SUPPLEMENTARY APPENDIX

Model structure

In this present study, we used a compartment model to simulate the dynamic transmission of HCV among populations and the natural history of hepatitis C, as well as the stages of engagement in the HCV cascade of care. The model structure is shown in Supplementary Figure 1. We classified the population into susceptible (never infected and susceptible to HCV), infected (chronically infected), and recovered (previously infected and could be reinfected) groups on the basis of HCV infection status. Both susceptible and recovered individuals can become infected at a rate (λ) that varies over time and is dependent on age, risk behaviors, and the prevalence of hepatitis C. A proportion (δ) of newly infected individuals spontaneously clear the infection, recover, and become susceptible to HCV again. The remaining newly infected individuals (1-δ) become chronically infected, and would be positive if tested for RNA. With the outcomes of death or simulated endpoints, individuals transitioned between several states: susceptible, recovered, infected, fibrosis (stages F0–F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC) states to death or simulated endpoints. The cascade of care consisting of screening, diagnosis, and treatment was also included in the model (unscreened, undiagnosed, diagnosed, receiving treatment, treatment success and treatment failure). The HCV screening process in this model involved initial screening of the population via the Ab testing, and if the Ab test was positive, then an HCV RNA test was performed to identify the infection status. An individual was diagnosed with HCV infection if the RNA test was positive or was considered previously infected if it was negative. The model population was categorized on the basis of the following factors: injection drug use status (PWID, ex-PWID, and never [general population]), age (0–19 years, 20–34 years, 35+ years), and sex. We assumed that only individuals aged 20–34 years were likely to initiate drug injection, changing from the general population to PWID.[1] With aging, PWID may either continue their drug use or cease it, with the latter group transitioning into ex-PWID. The parameter estimates and data inputs for the model are presented in Supplementary Table 1.

Model equations

We incorporated HCV transmission, the cascade of care, the chronic hepatitis C disease progression process, and demographics into the mode. The complete model specifically consisted of 1050 nonlinear ordinary differential equations and was solved numerically via the fourth-order Runge–Kutta method with a step size of 0.01 years. To simplify the equations, we used *i, j,* and *d* subscripts to denote the sex, age, and disease status of the population;

Sex:
- Male (i=1);
- female (i=2);

Population group:
- Aged 0-19 (j=1);
- Aged 20-34, non-PWID (j=2);
- Aged 20-34, PWID (j=3);
- Aged 20-34, ex-PWID (j=4);
- Aged35+, non-PWID (j=5);
- Aged35+, PWID (j=6);
- Aged35+, ex-PWID (j=7);

Disease progression:
- Health (d=0);
- No fibrosis (F0, d=1);
- Portal fibrosis without septa (F1, d=2);
- Portal fibrosis with few septa (F2, d=3);
- Numerous septa without cirrhosis (F3, d=4);
- Cirrhosis (F4, d=5);
- Decompensated cirrhosis (DC, d=6);
- Hepatocellular carcinoma (HCC, d=7)

Briefly, the model was constructed on the basis of a Susceptible (never infected)-Recovered (previously infected and recovered, may be reinfected)-Infected (currently infected and infectious)-Treatment (S-R-I-T) model structure and was further divided into a total of 15 compartments on the basis of screening and treatment status.

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Susceptible population

$S^{p}_{i,j,d}(t)$ = Never screened with the Ab test

$S^{r}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab-)

Recovered population

$R^{p}_{i,j,d}(t)$ = Never screened with the Ab test

$R^{r}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab+), not tested for RNA

$R^{k}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab+), and tested for RNA (result RNA-)

$R^{c}_{i,j,d}(t)$ = SVR

Infected population

$I^{p}_{i,j,d}(t)$ = Never screened with the Ab test

$I^{r}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab+), not tested for RNA

$I^{u}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab+), current RNA status unknown

$I^{k}_{i,j,d}(t)$ = Previously screened with the Ab test (result Ab+), tested for RNA (result RNA+), diagnosed as HCV-infected patients

$I^{c}_{i,j,d}(t)$ = Reinfection after SVR, current RNA status unknown

$T^{f}_{i,j,d}(t)$ = Failure to achieve SVR

Treatment population

$T^{1}_{i,j,d}(t)$ = First treatment

$T^{2}_{i,j,d}(t)$ = Second treatment

$T^{3}_{i,j,d}(t)$ = Third treatment

We let

$$A_{i,j,d} = (S^{p}_{i,j,d}, S^{r}_{i,j,d}, R^{p}_{i,j,d}, R^{r}_{i,j,d}, R^{k}_{i,j,d}, I^{p}_{i,j,d}, I^{r}_{i,j,d}, I^{u}_{i,j,d}, I^{k}_{i,j,d}, T^{1}_{i,j,d}, T^{2}_{i,j,d}, T^{3}_{i,j,d}, R^{c}_{i,j,d}, I^{c}_{i,j,d}, T^{f}_{i,j,d})$$

$M(A_{i,j,d})$ represents the movement of people due to aging, injection drug use, cessation, and death (refer to Supplementary Fig. 1 for the demographic structure).

$$M(A_{i,j,d}) = -\Big(\underbrace{\overbrace{a_1}^{\text{if } j=1} + \overbrace{a_2}^{\text{if } j=2,3,4}}_{\text{ageing}} + \underbrace{\overbrace{\varphi_{i,d}}^{\text{if } j=2}}_{\text{injecting drugs}} + \underbrace{\overbrace{v}^{\text{if } j=3,6}}_{\text{cessation}} + \underbrace{Dr_{i,j} + \overbrace{\mu}^{\text{if } j=3,6}}_{\text{death}}\Big)A_{i,j,d} + \begin{cases} b_i \text{ if } j=1 \text{ (birth)} \\ a_1 A_{i,j-1,d} \text{ if } j=2 \\ a_2 A_{i,j-3,d} \text{ if } j=5,6,7 \\ \varphi_i A_{i,j,d} \text{ if } j=3 \\ v_i A_{i,j,d} \text{ if } j=4,7 \end{cases}$$

$D(A_{i,j,d})$ represents the disease progression of individuals with chronic HCV infection (refer to Supplementary Fig. 1). Notably, patients who reached SVR before stage F4 ($R^{c}_{i,j,d}$, $d < 5$) remained in their current disease state without disease progression in the model

$$D(\mathrm{A}_{i,j,d}) = \begin{cases} -\xi_{F0F1}A_{i,j,d} \text{ if } d=1 \\ \xi_{F0F1}A_{i,j,d-1} - \xi_{F1F2}A_{i,j,d} \text{ if } d=2 \\ \xi_{F1F2}A_{i,j,d-1} - \xi_{F2F3}A_{i,j,d} \text{ if } d=3 \\ \xi_{F2F3}A_{i,j,d-1} - \xi_{F3F4}A_{i,j,d} \text{ if } d=4 \\ \xi_{F3F4}A_{i,j,d-1} - (\overbrace{\rho_{F4DC}}^{\text{if SVR}}\xi_{F4DC} + \overbrace{\rho_{F4DC}}^{\text{if SVR}}\xi_{F4HCC} + \xi_{F4d})A_{i,j,d} \text{ if } d=5 \\ \xi_{F4DC}A_{i,j,d-1} - (\overbrace{\rho_{DCHCC}}^{\text{if SVR}}\xi_{DCHCC} + \xi_{DCd})A_{i,j,d} \text{ if } d=6 \\ \xi_{F4HCC}A_{i,j,d-1} + \xi_{DCHCC}A^{d-1}_{i,j} - \xi_{HCCd}A_{i,j,d} \text{ if } d=7 \end{cases}$$

For sex categories i=1, 2, population group j=1,...,7 and disease stage d=0,...,7, the equations describing each care cascade compartment are:

$$\frac{dS^{p}_{i,j,d}}{dt} = M(S^{p}_{i,j,d}) - (x_1 + \lambda_{i,j})S^{p}_{i,j,d}$$

$$\frac{dS^{r}_{i,j,d}}{dt} = M(S^{r}_{i,j,d}) + x_1 S^{p}_{i,j,d} - \lambda_{i,j}S^{r}_{i,j,d}$$

$$\frac{dR^{p}_{i,j,d}}{dt} = M(R^{p}_{i,j,d}) + \delta\lambda_{i,j}S^{p}_{i,j,d} - [x_1 y_1 + (1-\delta)\lambda_{i,j}]R^{p}_{i,j,d}$$

$$\frac{dR^{r}_{i,j,d}}{dt} = M(R^{r}_{i,j,d}) + \delta\lambda_{i,j}S^{r}_{i,j,d} - [x_2 y_2 + (1-\delta)\lambda_{i,j}]R^{r}_{i,j,d}$$

$$\frac{dR^{k}_{i,j,d}}{dt} = M(R^{k}_{i,j,d}) + x_1 y_1 R^{p}_{i,j,d} + x_2 y_2 R^{r}_{i,j,d} - (1-\delta)\lambda_{i,j}R^{k}_{i,j,d}$$

$$\frac{dI^{p}_{i,j,d}}{dt} = M(I^{p}_{i,j,d}) + D(I^{p}_{i,j,d}) + (1-\delta)\lambda_{i,j}S^{p}_{i,j,d} + (1-\delta)\lambda_{i,j}R^{p}_{i,j,d} - x_1 y_1 I^{p}_{i,j,d}$$

$$\frac{dI^{r}_{i,j,d}}{dt} = M(I^{r}_{i,j,d}) + D(I^{r}_{i,j,d}) + (1-\delta)\lambda_{i,j}S^{r}_{i,j,d} + (1-\delta)\lambda_{i,j}R^{r}_{i,j,d} - x_2 y_2 I^{r}_{i,j,d}$$

$$\frac{dI^{u}_{i,j,d}}{dt} = M(I^{u}_{i,j,d}) + D(I^{u}_{i,j,d}) + (1-\delta)\lambda_{i,j}R^{k}_{i,j,d} - y_3 I^{u}_{i,j,d}$$

$$\frac{dI^{k}_{i,j,d}}{dt} = M(I^{k}_{i,j,d}) + D(I^{k}_{i,j,d}) + x_1 y_1 I^{p}_{i,j,d} + x_2 y_2 I^{r}_{i,j,d} + y_3 I^{u}_{i,j,d} - \tau I^{k}_{i,j,d}$$

$$\frac{dT^{1}_{i,j,d}}{dt} = M(T^{1}_{i,j,d}) + D(T^{1}_{i,j,d}) + \tau I^{k}_{i,j,d} - \omega T^{1}_{i,j,d}$$

$$\frac{dT^{2}_{i,j,d}}{dt} = M(T^{2}_{i,j,d}) + D(T^{2}_{i,j,d}) + (1-\alpha)\omega T^{1}_{i,j,d} - \omega T^{2}_{i,j,d}$$

$$\frac{dT^{3}_{i,j,d}}{dt} = M(T^{3}_{i,j,d}) + D(T^{3}_{i,j,d}) + (1-\alpha)\omega T^{2}_{i,j,d} - \omega T^{3}_{i,j,d}$$

$$\frac{dR^{c}_{i,j,d}}{dt} = M(R^{c}_{i,j,d}) + D(R^{c}_{i,j,d}) + (T^{1}_{i,j,d} + T^{2}_{i,j,d} + T^{3}_{i,j,d})\alpha\omega - (1-\delta)\lambda_{i,j}R^{c}_{i,j,d}$$

$$\frac{dI^{c}_{i,j,d}}{dt} = M(I^{c}_{i,j,d}) + D(I^{c}_{i,j,d}) + (1-\delta)\lambda_{i,j}R^{c}_{i,j,d} - y_3 I^{c}_{i,j,d}$$

$$\frac{dT^{f}_{i,j,d}}{dt} = M(T^{f}_{i,j,d}) + D(T^{f}_{i,j,d}) + (1-\alpha)\omega T^{3}_{i,j,d}$$

Model calibration and validation

We calibrated the model through a three-stage process using demographic data, epidemiological characteristics of PWID, anti-HCV prevalence among PWID, and treatment

numbers, all sourced from published literature, government reports, and surveillance data. First, we calibrated the estimated population size with a simple total population model to match the government-reported population changes in China between 1950 and 2021.[2] Second, the total population model was extended on the basis of age and injection drug use status to calibrate the age distribution of the population in 2021 and the PWID prevalence.[3,4] Finally, we constructed a complete model as shown in Supplementary Figure 1, including HCV transmission, hepatitis C natural history, and the care cascade. The age-specific anti-HCV prevalence in 2006, the anti-HCV prevalence among PWID in 2010, and the treatment numbers from 2009 to 2014 were calibrated by re-running this complete model.[5,6] The data used for calibration are shown in Supplementary Table 2. The model outputs are consistent with the calibration data, and the calibration results are shown in Supplementary Figure 2.

We compared the model outputs with data not used for calibration or parameterization to externally validate the model. The model-predicted overall prevalence of anti-HCV in 2015 was estimated at 0.98% (0.89–1.04%), within the range of expert estimates of 1.21% (0.93–1.49%)[7] (Supplementary Fig. 3). The model predicted an overall HCV prevalence of 0.63% (0.60–0.72%) in 2015, within the reported range of 0.7% (0.5–0.8%)[7] (Supplementary Fig. 4). In addition, to further assess the accuracy of the model in responding to HCV incidence, we compared the number of diagnosed cases per year estimated by the model with the number of diagnosed HCV cases reported annually by the Chinese Centre for Disease Control and Prevention (CCDC).[8] The results showed that the number of diagnosed cases estimated by our model was consistent with the data reported by the CCDC (Supplementary Fig. 5), indicating that the model reasonably captured the trend of diagnosed HCV cases over time. To approximate the number of new infections, we adjusted the CCDC reported number of new HCV cases for underreporting and asymptomatic infection using a diagnosis rate of 22.51%.[9] This adjusted estimate was consistent with the annual incidence predicted by our model, further supporting its accuracy in capturing HCV transmission dynamics in China (Supplementary Fig. 6).

Treatment regimens

In China, interferon (IFN) or pegylated interferon (Peg-IFN) plus ribavirin (RBV) was recommended by clinical guidelines as the conventional treatment for HCV infections before 2018.[10] Owing to the high efficacy of direct-acting antivirals (DAAs), the guidelines were updated in 2019 to recommend DAAs as first-line treatments for hepatitis C patients[11]. In addition, the average DAAs price were reduced by 85% following China's national negotiation of drug prices, significantly increasing the accessibility of DAAs in China.[12] Therefore, we modelled different treatment phases: treatment with Peg-IFN+RBV for 48 weeks (pre-2018), treatment with DAAs for 12 weeks for patients with stages F0-F4 and treatment with DAAs for 24 weeks for patients with DC-HCC (post-2018). According to previous studies, the SVR rate of Peg-IFN + RBV varies by disease stage, with rates of 0.54 pre-F3 and 0.36 post-F3.[13-15] With the introduction of DAAs into the market in China in 2018, we assumed that the SVR rate had improved to 90% (85–95%), which is supported by clinical trials that typically reported SVR rates of approximately 90% and above.[16-19] According to the Guideline for the Prevention and Treatment of Hepatitis C (2022 version), treatment with the pangenotypic regimen of sofosbuvir/velpatasvir (SOF + VEL) was used in the model as it has a high SVR rate across genotypes.

Simulation strategies

In the present study, we evaluated strategies for screening, diagnosing, treating and manag hepatitis C in China, with a focus on scaling up screening and treatment. For each simulated strategy, individuals who had never been screened would receive their first anti-HCV antibodie (Ab) test at set primary screening rates (6%, 8%, 10%, 12% and 14%). Individuals who tested positive for Ab needed confirmation through an HCV RNA test, and a positive RNA test confirmed the diagnosis of HCV infection. For non re-screening strategies, individuals would undergo a single screening, after which there would not be any further screenings. For re-screening strategies, individuals who previously tested Ab- would be re-screened, starting with the Ab test. Moreover, individuals who previously tested Ab+ but RNA- (e.g., spontaneous clearances or cured cas-

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es) would be re-screened, starting with the RNA test. Considering that daily social behaviors and habits may change in individuals diagnosed with HCV infection, we assumed that their risk of HCV transmission would be reduced by 50% (40–60%).[20] People diagnosed with infection receive initial treatment at set treatment rates (80%, 85%. 90%, 95%). For this model, we assumed that infected individuals receiving treatment would not transmit HCV,[21] and that patients with hepatitis C who failed initial treatment would be able to be re-treated for a maximum of 3 treatments. Patients who achieved an sustained virological response (SVR) prior to the F4 stage were assumed to be at no risk of progression, whereas those who achieved an SVR at or after the F4 stage had a lower risk of developing liver disease. For patients who fail to achieve SVR, the risk of progression is equal to that of untreated patients.