Supplementary material

Treatment scale-up to achieve global hepatitis C virus incidence and mortality elimination targets: a cost-effectiveness model

Nick Scott, Emma McBryde, Alexander Thompson, Joseph Doyle, Margaret Hellard

Appendix A: Detailed methodology

Model description

We used an open deterministic compartmental model of HCV transmission and liver disease progression extending the model from Scott et al. [1] (Figure A1). METAVIR scores were used to classify stages of liver disease, and individuals were distinguished as either: acutely infected (**A**); chronically infected with liver fibrosis in stage **F0**–**F4**; chronically infected with decompensated cirrhosis (**DC**); chronically infected with hepatocellular carcinoma (**HCC**); first year or more than one year post liver transplant (**LT1** and **LT2** respectively); chronically infected and in treatment achieving sustained viral response (SVR) (**T0 to T4**—treated from liver fibrosis stage F0 to F4 respectively); or susceptible (**S0 to S4**—infection naïve or previously achieving spontaneous clearance or SVR through treatment from liver fibrosis stage F0 to F4 respectively). Individuals were classified by injecting drug use status (i=1 indicating current PWID, i=0 indicating former PWID) and whether they had previously failed treatment (j=0 indicating never failed treatment, j=1 indicating failed treatment), and the model was stratified by age categories (20–24, 25–29, 30–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85+) that were assumed to mix proportionally.

People in the model moved between identical compartments of the i stratification due to cessation or relapse into injecting drug use at fixed rates η and $r_{relapse}$ respectively. All-cause mortality occurred for each compartment at a rate depending on age and injecting drug use status (Table B1), and mortality rates for the DC, HCC, LT1 and LT2 compartments were increased by $r_{DCdeath}$, $r_{HCCdeath}$, $r_{LT1death}$ and $r_{LT2death}$ respectively. The model assumed that people with liver fibrosis in stage F3 or less did not have an increased risk of mortality to those not infected (however they did have decreased health utilities, see Table B3). The total population was held constant by the entry of new PWID assumed to be 20 years old, susceptible and previously untreated ($S0_{1,0}$).

Susceptible PWID became acutely infected at a rate proportional to: a fixed value π; the proportion of PWID who were currently infected; and a relative incidence function capturing changes to the Australian drug markets (see below). Newly infected PWID with no prior liver fibrosis spent a period $1/r_{AF0}$ in the acute stage of infection before a proportion δ spontaneously cleared infection and again became susceptible to infection, while the remaining proportion (1-δ) became chronically infected and entered liver fibrosis stage F0. Re-infection is a significant issue among PWID [2] and was modelled to occur at the same rate as initial infection. If PWID who had previously been cured were re-infected then they re-entered the furthest disease stage they had progressed to, and were assumed to not spontaneously clear infection. Spontaneous clearance among these individuals has

been observed, however it occurs at a reduced rate since they previously failed to spontaneously clear. Assuming that re-infection that occurs following treatment always fails to spontaneously clear will lead to higher estimates of required treatment numbers and conservative estimates of cost-effectiveness. Liver disease progressed at rates obtained from the literature (Table B2), and average liver transplant wait times were modelled ($1/r_{DCLT}$ and $1/r_{HCCLT}$ from the DC and HCC stages respectively).

A proportion p_{com} of current PWID were assumed to adhere to treatment, so that for a given treatment efficacy α, the proportions α and αp_{com} of former PWID and current PWID respectively achieved SVR when offered treatment. Individuals who were assumed to achieve SVR moved to the treatment compartment matching their liver fibrosis stage (T0 to T4) and after a period ω, achieved SVR and moved to the corresponding susceptible compartment (S0 to S4). The remaining proportions of current and former PWID ($1-\alpha$ and $1- \alpha p_{com}$ respectively) who failed treatment were moved to the j=1 stratification and where they continued liver disease progression without any re-treatment. Re-treatment of these individuals with alternate therapies was modelled by extending treatment durations and increasing treatment efficacy. No regression of liver fibrosis was modelled following SVR; however people who were treated and achieved SVR from the F4 stage were modelled to have some risk of decompensation or of developing hepatocellular carcinoma, moving to the DC and HCC compartments at rates r_{SVR4DC} and $r_{SVR4HCC}$ respectively.

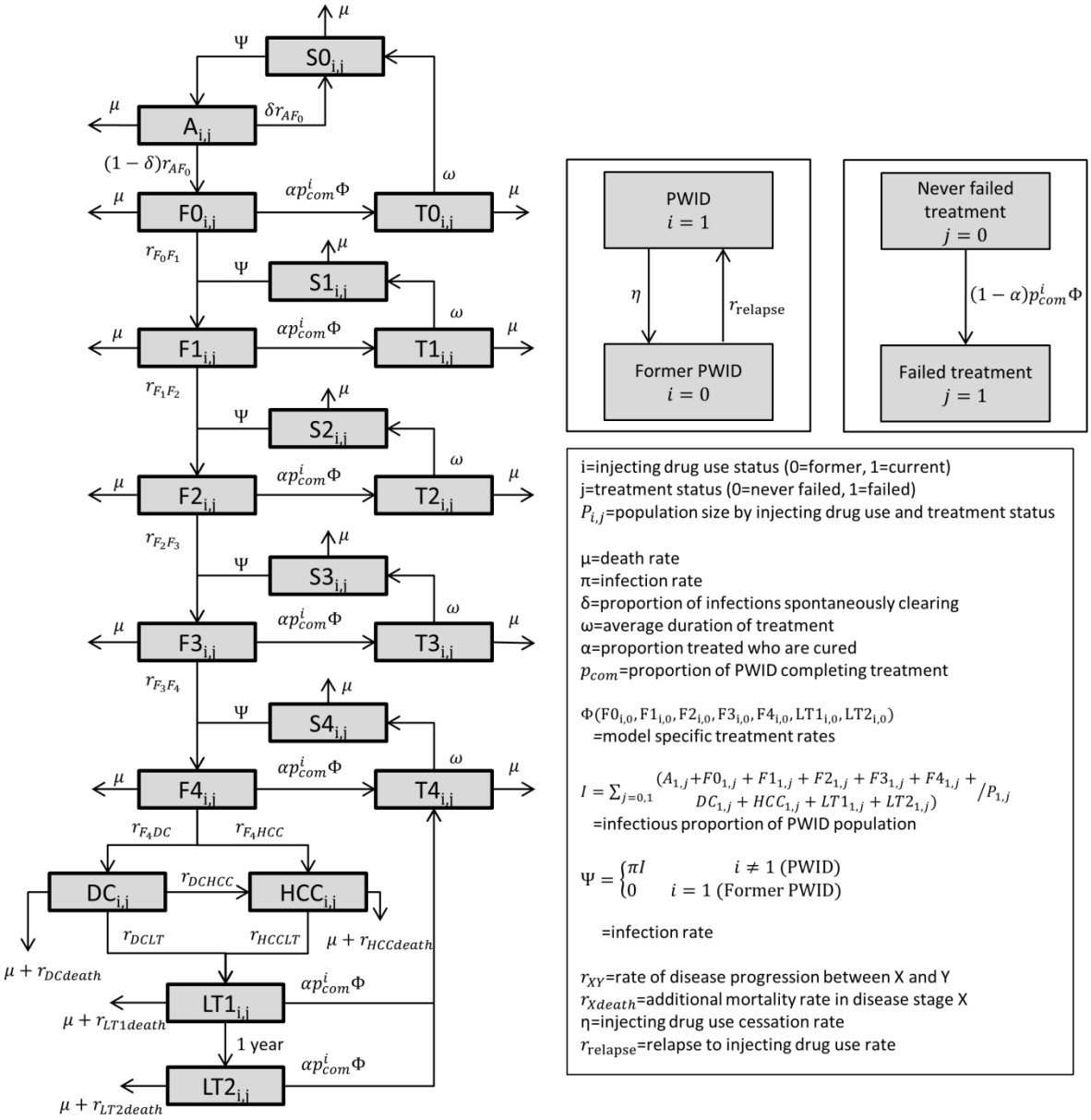

Figure A1: Model schematic

Relative incidence function

Following a period of increasingly available and higher purity heroin in Australia prior to 2000 [3], a dramatic supply reduction in 2001 resulted in more expensive and lower purity heroin [4, 5], which led to an overall reduction in the amount of injecting that occurred [6]. These changes to the Australian drug market are believed to have influenced the relative rates of HCV transmission and mortality among PWID over time, both of which are relevant to the current proportions of HCV-infected individuals in early versus advanced stages of liver disease. To achieve a more accurate starting point for the distribution of disease stages, and to attempt to more accurately model the

HCV epidemic dynamics, the model was started in 1950 and both the mortality rates among PWID and the infection parameter π have been scaled as follows [7]. We defined a function *rel_inc* (Figure A2) to approximate relative drug market activity and associated risks during this period: the function *rel_inc* is assumed to linearly increase from 1 to 2.5 between 1950 and 2000, when it linearly reduces to 1 in 2005 and remains constant. The height was determined by taking the ratio of mortality associated with injecting drug use, which increased throughout this period by a factor of approximately 2.25, to the number of injecting drug users, which only increased by a factor of approximately 1.5 [8].

For several alternate relative incidence functions, the modelled prevalence of chronic HCV among PWID over time and the percentage of HCV-infected PWID with early (stage F0/F1) liver disease in 2015 are compared to epidemiological data and outputs using the original *rel_inc* function in Table A1.

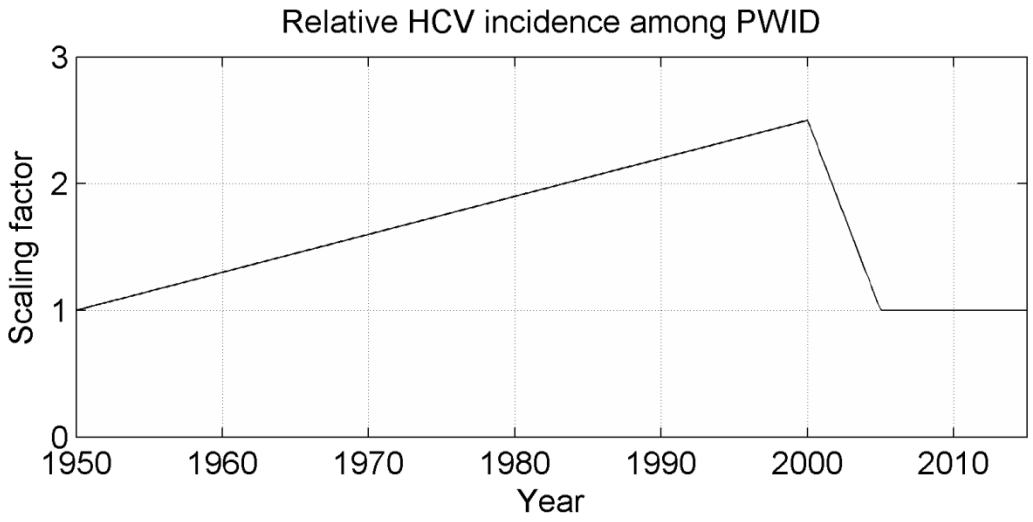

Figure A2: Relative incidence function. To represent relative changes to drug market activity between 1950 and 2015, the HCV transmission risk parameter among PWID was scaled by a factor *rel_inc*.

Using the *rel_inc* function from Figure A2, the model was able to produce a peak in prevalence among PWID of approximately 56% in 2003 and resulted in 61% of HCV-infected PWID in 2015 having early liver disease (Table A1). This is a reasonable fit to the estimated peak in prevalence of 55% in the early-2000s [9] and the estimated 66% of HCV-infected PWID being in F0/F1 stages [10].

When a constant function or a function where the increase in relative incidence only started in the 1990s was used, no peak in HCV prevalence among PWID was reproduced. When the original function was used but with an increased height, the resulting peak in prevalence was too high, and the percentage of PWID with early liver disease was lower than with the original version. When a function with relative incidence constant until 2000, after which it halved was used, a realistic peak in prevalence was produced, but with a slightly smaller percentage of PWID in an early liver disease stage than the original version.

Table A1: Sensitivity of the relative incidence function on model fit. In each case chronic HCV prevalence among PWID is 50% in 2015.

Name	Description of rel_inc function	Percentage of PWID in stage F0/F1 in 2015	Percentage of PWID in stage F3/F4 in 2015	Peak in prevalence among PWID
Original	Increase from 1 to peak of 2.5 in 2000; decrease to 1 in 2005; constant onwards.	61%	11%	56% in 2003
Peak only in 1990s	1 until 1990; increase to 2.5 in 2000; decrease to 1 in 2005; constant onwards.	69%	7%	No peak; monotonic increasing
Increased height	Original, but with height of peak increased to 4.	56%	12%	63% in 2002
Flat	Constant (=1) for whole period.	69%	8%	No peak; monotonic increasing
Flat then reduced	2 until 2000; decrease to 1 in 2005; constant onwards.	57%	14%	57% in 2002

Model calibration

The model was started in 1950 with a population of 1000 20-24 year olds, 44% of whom were current PWID and 56% of whom were former PWID (the combination of cessation, relapse and mortality rates meant that these were the equilibrium proportions; the ratio of occasional to regular injecting drug users has remained stable between 1950 and 2015 [11], so the rates of cessation from and relapse into injecting drug use throughout this period have been approximated as constant). HCV-infection was then introduced to 10% of PWID in the model (N=44). The model was initially run without any treatments to approximate the currently low uptake under old treatment regimens [12, 13, 14, 15], and chronic HCV prevalence among current injectors was calibrated to 50% [9] in 2015 by varying the infection parameter π.

In Australia, an estimated 230,000 people are chronically infected with HCV [16], and an estimated 184,000 (80%) of these individuals acquired their infection through injection drug use [11]. It is also estimated that the prevalence of chronic HCV is 50% [9] among approximately 80,000 current PWID in Australia [11], and so when calculating outputs the model populations were scaled to represent 40,000 HCV-infected PWID and 144,000 HCV-infected former PWID, as described in the Scenarios section. Non-IDU acquired infections were not considered in the model (see discussion in main body), but the proportion of all HCV infections that were IDU-acquired was varied in the sensitivity analysis. The model burn-in period and projected burden of disease with no intervention (base case) is shown in Figure A3—neither the HCV prevalence or disease distribution are assumed to be in equilibrium in 2015.

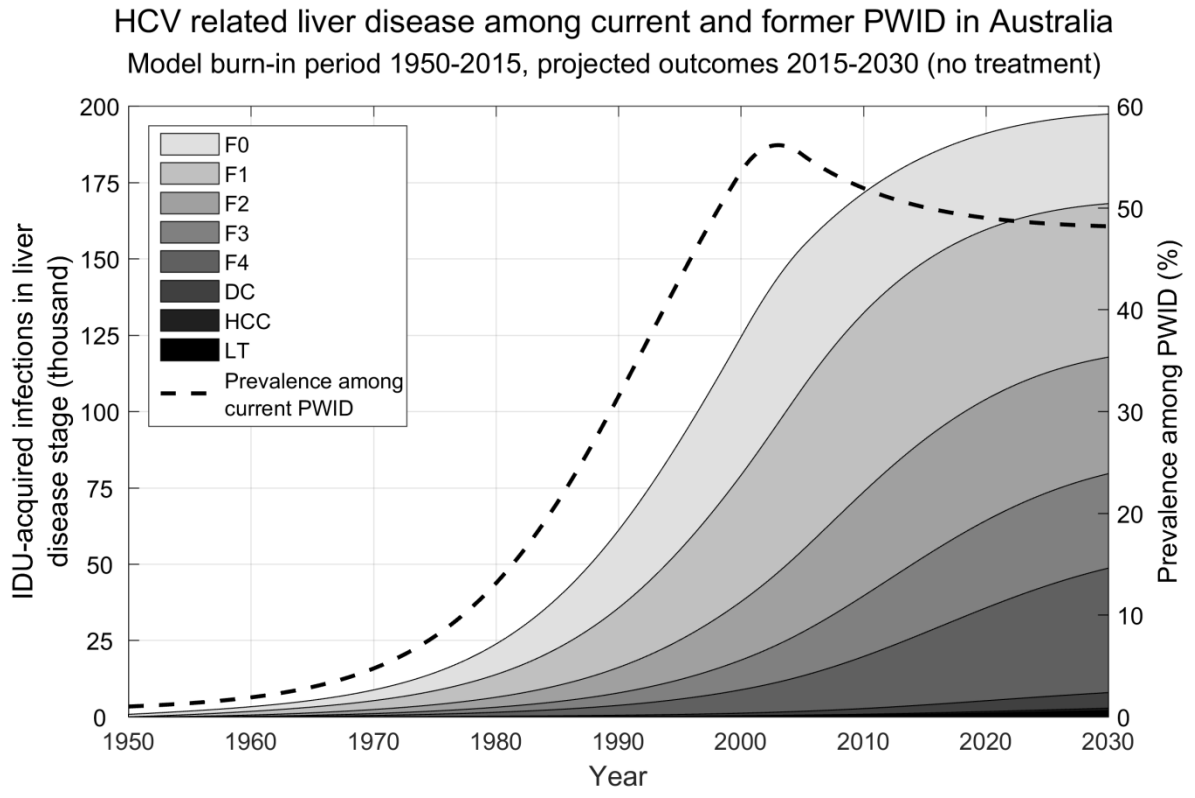

Figure A3: Estimated burden of HCV-related liver disease 1950-2030. Model burn-in period from 1950 to 2015 includes changes to the relative incidence of HCV according to Figure A2.

Treatment scale-up

We assumed that when implemented, a fixed total number of treatment courses would be available per year, and that this annual number of treatments would continue to be available for the next 15 years even if not utilised [17, 18, 19, 20, 21]. We considered treatment scale-up to be in the range 1,000 courses per year (representing 0·5% of IDU-acquired infections or 12·5/1000 PWID) to 10,000 courses per year (representing 5% of IDU-acquired infections or 125/1000 PWID), which is consistent with previous models that have considered treatment scale-up among PWID of 2-16% of the infected population per year [17, 19, 22].

Harm reduction scale-up

In Australia between 2000 and 2010 needle and syringe programs (NSPs) are estimated to have reduced HCV infections by approximately 15–43%, for a total cost of AUS$245 million [23]. Moreover, modelling studies indicate that further scale-up of harm reduction interventions such as NSPs and opioid substitution therapy (OST) could reduce HCV prevalence by up to a third [24]. For this analysis a more modest scale-up of NSP and OST programs was assumed, which would reduce the risk of new infections by 10%. This was implemented by scaling the infection rate parameter from 2015 onwards to 90% of its pre-2015 value for all scenarios, including the base case of no treatment. Therefore the (non-healthcare) costs of this scale-up were not included in the analysis.

Parameters

Population, HCV-related, health-related and cost parameters are provided in Appendix B.

As the cost of DAAs is remains uncertain, we assumed a base scenario and tested upper and lower bounds in the sensitivity analysis. The base value was taken to be AUS$30,000 (for 12 weeks of treatment) for genotype 1 and 2, and AUS$60,000 (for 24 weeks of treatment) for genotype 3, averaged over the Australian genotype distribution (Appendix B). The upper and lower bounds tested in the sensitivity analysis were AUS$20,000 and AUS$40,000 for 12 weeks of therapy respectively (and double for 24 weeks of therapy, again averaged over the Australian genotype distribution).

Scenarios

Base case (best supportive care)

No treatments were available. Total discounted cost and QALYs were calculated separately for current and former PWID, before being combined.

For the population of current PWID (both HCV-infected and susceptible), the average discounted person years spent in each compartment between 2015 and 2030 was calculated by integrating the size of each compartment over time, discounted with a continuously compounding rate of 3% per annum. Discounted total costs and QALYs accrued during this period were calculated by multiplying the average discounted person years spent in each compartment by the associated annual costs and heath utilities (Appendix B). Total costs and QALYs were then scaled up to represent the estimated 80,000 PWID in Australia [11].

For the population of former PWID, costs and QALYs were calculated analogously, and then scaled up to represent the estimated 144,000 HCV-infected former PWID in Australia. Note that this also involved scaling up the population of non-infected former PWID, however they did not contribute to costs and any additional QALYs they accrued did not affect ICERs.

Reaching WHO mortality targets by treating advanced liver disease

The model was repeatedly run with the annual number of treatments available for people with liver fibrosis stage F3 or worse incrementally increased from 1,000 per year until the total number of liver-related deaths in 2030 was 65% of the total liver-related deaths in 2015. Treatments were allocated proportionally across injecting drug use status (i.e. patients were treated irrespective of whether they were current of former PWID), and if the number of treatments available was greater than the number of HCV-infected people with advanced liver disease, the remaining treatments were allocated to HCV-infected people with early liver disease, proportionally across injecting drug use status. Once the minimum number of annual treatments to reach the WHO mortality target was established, the total discounted costs (including the cost of treatment) and QALYs accrued between 2015 and 2030 were calculated analogously to the base case.

Reaching WHO incidence targets by treating current PWID

The model was repeatedly run with the annual number of treatments available to current PWID incrementally increased from 1,840 per year until the total number of incident cases in 2030 was less than 80% of the total incident cases in 2015. Treatments were allocated proportionally across liver disease stages, and if the number of treatments available was greater than the number of current PWID eligible for treatment, remaining treatments were allocated to former PWID, proportionally across disease stages. Once the minimum number of annual treatments to reach the WHO incidence

target was established, the total discounted costs (including the cost of treatment) and QALYs accrued between 2015 and 2030 were calculated analogously to the base case.

Allocating treatment resources to reach WHO incidence and mortality targets

In this scenario for each treatment number the effect of allocating treatments between current PWID and late liver disease stage was also tested as follows. For each fixed number of treatments, separate scenarios were run with the proportion of treatments allocated to people with late liver disease stage, p, increased from 0 to 1. This meant that current PWID with advanced liver disease, former PWID with advanced liver disease and current PWID with early liver disease were given proportions

$$\mathrm{T_{adv\&PWID}} = \frac{\text{number of PWID with advanced liver disease}}{\mathrm{p} * (\text{number of people with advanced liver disease}) + (1-\mathrm{p}) * (\text{number of PWID})}$$

$$\mathrm{T_{adv\&formerPWID}} = \mathrm{p} * (1 - \mathrm{T_{adv\&PWID}})$$

$$\mathrm{T_{early\&PWID}} = (1-\mathrm{p}) * (1 - \mathrm{T_{adv\&PWID}})$$

of the available treatments respectively. Where the number of treatments available was greater than this, they were allocated to former PWID with early liver disease. If no allocation (p) was able to reach both WHO targets then the total available number of treatments was increased and the process repeated. When treatment numbers were sufficient that both WHO targets were reached, the allocation achieving this was noted, and the total costs and QALYs accrued between 2015 and 2030 were calculated analogously to the base case.

Sensitivity analysis

A Monte Carlo uncertainty analysis was conducted to get confidence intervals for the number of treatments required to reach WHO eliminations targets, and the associated total costs and QALYs. Uncertainties of health utilities and annual disease transition probabilities were assumed to be normally distributed (and hence uncertainties in disease transition rates were log-normally distributed), using mean and variance estimates from the literature (Appendix B). These uncertainties were parametrised as probability distributions and 1000 simulations were undertaken using random, independent parameter draws. 95% confidence intervals were taken as the 2.5th and 97.5th percentiles of the resulting outputs.

One-way sensitivity analyses were also undertaken to test the impact when: the cost of treatment was AUS$20,000-80,000; initial chronic HCV prevalence was set to either 40% or 60% instead of 50%; the discounting rate was increased from 3% to 5%; the SVR rate was 90% or 99% instead of 95%; the length of injecting career was halved from 17 to 8·5 years; treatment duration was 8 weeks or 48 weeks for all genotypes; either 60% or 90% of HCV infections in Australia were IDU-acquired instead of 80%; the number of PWID in Australian was 60,000 or 100,000 instead of 80,000 (i.e. 0.25% or 0.42% of the population, instead of 0.33%); and when additional harm reduction was not introduced or was scaled up to reduce incidence by 20% instead of 10%.

Appendix B: Model parameters, disease progression rates, health utilities and healthcare costs.

Demographic, mortality, infection and treatment parameters are shown in Table B1; liver disease progression and health state transition rates are show in Table B2; health utilities for various liver disease stages are shown in Table B3; and the total annual and one-off costs associated with HCV management and treatment are shown in Table B4 for various stages of liver disease.

Healthcare and other costs associated with disease management or treatment were determined in focus group consultation with hepatology and infectious diseases experts. For a typical patient in each liver disease stage, specialist and general practitioner consultation frequency, as well as the frequency that tests and procedures would be requested were agreed upon for the current standard of care. The costs of each consultation, test or procedure were then taken from the Medicare Benefits Scheme [25] and the Pharmaceutical Benefits Scheme [26] and are published elsewhere [1].

Table B1: Demographic, HCV infection and HCV treatment model parameters.

Demographic information	Estimate	Symbol	References and comments
Mean age at first injection	20 years		[27]
Duration of injecting career	17 years	$1/\eta$	[28]
Annual probability of drug relapse to IDU	0.027	$1-\exp(-r_{relapse})$[a]	[29, 30]
Mortality ratios			
Annual non liver-related mortalities for PWID (per 1000 person years)			
20–24 years old	0.96	$1-\exp(-\mu_1)$	[31]
25–29 years old	0.96	$1-\exp(-\mu_1)$	[31]
30–34 years old	1.12	$1-\exp(-\mu_2)$	[31]
35–44 years old	0.18	$1-\exp(-\mu_3)$	[31]
45-54 years old	0.22	$1-\exp(-\mu_4)$	Assumed to equal the general Australian population. Values from Victoria life tables [32], assuming 60% male PWID [33].
55-64 years old	0.53	$1-\exp(-\mu_5)$	
65-74 years old	1.38	$1-\exp(-\mu_6)$	
75-84 years old	4.28	$1-\exp(-\mu_7)$	
85+ years old	14.96	$1-\exp(-\mu_8)$	

Annual non liver related mortalities for former PWID (per 1000 person years)			
20–24 years old	0.044	1-exp(-μ_1)	
25–29 years old	0.051	1-exp(-μ_2)	Assumed to equal the general Australian population. Values from Victoria life tables [32], assuming 60% male population [33].
30–34 years old	0.062	1-exp(-μ_3)	
35–44 years old	0.100	1-exp(-μ_4)	
45-54 years old	0.222	1-exp(-μ_5)	
55-64 years old	0.534	1-exp(-μ_6)	
65-74 years old	1.376	1-exp(-μ_7)	
75-84 years old	4.282	1-exp(-μ_8)	
85+ years old	14.956	1-exp(-μ_9)	
Annual probability of PWID infection	5.6%	π	Calibration parameter.
Spontaneous clearance	0.26	δ	[34] Range 0·22-0·29. Uniform distribution assumed for uncertainty analysis.
Genotype distribution in Australia			
Genotype 1	55%		[35]
Genotype 2	7%		[35]
Genotype 3	38%		[35]
Treatment			
Probability of PWID completing treatment	0.892	p_{com}	[36]
Genotype weighted SVR probability			
Mild chronic HCV	0.95	α	For Genotype 1: [37, 38, 39, 40] assumed equally efficacious across genotypes.
Moderate chronic HCV	0.95	α	Assumed equally efficacious for mild and moderate liver disease stages.
Treatment duration			
Genotype 1 and 2	12 weeks		[37, 38, 39, 41]
Genotype 3	24 weeks		
Australian weighted average	16.56 weeks	52/ω	

[a] Annual transition probabilities are converted to rates.

Table B2: Liver disease and health state progression rates.

Annual health state transition probabilities	Estimate	Distribution for uncertainty analysis	Standard deviation	Rate parameter[a]	Refs.
Acute infection to mild (F0)[b]	52/12	52/TNormal(1,26)[c]	52/2	$1-\exp(-r_{AF0})$	[42]
F0 to F1					
Former PWID	0.106	TNormal(0.094,0.205)	0.028	$1-\exp(-r_{F0F1})$	[43]
Current PWID	0.116	TNormal(0.059,0.228)	0.042	$1-\exp(-\hat{r}_{F0F1})$	[43]
F1 to F2					
Former PWID	0.074	TNormal(0.064,0.175)	0.028	$1-\exp(-r_{F1F2})$	[43]
Current PWID	0.085	TNormal(0.065,0.110)	0.011	$1-\exp(-\hat{r}_{F1F2})$	[43]
F2 to F3					
Former PWID	0.106	TNormal(0.092,0.187)	0.033	$1-\exp(-r_{F2F3})$	[43]
Current PWID	0.085	TNormal(0.049,0.147)	0.025	$1-\exp(-\hat{r}_{F2F3})$	[43]
F3 to F4					
Former PWID	0.105	TNormal(0.092,0.187)	0.024	$1-\exp(-r_{F3F4})$	[43]
Current PWID	0.130	TNormal(0.053,0.319)	0.067	$1-\exp(-\hat{r}_{F3F4})$	[43]
F4 to DC	0.037	TNormal(0.030,0.092)	0.016	$1-\exp(-r_{F4DC})$	[44]
F4 to HCC	0.010	TNormal(0.009,0.038)	0.007	$1-\exp(-r_{F4HCC})$	[44]
DC to HCC	0.068	TNormal(0.041,0.099)	0.015	$1-\exp(-r_{DCHCC})$	[44]
DC to liver transplant	0.033	TNormal(0.017,0.049)	0.008	$1-\exp(-r_{DCLT})$	[44]
DC to death	0.138	TNormal(0.074,0.202)	0.032	$1-\exp(-r_{DCdeath})$	[44]
HCC to liver transplant	0.100	TNormal(0.050,0.180)	0.033	$1-\exp(-r_{HCCLT})$	[44]
HCC to death	0.605	TNormal(0.545,0.676)	0.033	$1-\exp(-r_{HCCdeath})$	[44]
Liver transplant to death in year 1	0.169	TNormal(0.127,0.210)	0.021	$1-\exp(-r_{LT1death})$	[44]
Liver transplant to death in years 2+	0.034	TNormal(0.024,0.043)	0.005	$1-\exp(-r_{LT2death})$	[44]
S4 to DC	0.02	TNormal(0.02,0.005)	0.005	$1-\exp(-r_{SVR4DC})$	Expert opinion
S4 to HCC	0.02	TNormal(0.02,0.005)	0.005	$1-\exp(-r_{SVR4HCC})$	

[a] Annual transition probabilities are converted to rates; normally distributed parameters are converted to log-normal parameters.

[b] Mean time in acute phase 12 weeks; range 1 week – 6 months; standard deviation 2 weeks.

[c] TNormal(a,b), Normal distribution truncated between a and b.

Table B3: Health utilities for various liver disease and health states.

Health state utilities	Estimate	Distribution for uncertainty analysis	Standard deviation	Symbol	Refs.
Spontaneous viral clearance, never infected	0.93	TNormal(0.928,0.932)	0.01	q_S	[44]
Sustained virological response					
After treatment	0.93	TNormal(q_F012,q_S)	0.01	q_svr0	[45, 46, 47]
Acute HCV	0.77	TNormal(0,q_S)	0.12	q_A	
Mild chronic HCV (F0/F1/F2)	0.77	TNormal(0,q_S)	0.12	q_F012	[45, 46, 47]
Moderate chronic HCV (F3)	0.66	TNormal(0,q_F012)	0.15	q_F3	[45, 46, 47]
Compensated cirrhosis (F4)	0.55	TNormal(0,q_F3)	0.24	q_F4	[45, 46, 47]
Decompensated cirrhosis/liver failure	0.45	TNormal(0,q_F4)	0.14	q_DC	[45, 46, 47]
Hepatocellular carcinoma	0.45	TNormal(0,q_F4)	0.14	q_HCC	[45, 46, 47]
Liver transplantation year 1	0.45	TNormal(q_HCC,1)	0.14	q_LT1	[45, 46, 47]
Liver transplantation year 2+	0.67	TNormal(q_LT1,1)	0.14	q_LT2	[45, 46, 47]
During treatment					
Treatment from F0-F2	0.77	TNormal(q_F012,q_S)	0.12	q_T012	Assumed
Treatment from F3	0.66	TNormal(q_F3,q_S)	0.15	q_T3	Assumed
Treatment from F4 or worse	0.55	TNormal(q_DC,q_F3)	0.24	q_T4	Assumed

Table B4: Annual and one-off costs associated with managing chronic HCV infection and treatment, for various stages of liver disease.

Type of cost		Value (2014 Australian dollars)	Reference
Annual costs of managing chronic HCV			[25, 26]
Mild chronic HCV (F0-F2)		$446.70	[25, 26]
Moderate chronic HCV (F3)		$690.85	[25, 26]
Compensated cirrhosis (F4)		$935.05	[25, 26]
Decompensated cirrhosis (DC)			
	Hepatic Encephalopathy	*$20,053.03*	[25, 26]
	Diuretic Sensitive Ascites	*$3,792.38*	[25, 26]
	Refractory Ascites	*$29,264.28*	[25, 26]
	Variceal Haemorrhage	*$68,567.43*	[25, 26]
	Weighted average	$15,202.43	
Hepatocellular carcinoma (HCC)		$10,759.75	[25, 26]
One-off costs of transition between states			
Initial diagnosis of HCV		$936.63	[25, 26]
Achieving SVR from treatment		$303.55	[25, 26]
Transition to F4		$565.67	[25, 26]
Transition to HCC		$970.20	[25, 26]
Liver transplant		$145,565.00	[48]
Costs associated with treatment			
Mild or moderate HCV			
	Genotype 1 or 2	*$31,779.60*	[25, 26]
	Genotype 3	*$62,377.15*	[25, 26]
	Weighted average	$35,806.67	
Compensated cirrhosis (all genotypes)		$62,377.15	[25, 26]
Other costs			
Ongoing annual costs after achieving SVR from treatment with compensated cirrhosis		$557.62	[25, 26]
Additional annual costs of care for PWID with chronic HCV		$34.22	[25, 26]

Appendix C: Model equations

This appendix describes the equations used to model the scenarios with no treatment; prioritising treatment to advanced liver disease patients to achieve the World Health Organisation (WHO) mortality reduction targets; prioritising treatment to people who inject drugs (PWID) to achieve the WHO incidence reduction target; and allocating treatments in order to achieve both elimination targets.

Notation

Denote each compartment with three subscripts, for example $S0_{i,j,k}$, where the i stratification represents former (i=0) or current (i=1) injecting drug users, the j stratification represents people who have never failed treatment (j=0) or previously failed treatment (j=1), and the k stratification represents the age categories 20–24, 25–29, 30–34, 35–44, 45–54, 55–64, 65–74, 75–84 and 85+ years old for k=1,…,9 respectively.

In order to simplify expressions, we will use vector and matrix notation. Let

$$X_{i,j,k} = (S0_{i,j,k}, S1_{i,j,k}, S2_{i,j,k}, S3_{i,j,k}, S4_{i,j,k}, A_{i,j,k}, F0_{i,j,k}, F1_{i,j,k}, F2_{i,j,k}, F3_{i,j,k}, F4_{i,j,k},$$
$$DC_{i,j,k}, HCC_{i,j,k}, LT1_{i,j,k}, LT2_{i,j,k}, T0_{i,j,k}, T1_{i,j,k}, T2_{i,j,k}, T3_{i,j,k}, T4_{i,j,k})^T ;$$

be the column vector of model compartments; let

$$I = \frac{\sum_{\substack{j=0,1 \\ k=1,\dots,9}} A_{1,j,k} + F0_{1,j,k} + F1_{1,j,k} + F2_{1,j,k} + F3_{1,j,k} + F4_{1,j,k} + DC_{1,j,k} + HCC_{1,j,k} + LT1_{1,j,k} + LT2_{1,j,k}}{\sum_{\substack{j=0,1 \\ k=1,\dots,9}} S0_{1,j,k} + S1_{1,j,k} + S2_{1,j,k} + S3_{1,j,k} + S4_{1,j,k} + A_{1,j,k} + F0_{1,j,k} + F1_{1,j,k} + F2_{1,j,k} + F3_{1,j,k} + F4_{1,j,k} + DC_{1,j,k} + HCC_{1,j,k} + LT1_{1,j,k} + LT2_{1,j,k} + T0_{1,j,k} + T1_{1,j,k} + T2_{1,j,k} + T3_{1,j,k} + T4_{1,j,k}}$$

be the proportion of PWID who are infectious at each point in time; let

$$\Psi = \begin{cases} \pi * rel\_inc(t) * I, & i = 1 \ (current\ PWID) \\ 0, & i = 0 \ (former\ PWID) \end{cases}$$

be the scaled infection parameter (where infection is only allowed among current PWID); let

$$M = \begin{bmatrix}
-\Psi & 0 & 0 & 0 & 0 & \delta r_{AF0} & 0 & 0 & 0 & 0 & 0 \\
0 & -\Psi & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -\Psi & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -\Psi & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\Psi - r_{SVR4DC} - r_{SVR4HCC} & 0 & 0 & 0 & 0 & 0 & 0 \\
\Psi & 0 & 0 & 0 & 0 & -r_{AF0} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & (1-\delta) r_{AF0} & -r_{F0F1} & 0 & 0 & 0 & 0 \\
0 & \Psi & 0 & 0 & 0 & 0 & r_{F0F1} & -r_{F1F2} & 0 & 0 & 0 \\
0 & 0 & \Psi & 0 & 0 & 0 & 0 & r_{F1F2} & -r_{F2F3} & 0 & 0 \\
0 & 0 & 0 & \Psi & 0 & 0 & 0 & 0 & r_{F2F3} & -r_{F3F4} & 0 \\
0 & 0 & 0 & 0 & \Psi & 0 & 0 & 0 & 0 & r_{F3F4} & -r_{F4DC} - r_{F4HCC} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & r_{F4DC} + r_{SVR4DC} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & r_{F4HCC} + r_{SVR4HCC} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$\begin{bmatrix}
0 & 0 & 0 & 0 & \omega & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \omega & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \omega & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \omega & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \omega \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-r_{DCHCC} - r_{DCLT} - r_{DCdeath} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
r_{DCHCC} & -r_{HCCLT} - r_{HCCdeath} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
r_{DCLT} & r_{HCCLT} & -1 - r_{LT1death} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & r_{LT2death} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\omega & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\omega & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -\omega & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -\omega & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\omega
\end{bmatrix}$$

be the 20x20 matrix describing movements between compartments of the same i, j and k stratification; let $\hat{M}$ be the same matrix but with the parameters r_{F0F1}, r_{F1F2}, r_{F2F3} and r_{F3F4} replaced with the disease progression rates among PWID ($\hat{r}_{F0F1}$, $\hat{r}_{F1F2}$, $\hat{r}_{F2F3}$ and $\hat{r}_{F3F4}$ respectively); and Let

$$Age_{i,j} = \begin{pmatrix} -1/5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1/5 & -1/5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1/5 & -1/5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1/5 & -1/10 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1/10 & -1/10 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1/10 & -1/10 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1/10 & -1/10 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1/10 & -1/10 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1/10 & 0 \end{pmatrix} * \begin{pmatrix} X_{i,j,1} \\ X_{i,j,2} \\ X_{i,j,3} \\ X_{i,j,4} \\ X_{i,j,5} \\ X_{i,j,6} \\ X_{i,j,7} \\ X_{i,j,8} \\ X_{i,j,9} \end{pmatrix}$$

be the net movement of people due to ageing, so that $Age_{i,j}[k]$, the k'th component of the vector $Age_{i,j}$, represents the net movement of people into and out of the k'th age category.

Treatment allocation function

Define a time-varying treatment vector $\Phi_{i,j,k}$, where the a'th component, $\Phi_{i,j,k}[a]$, gives the number of treatments allocated to the a'th compartment of the vector $X_{i,j,k}$. The entries in $\Phi_{i,j,k}$ at each point in time are determined by the total number of treatments available (n) and the proportion of treatments that are preferentially given to people with advanced liver disease compared to PWID (p) as follows.

Let the total number of PWID, total number of former PWID with advanced liver disease, and total number PWID with advanced liver disease who are eligible for treatment be denoted by

$$PWID_{treat} = \frac{80{,}000}{\sum_{a,j,k} X_{1,j,k}[a]} * \sum_{k=1,\dots,9} F0_{1,0,k} + F1_{1,0,k} + F2_{1,0,k} + F3_{1,0,k} + F4_{1,0,k} + LT1_{1,0,k} + LT2_{1,0,k}$$

$$AdFormer_{treat} = \frac{144{,}000}{\sum_{a,j,k} X_{0,j,k}[a]} * \sum_{\substack{k=1,\dots,9 \\ i=0,1}} F3_{0,0,k} + F4_{0,0,k} + LT1_{0,0,k} + LT2_{0,0,k}$$

$$AdPWID_{treat} = \frac{80{,}000}{\sum_{a,j,k} X_{1,j,k}[a]} * \sum_{k=1,\dots 9} F3_{1,0,k} + F4_{1,0,k} + LT1_{1,0,k} + LT2_{1,0,k}$$

respectively, where each total has been scaled to represent the estimated 80,000 PWID and 144,000 HCV infections among former PWID in Australia [9, 11, 16]. Note that $\sum_{a,j,k} X_{1,j,k}[a]$ is the total number of PWID in the model; and $\sum_{a,j,k} X_{0,j,k}[a]$ is the total number of former PWID in the model. Then for any treatment allocation prioritisation p, the proportion of treatments allocated to eligible PWID with advanced liver disease is

$$\Omega = \frac{AdPWID_{treat}}{p * (AdPWID_{treat} + AdFormer_{treat}) + (1-p) * PWID_{treat}}$$

For a given treatment number n, and arbitrary model compartment Y, define the functions

$$f(n,Y) = min\left\{n * \Omega * \frac{Y}{AdPWID_{treat}}, Y\right\}$$

$$g(n,Y) = min\left\{n * p * (1-\Omega) * \frac{Y}{Ad_{treat} - AdPWID_{treat}}, Y\right\}$$

$$h(n,Y) = min\left\{n * (1-p) * (1-\Omega) * \frac{Y}{PWID_{treat} - AdPWID_{treat}}, Y\right\}$$

used to determine the number of treatments allocated to compartments containing PWID with advanced liver disease, former PWID with advanced liver disease, and PWID with early liver disease respectively. This assumes, for example, that once the number of treatments available to PWID with advanced liver disease is determined, they are allocated proportionally over the F3, F4, LT1 and LT2 compartments. Then for k=1,…,9, the treatment function is given by

$$\Phi_{1,0,k} = (0,0,0,0,0,0, h(n, F0_{1,0,k}), h(n, F1_{1,0,k}), h(n, F2_{1,0,k}), f(n, F3_{1,0,k}), f(n, F4_{1,0,k}),$$

$$0,0, f(n, DC_{1,0,k}), f(n, HCC_{1,0,k}), 0,0,0,0,0)^T$$

$$\Phi_{0,0,k} = (0,0,0,0,0,0,0,0,0, g(n, F3_{0,0,k}), g(n, F4_{0,0,k}), 0,0, g(n, DC_{0,0,k}), g(n, HCC_{0,0,k}), 0,0,0,0,0)^T$$

$$\Phi_{1,1,k} = \mathbf{0}$$

$$\Phi_{0,1,k} = \mathbf{0}$$

for $t \geq 2015$, and

$$\Phi_{\mathrm{i,j,k}} = \mathbf{0} \text{ for } t < 2015.$$

Further, if there are any leftover treatments n', where $n' = n - \sum_{i,j,k,a} \Phi_{i,j,k}[a] > 0$, they are allocated proportionally over remaining eligible people (including former PWID with early liver disease) by adding the following terms to entries of $\Phi_{\mathrm{i,j,k}}$. For $a \in \{7,8,9,10,11,14,15\}$, set

$$\Phi_{i,0,k}[a] = \Phi_{i,0,k}[a] + \frac{X_{i,0,k}[a] * n'}{\sum_{\substack{k=1,\dots,9 \\ i=0,1}} F0_{i,0,k} + F1_{i,0,k} + F2_{i,0,k} + F3_{i,0,k} + F4_{i,0,k} + LT1_{i,0,k} + LT2_{i,0,k}}$$

where again $X_{i,0,k}[a]$ denotes the a'th compartment in the vector $X_{i,0,k}$.

The proportions αp_{com} and α of current and former PWID who are assumed to successfully complete treatment will then be moved into the corresponding treatment compartments as defined by the function $\widehat{\Phi}_{i,j,k}$:

$$\widehat{\Phi}_{i,j,k} = \alpha * (p_{com})^i * (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,\Phi_{i,j,k}[7],\Phi_{i,j,k}[8],\Phi_{i,j,k}[9],\Phi_{i,j,k}[10],\Phi_{i,j,k}[11] + \Phi_{i,j,k}[14] + \Phi_{i,j,k}[15])^T$$

Initial conditions

In all cases the models were started in 1950 with a population of 1000 20-24 year olds, 44% of whom were PWID and 56% of whom were former PWID, and 10% of PWID HCV-infected (i.e. $\mathrm{S0}_{0,0,1} = 560$, $\mathrm{S0}_{1,0,1} = 396$, $\mathrm{F0}_{1,0,1} = 44$, and all other compartments zero).

No treatment

For k=1,…,9, the equations describing the baseline scenario are:

$$\frac{dX_{1,0,k}}{dt} = \widehat{M}X_{1,0,k} + r_{relapse}X_{0,0,k} - \eta X_{1,0,k} - \mu_k X_{1,0,k} + Age_{1,0}[k]$$

$$\frac{dX_{0,0,k}}{dt} = MX_{0,0,k} - r_{relapse}X_{0,0,k} + \eta X_{1,0,k} - \mu_k X_{0,0,k} + Age_{0,0}[k]$$

$$\frac{dX_{1,1,k}}{dt} = \widehat{M}X_{1,1,k} + r_{relapse}X_{0,1,k} - \eta X_{1,1,k} - \mu_k X_{1,1,k} + Age_{1,1}[k]$$

$$\frac{dX_{0,1,k}}{dt} = MX_{0,1,k} - r_{relapse}X_{0,1,k} + \eta X_{1,1,k} - \mu_k X_{0,1,k} + Age_{0,1}[k]$$

Treatment to reach WHO mortality reduction target

Here, we set p=1 for the treatment function, and for k=1,…,9 the equations are:

$$\frac{dX_{1,0,k}}{dt} = \widehat{M}X_{1,0,k} + r_{relapse}X_{0,0,k} - \eta X_{1,0,k} - \mu_k X_{1,0,k} + Age_{1,0}[k] - \Phi_{1,0,k} + \widehat{\Phi}_{1,0,k}$$

$$\frac{dX_{0,0,k}}{dt} = MX_{0,0,k} - r_{relapse}X_{0,0,k} + \eta X_{1,0,k} - \mu_k X_{0,0,k} + Age_{0,0}[k] - \Phi_{0,0,k} + \widehat{\Phi}_{0,0,k}$$

$$\frac{dX_{1,1,k}}{dt} = \widehat{M}X_{1,1,k} + r_{relapse}X_{0,1,k} - \eta X_{1,1,k} - \mu_k X_{1,1,k} + Age_{1,1}[k] + (1 - \alpha p_{com})\Phi_{1,0,k}$$

$$\frac{dX_{0,1,k}}{dt} = MX_{0,1,k} - r_{relapse}X_{0,1,k} + \eta X_{1,1,k} - \mu_k X_{0,1,k} + Age_{0,1}[k] + (1-\alpha)\Phi_{0,0,k}$$

Treatment to reach WHO incidence reduction target

Here, we set p=0 for the treatment function, and for k=1,…,9 the equations are:

$$\frac{dX_{1,0,k}}{dt} = \widehat{M}X_{1,0,k} + r_{relapse}X_{0,0,k} - \eta X_{1,0,k} - \mu_k X_{1,0,k} + Age_{1,0}[k] - \Phi_{1,0,k} + \widehat{\Phi}_{1,0,k}$$

$$\frac{dX_{0,0,k}}{dt} = MX_{0,0,k} - r_{relapse}X_{0,0,k} + \eta X_{1,0,k} - \mu_k X_{0,0,k} + Age_{0,0}[k] - \Phi_{0,0,k} + \widehat{\Phi}_{0,0,k}$$

$$\frac{dX_{1,1,k}}{dt} = \widehat{M}X_{1,1,k} + r_{relapse}X_{0,1,k} - \eta X_{1,1,k} - \mu_k X_{1,1,k} + Age_{1,1}[k] + (1-\alpha p_{com})\Phi_{1,0,k}$$

$$\frac{dX_{0,1,k}}{dt} = MX_{0,1,k} - r_{relapse}X_{0,1,k} + \eta X_{1,1,k} - \mu_k X_{0,1,k} + Age_{0,1}[k] + (1-\alpha)\Phi_{0,0,k}$$

Treatment to reach both WHO elimination targets

Here, we let p range from 0 to 1 in increments of 0.1 and determine whether any allocation has achieved both targets. If not, the total number of available treatments is increased and the process repeated. For k=1,…,9 the equations are:

$$\frac{dX_{1,0,k}}{dt} = \widehat{M}X_{1,0,k} + r_{relapse}X_{0,0,k} - \eta X_{1,0,k} - \mu_k X_{1,0,k} + Age_{1,0}[k] - \Phi_{1,0,k} + \widehat{\Phi}_{1,0,k}$$

$$\frac{dX_{0,0,k}}{dt} = MX_{0,0,k} - r_{relapse}X_{0,0,k} + \eta X_{1,0,k} - \mu_k X_{0,0,k} + Age_{0,0}[k] - \Phi_{0,0,k} + \widehat{\Phi}_{0,0,k}$$

$$\frac{dX_{1,1,k}}{dt} = \widehat{M}X_{1,1,k} + r_{relapse}X_{0,1,k} - \eta X_{1,1,k} - \mu_k X_{1,1,k} + Age_{1,1}[k] + (1-\alpha p_{com})\Phi_{1,0,k}$$

$$\frac{dX_{0,1,k}}{dt} = MX_{0,1,k} - r_{relapse}X_{0,1,k} + \eta X_{1,1,k} - \mu_k X_{0,1,k} + Age_{0,1}[k] + (1-\alpha)\Phi_{0,0,k}$$

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