we can compare our results with, the clinical experts we have consulted are in agreement that HCV prevalence has been increasing with time in the Punjab province. We note here that the above results have been generated with the PSoC implemented from year 35 onwards in the burn-in period. Finally, at the level of an individual HCV patient, we compare the outcomes from the natural history component of the model to that estimated by Aggarwal et al. (2017). The authors estimated a survival period of 30.25 years for patients receiving no treatment. Our model provides an estimate of 30.75 life years (95% CI: 29.97-31.53).

We are now able to estimate the impact of treatment with DAAs on population-level outcomes. We do this by introducing the DAAs - SOF + LED and SOF + DAC - into the model after the burn-in period ends at various treatment uptake rates - at 30%, slightly higher than the current rate, up to 90% of those chronically infected - and then running the model for 10 years. Note that these DAAs are introduced simultaneously, with SOF + LED provided to G1 and G4 patients and SOF + DAC provided to G3 patients. The HCV antibody, RNA and IDU prevalences at each uptake rate are depicted in Figures 4a - 4c.

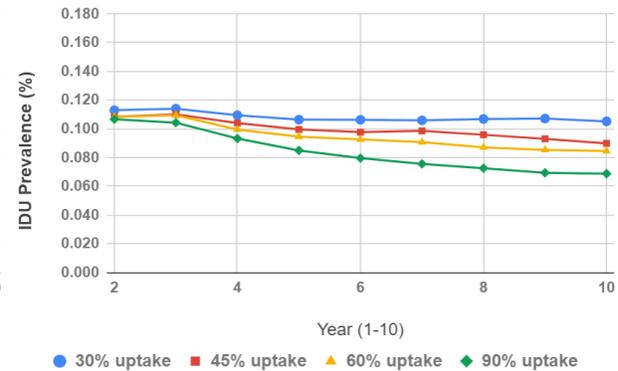
We see that it is only at treatment uptake rates of approximately 90% that control over the rate at which new cases of HCV (HCV RNA prevalence) occur is achieved. This is consistent with the field



(a) HCV antibody prevalence



(b) HCV RNA prevalence



(c) IDU prevalence

Figure 4: Effect of introducing DAAs at varying treatment uptake rates on epidemiological outcomes.

experience of our clinical expert, in that near-universal screening and treatment programs, especially for high-risk groups, are required to control HCV incidence. Note that given that we do not explore uptake rates between 60% and 90% in this set of experiments, we cannot determine the exact uptake rate at which RNA prevalence stops increasing. We plan to determine this in future experiments.

We also see that the IDU prevalence decreases with uptake rate - this is likely because we assume that an IDU stops injecting drug use once he/she begins treatment. In future analyses, we plan to conduct sensitivity analyses around this and the broader assumption that agents who start treatment cease transmission-capable behaviour, given the existence of evidence to the contrary in the Western setting among IDUs (He et al. 2016). However, this result illustrates the benefit of the ‘treatment-as-prevention’ notion for infectious diseases - the decrease in IDU prevalence due to screening and treatment also impacts the spread of the disease via attenuation of a key transmission mode.

The above are preliminary experiments intended to demonstrate potential uses of the model. We plan to conduct multiple analyses using the model: (a) determining the uptake rate at which the WHO incidence target is achieved; (b) cost-effectiveness of DAAs taking their epidemiological impact into consideration; (c) cost-effectiveness of harm-reduction and public health education programs for HCV.

## 5 DISCUSSION

In this paper, we present an agent-based model of HCV transmission dynamics developed for the Indian context. Due to space limitations, we present only the key features of the model in this paper, and not a complete description - for example, we have not been able to provide natural history model details. We

also present preliminary simulation experiments conducted using the calibrated model. A list of planned analyses using the model is provided in Section 4. In addition, we anticipate that the model can be adapted for simulating the transmission dynamics of HIV and HBV as well.

Among possible enhancements to the model, we are working on the incorporation of IDU interaction networks based on real-world patterns of injecting drug use, similar to the work by Rolls et al. (2012). The incorporation of such a network will allow development of an optimal screening, surveillance, and targeted education campaign. Also, the model will be calibrated to HCV prevalence in India in its entirety when considering DAA cost-effectiveness from the Indian perspective as a whole.

A key challenge encountered in developing the model involves lack of data regarding certain aspects of HCV transmission and epidemiology in India. We have discussed these in Section 3, but a key aspect involves the lack of longitudinal data regarding HCV prevalence in the Indian context. Therefore, we were unable to validate the prevalence values generated by the model over time to the actual trends in HCV prevalence in the Indian context. We instead calibrate our model by trying to match the prevalence values at the end of the burn-in period to those reported in the most recent studies regarding HCV prevalence in the Indian context. Since the analyses with DAAs will be conducted only after the end of the burn-in period, if the state of the simulation - represented by the overall population of agents, the HCV antibody and RNA prevalences, the IDU prevalence, and the relative contributions of various transmission modes to HCV prevalence - at the end of the burn-in period approximates that reported in the studies chosen for validation, we can use the model to conduct analyses regarding the impact of HCV interventions on the future state of the system.

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