Validation of model

The majority of the literature considers PWID populations and the first section validates the PWID and the general population models. Section 2 considers the addition of the prison model.

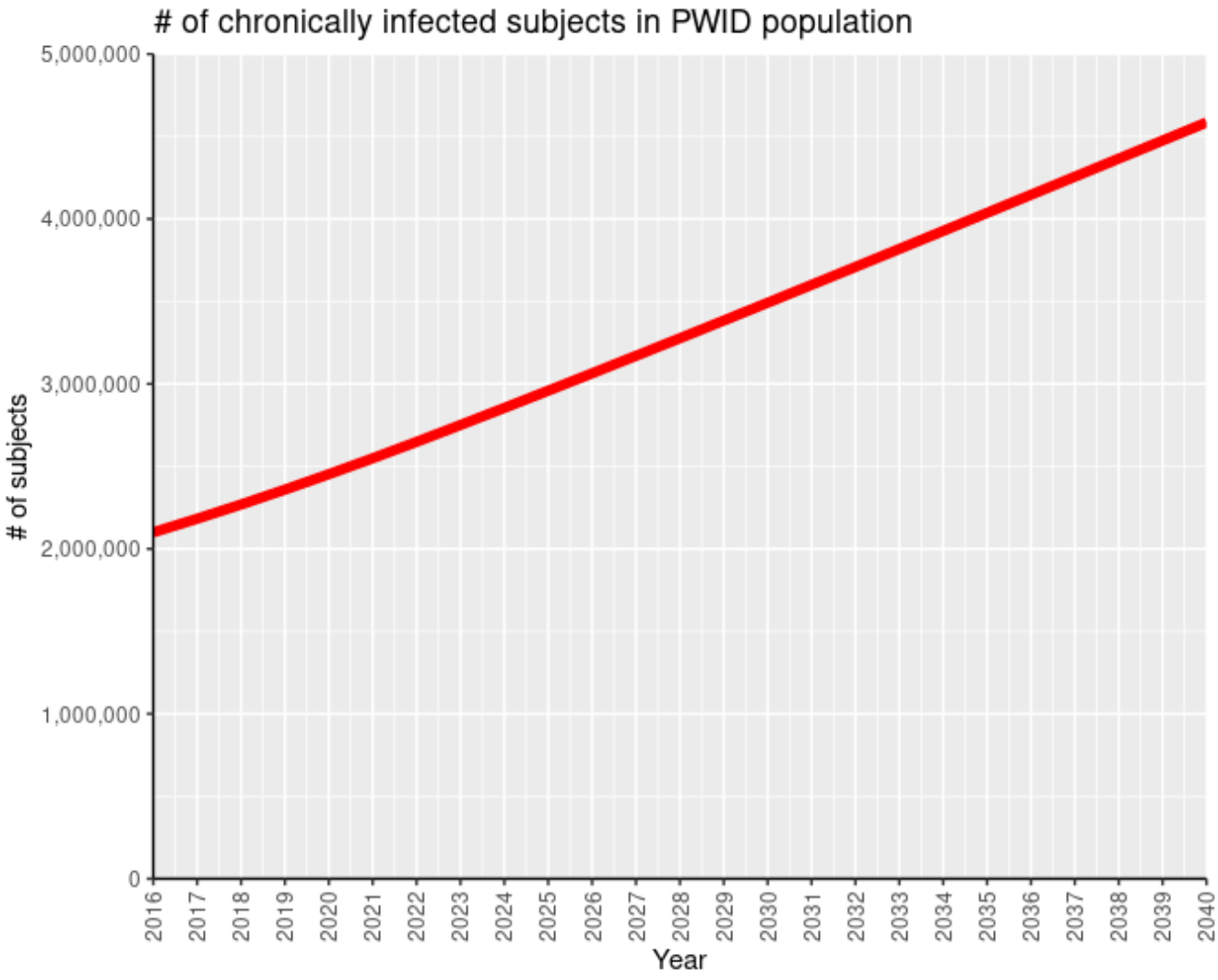
Section 1 PWID and general population model.

With a limited number of fitting points each with wide confidence intervals, there are numerous HCV epidemic scenarios that pass through them. 250 different scenarios were considered and the scenario below was chosen giving good fits to the available data, with a moderate growth rate for the PWID population.

Fitting points

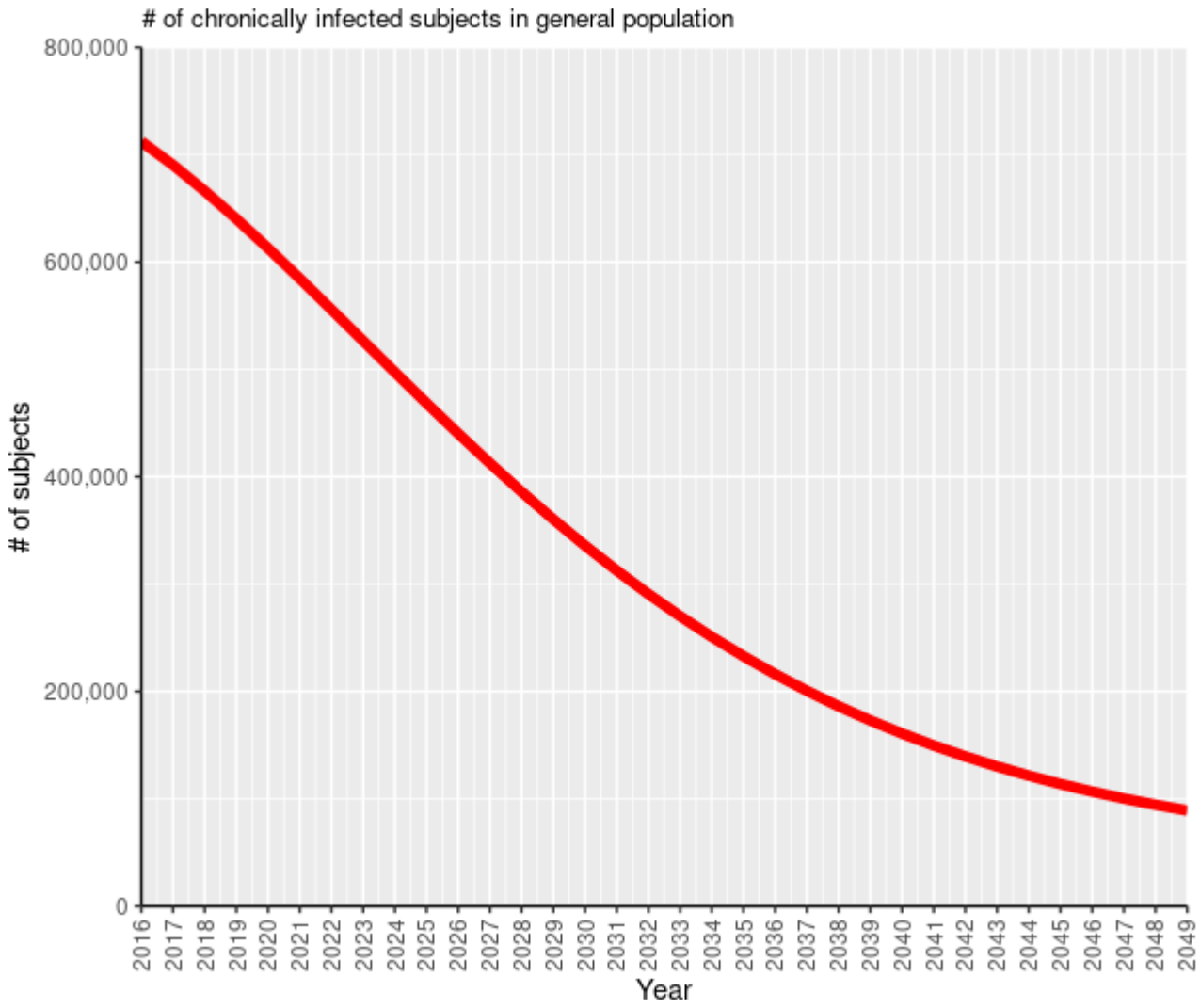
In 2016 there were 3.5 million subjects with HCV, 60% were in PWID and 20% in the general population. See Figures 1 and 2 confirming the actual numbers.

Figure 1 HCV prevalence against year for PWID population



Note that the growth assumes no treatment and a growing PWID population (see Figure 3)

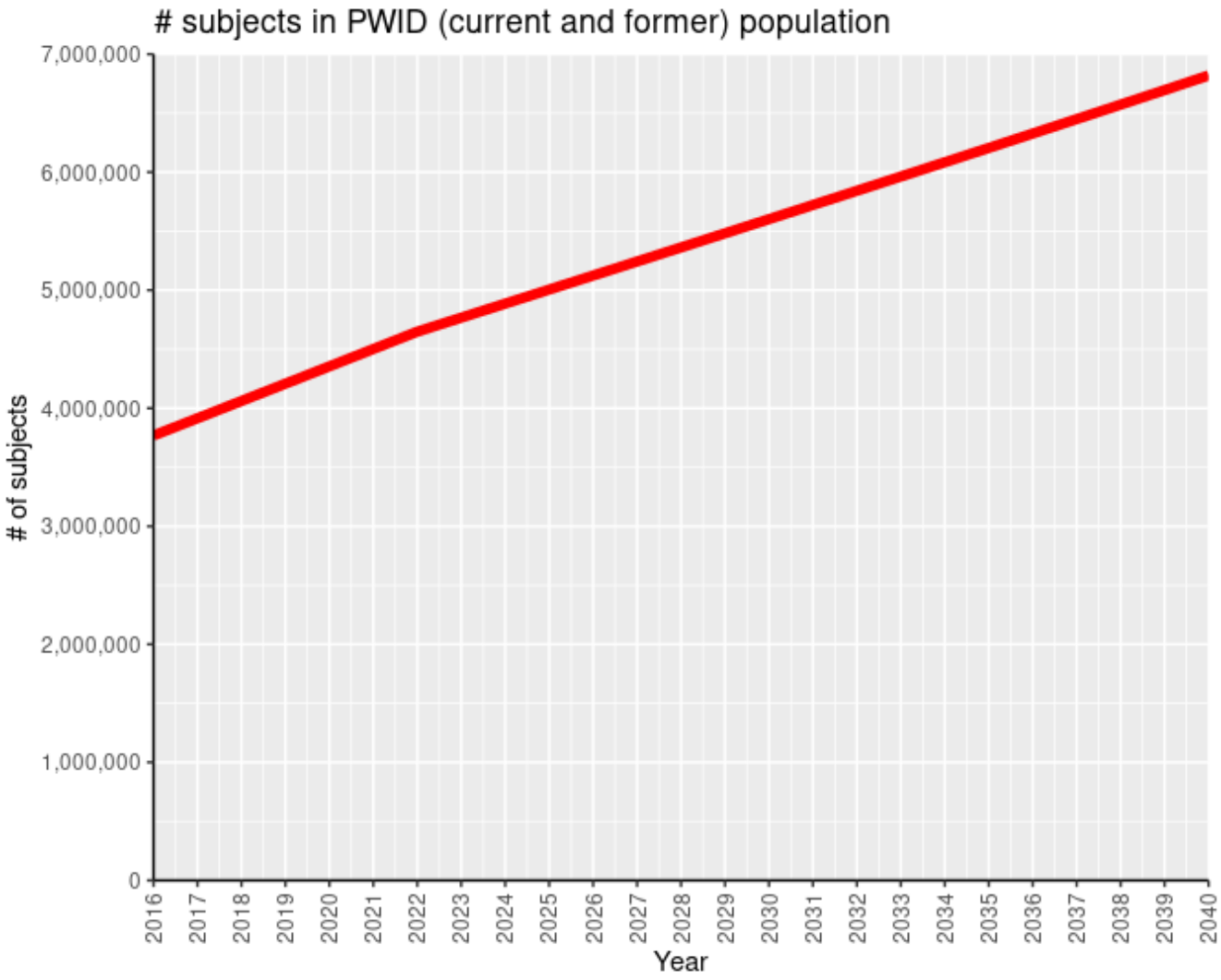
Figure 2 HCV prevalence against year for general population



Population growth

It is unlikely that the PWID population will remain constant. The model assumes an approximate 75% increase in 25 years.

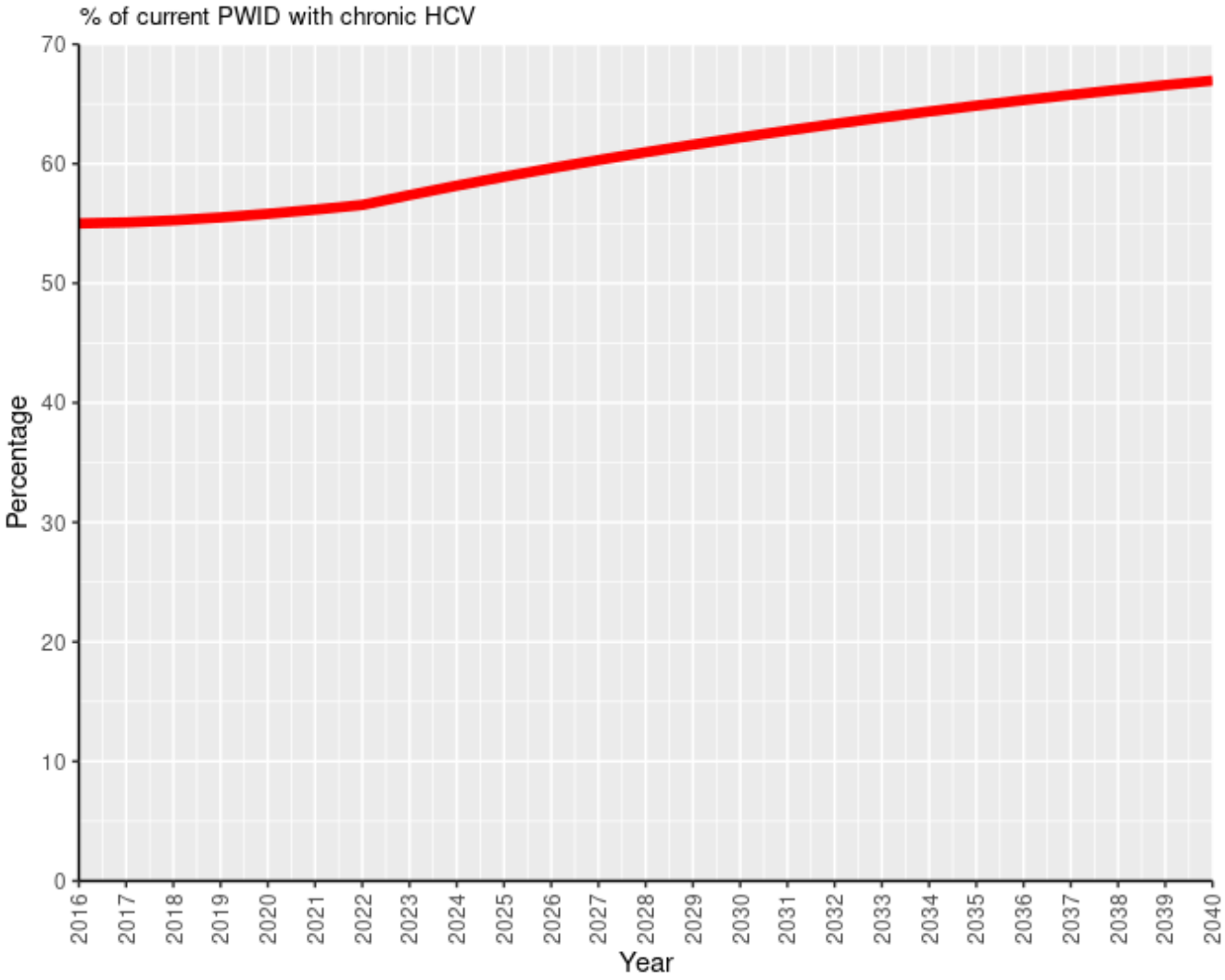
Figure 3 PWID population (includes all HCV+ and susceptible subjects)



Incidence

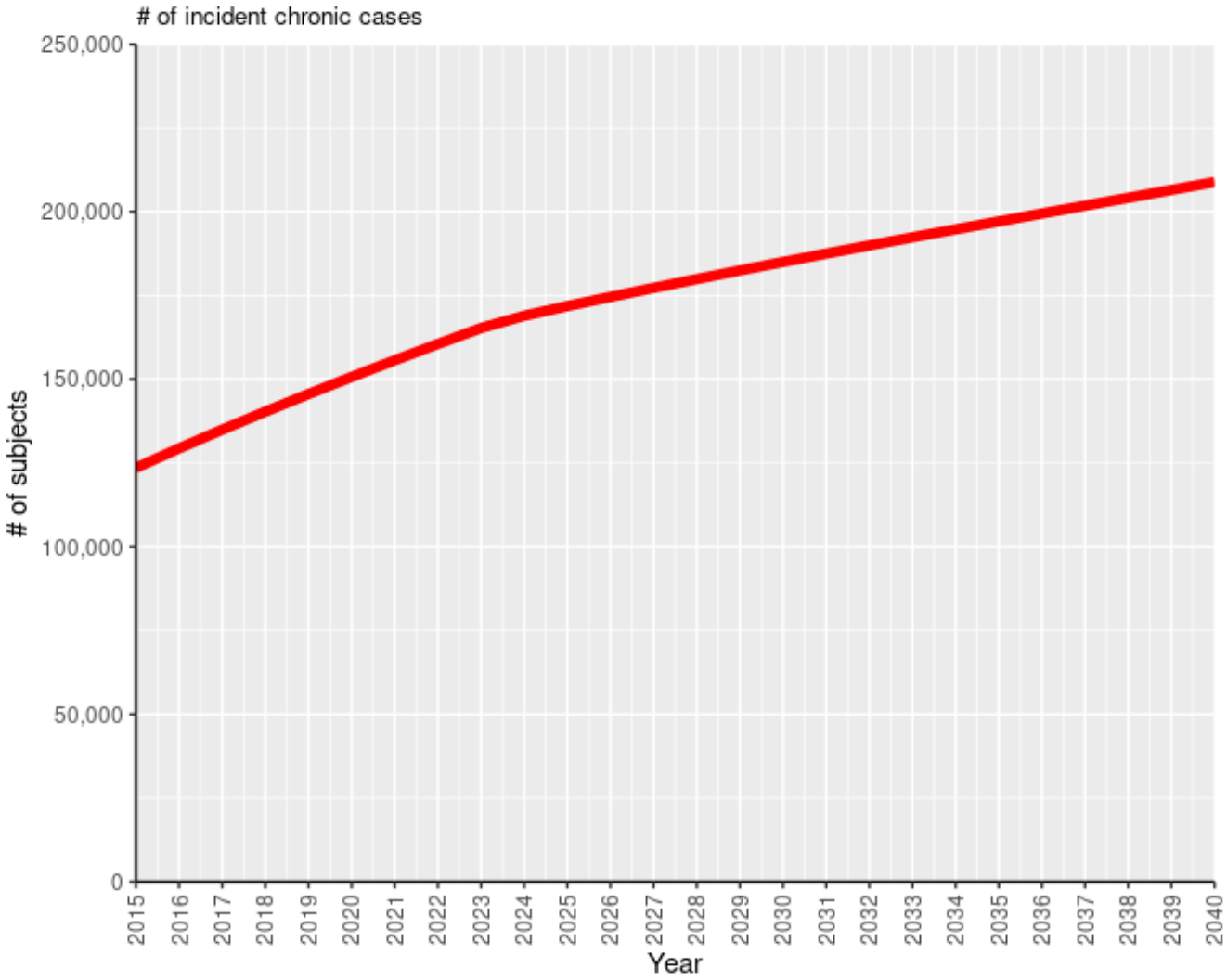
In 2016 a fitting point of 55% of the current PWID population was used, confirmed in Figure 4.

Figure 4 Percentage of current PWID with chronic HCV from fitting point

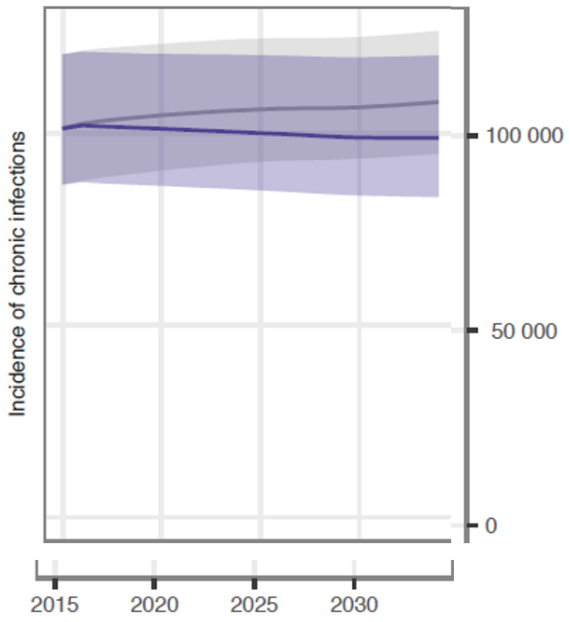


The absolute incidence is difficult to measure via survey and many of the estimates are obtained form modeling. This model also includes a period prior to 2016 of increased incidence of HCV infection within the US. Figure 5 shows the absolute HCV incidence predictions from 2016 to 2040, assuming no changes to the baseline treatment levels (which are implicitly models via parameter and model fitting).

Figure 5 Number of incidents cases among PWID population



The 2015 figure is close to the upper bound of the estimate from Heffernan (the relevant estimate is the gray line with the gray shaded 95% confidence intervals. Heffernan does not assume an increase in HCV incidence between 2010 and 2018 and assumes a constant PWID population.



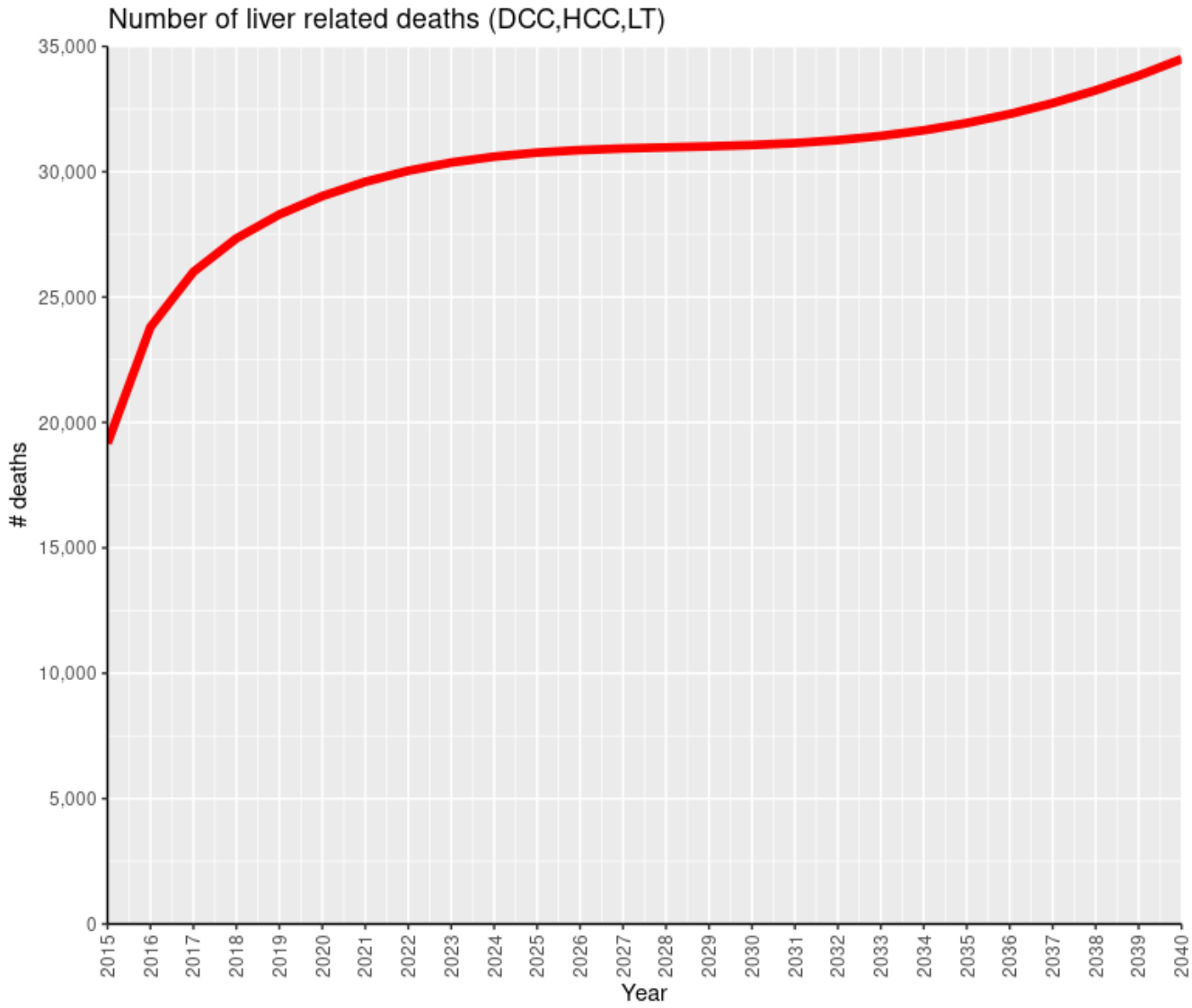
Note the incidence of HCV in the general population is very low and will have a negligible effect.

Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M. & Hallett, T. B. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *The Lancet* **393**, 1319–1329 (2019).

Mortality

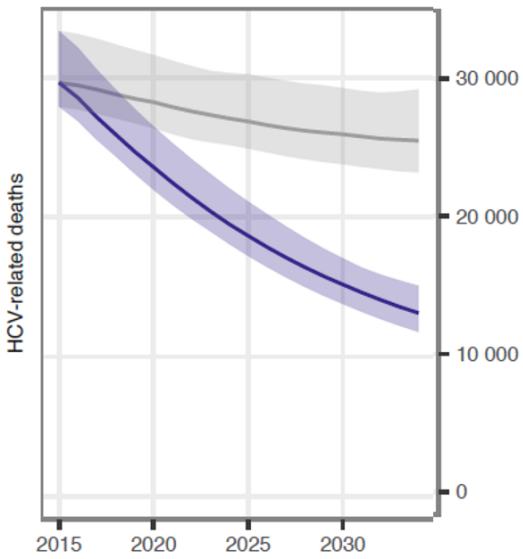
Stages DC,HCC and post Liver transplant are assumed to incur additional liver related mortality above the baseline population mortality rates.

Figure 6 Liver related deaths from general and PWID population



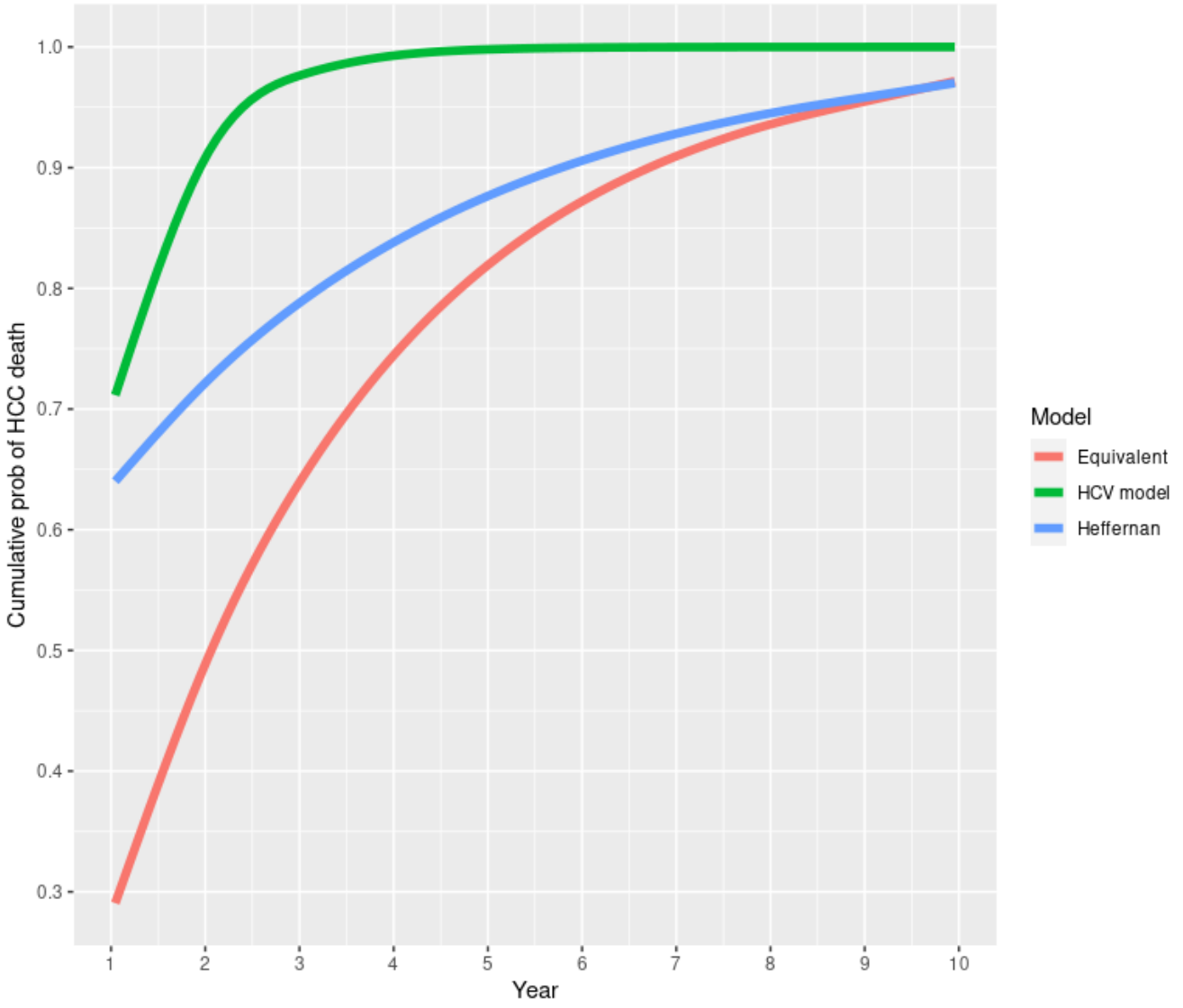
There is no direct comparison with Heffernan as their model for mortality has two differences:

1. They included F4 in their mortality totals (with a mortality probability of 3% per year).
2. HCC was the dominant category in terms of deaths in common with the HCV model, but they allowed a two part mortality model, with a probability of death of 0.64 in the first year and 0.235 in subsequent years.



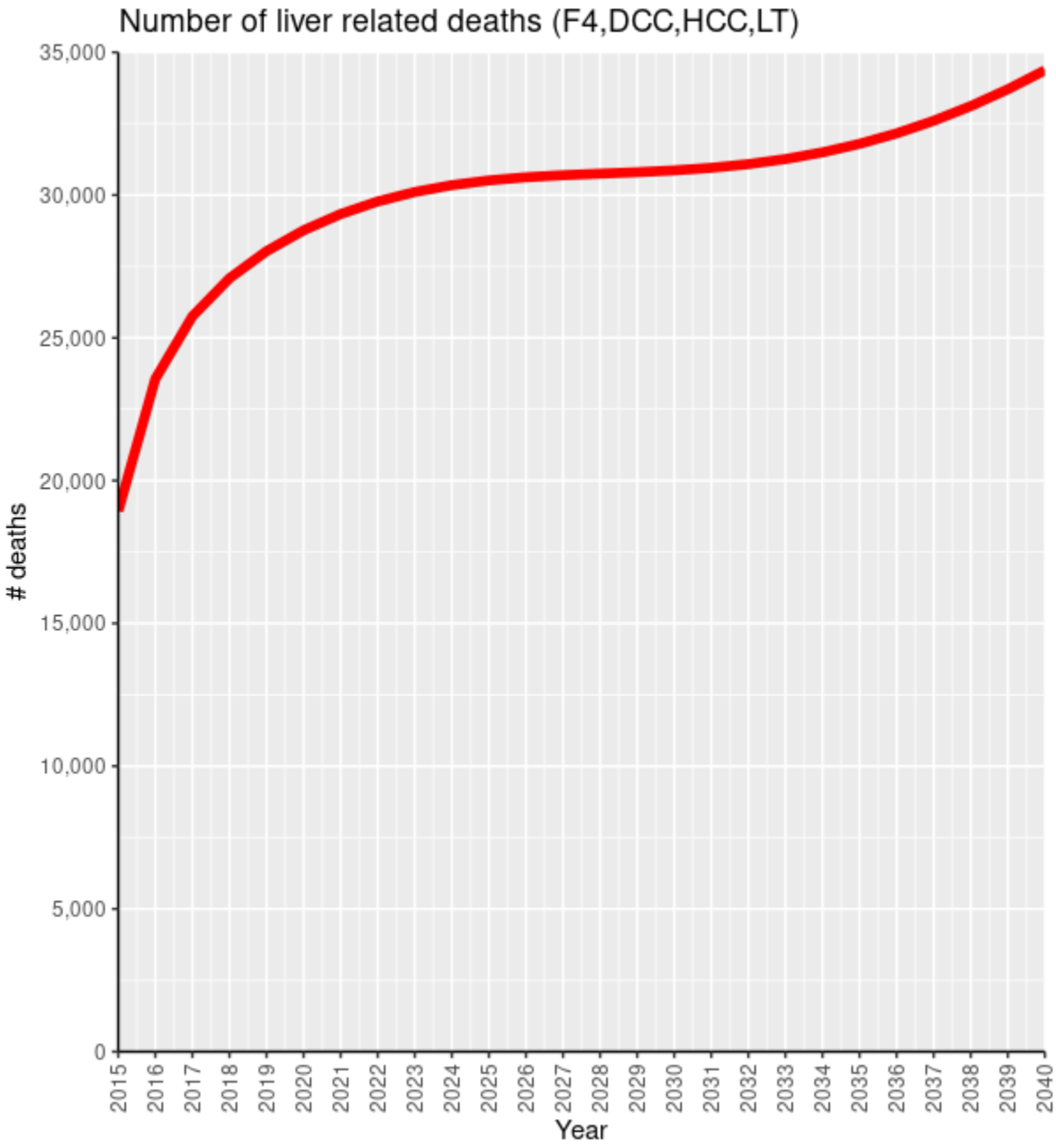
The mortality in the HCC stage in the HCV model is higher than Heffernan and taken as 0.71 at all stages. To make these roughly comparable to the two stage Heffernan modeling, we can adjust the HCC stage probability of death down to 0.29 and then the HCV model and the Heffernan model have the same ten year risk. Figure 7 shows in green the current HCV model mortality risk for those at the HCC stage, which is higher than that assumed in the Heffernan model, shown in blue. Reducing the HCV mortality probability of 0.71 to 0.29 in the HCV model gives the same 10 year risk as the Heffernan model (red line).

Figure 7 Cumulative mortality probabilities for HCC stage



Repeating Figure 6, but also including deaths from F4 and incorporating the adjusted mortality risk for HCC derived above gives the mortality shown in Figure 8 (Note as few subjects progress to LT stages, this only has a small effect).

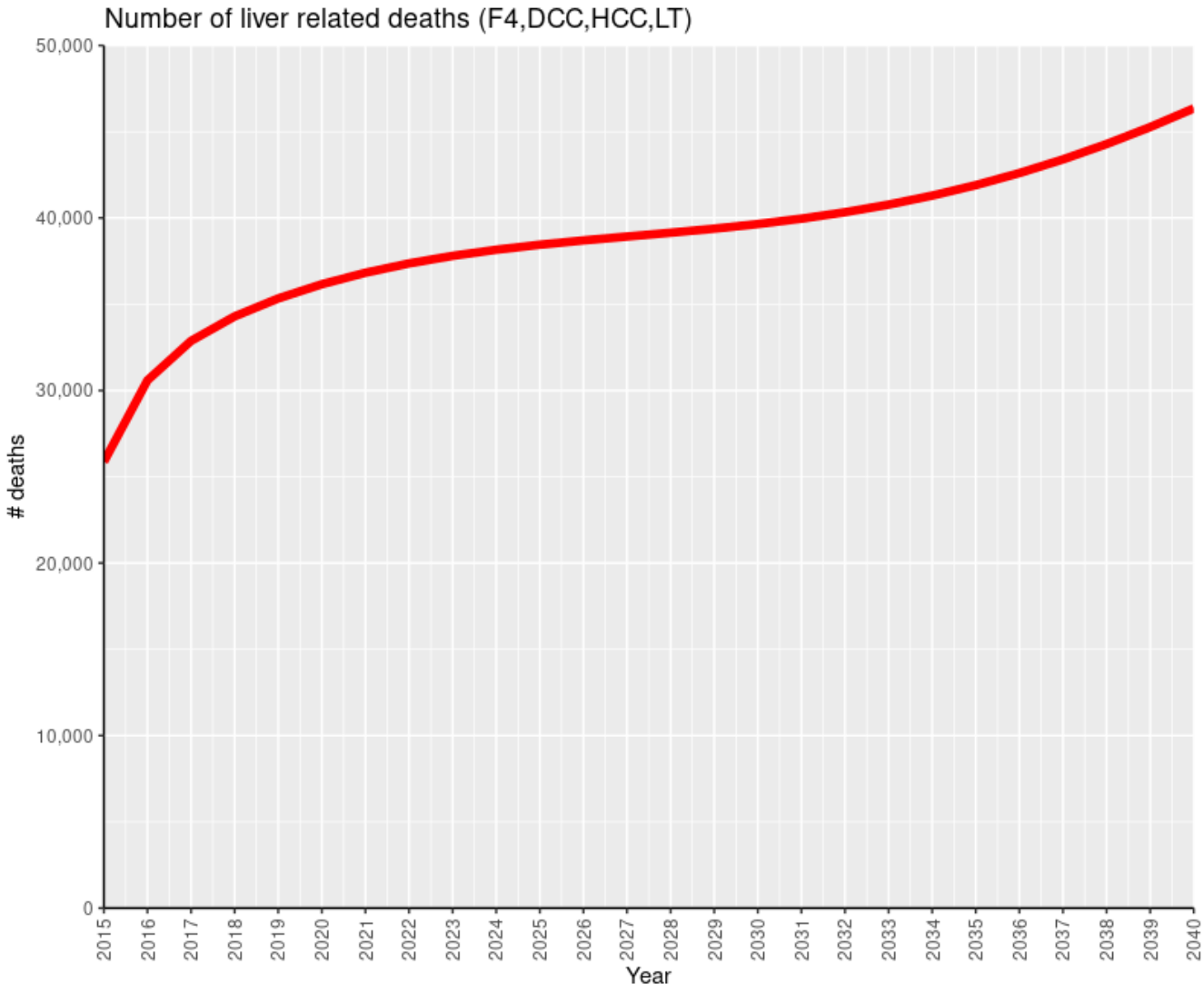
Figure 8 Liver related mortality including the stage **F4**



This is consistent with the Heffernan estimate remembering that there is a increasing trend of PWID in the HCV model and Heffernan assumes no growth.

Retaining the higher mortality in the HCV model and the number of deaths is about 25% higher than the Heffernan model, shown in Figure 9.

Figure 9 Assuming the mortality rates in the HCV model (death rate for HCC stage is the dominant parameter)



Non-liver related mortality estimates

The base line mortality age stratified rates from **Xu** are shown here:

Table 10 Base line mortality rates in the US (2018)

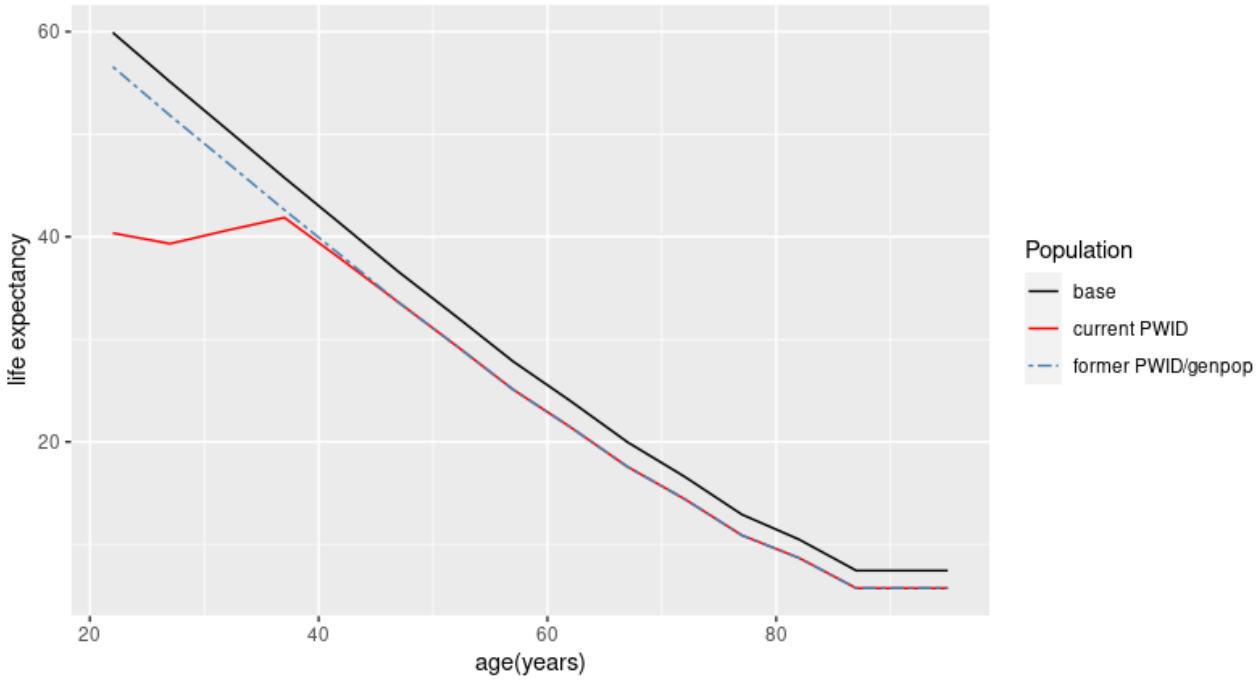
Parameter	Value	Units
20 -24 year old	0.702	per 1000 years
25 -29 year old	1.288	per 1000 years
30 -34 year old	1.288	per 1000 years
35 -44 year old	1.947	per 1000 years
45 -54 year old	3.959	per 1000 years
55 -64 year old	8.8867	per 1000 years
65 -74 year old	17.833	per 1000 years
75 -84 year old	43.861	per 1000 years
85+ year old	134.4507	per 1000 years

Alvai estimates on average a 5 year reduction in life expectancy for populations with a non-drug related HCV diagnosis. Using **PHE** mortality tools a 5 year reduction in life expectancy from the age of 20 on-wards is equivalent to a 30% increase in the mortality rates in Table 1. Consequently for the general population and former PWID population the background mortality rates were taken as 1.3 * the mortality rates in Table 1.

The mortality rates in the current PWID were estimated using the former to current multipliers taken from Scott.

The age related life expectancy for the three groups, base, general population/former PWID and current PWID were calculated using the PHE methodology and are shown in Figure 11.

Figure 11 Age related life expectancy for HCV model



Xu: Mortality in the United States 2018. NCHS data brief NO 355, January 2020
Alvai: Lower Life expectancy among people with HCV. Journal of Viral Hepatitis, 2014, 21, e10–e18
PHE: https://CRAN.R-project.org/package=PHEindicatormethods June 2020

Section 2 Including the prison population

There doesn't appear to be any literature modeling PWID, gen pop and the prison population in the US. Consequently the validation is limited to the fitted points and comparisons of models with and without the prison population.

Fitting points

The most important flows are those between PWID and prison, with high rates of incarceration from the PWID population. Stome (2018) estimates that 58% of the PWID population have ever been incarcerated. Assuming an injecting career length of 17 years we can estimate that:

$1-(1-p)^{17}=0.58$, where p is the annual incarceration probability of a PWID, giving an estimate of p as 0.05.

The prison population scaling (which depends on the scaling of the PWID and general population) requires the estimates in the shaded rows and the actual scaling process is described in the following section.

Table 12 Prison model parameters

Variable	Value	Reference
Prison pop in 2015	2,173,800	https://bjs.ojp.gov/content/pub/pdf/cpus15.pdf [1]
% of PWID population ever incarcerated	58%	Stone (2018) [2]
% of incarcerated population with chronic HCV in 2015	12%-35% **(B)**	https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5201a1.htm [3]
% of incarcerated with HCV who are PWID	50% **(A)**	Dolan (2015) estimate [4]
Prob of former PWID incarcerated in a year	0.01	Estimate – assume 3 * rate of gen pop
Prob of gen pop incarcerated in a year	0.0035 (prev of 700/100000 assuming an average duration of 2 years)	https://en.wikipedia.org/wiki/Incarceration_in_the_United_States [5]
Average sentence duration	3 years	Stone (2021) [6]
Incarcerated relative risk (to PWID) of background mortality	1.2	Estimate – probably higher
Incarcerated relative risk (to PWID) of liver related	1.2	Estimate – probably higher

mortality		
Increase in HCV infections rate for incarcerated	2.8	Stone (2021) [6]
Reduction in incarceration due to prevention programs	30%	Stone (2021) [6]
% of incarcerated non PWID who return to gen pop	20%	Estimate

Note A and B are described in the prison population fitting section

Some of these parameters are likely to be age dependent, but whether age stratified estimates are available?

The stage transition rates for the prison model are assumed to be the same as the current/former PWID model. The prison model is parameterized separately so the transition rates can be adjusted.

Fitting the prison population

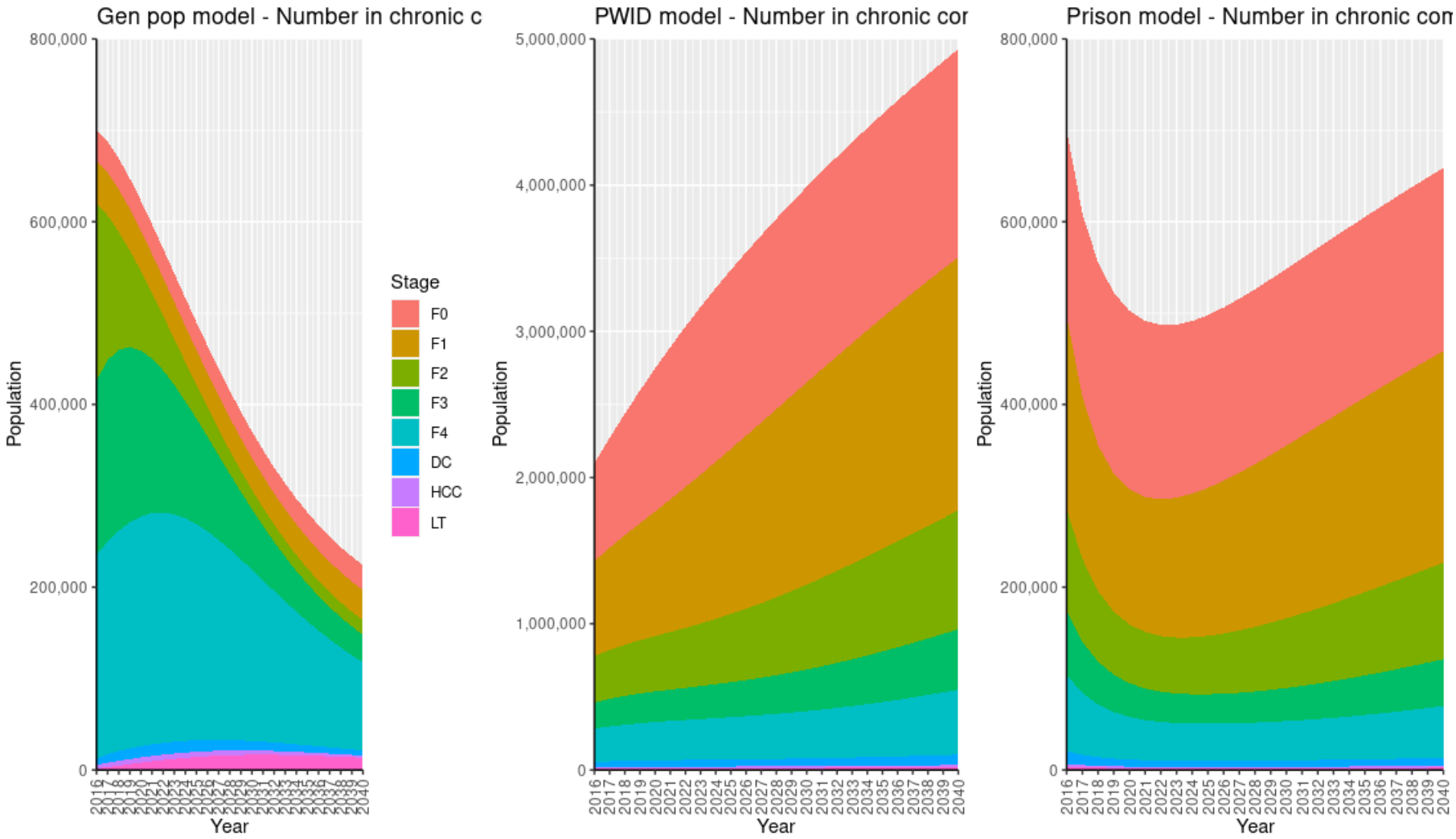
1. Extract the PWID (format and current) population for 2015
2. Scale the population such that A is 50% in the PWID population and (1-A) in the former population
3. Assume 20% (this has to be consistent with the previous assumption that 60% of HCV are PWID and 20% are general population ref Tatar [7]) of 3,500,000 HCV positive subjects in 2015 are incarcerated
4. Scale the starting prison population such that the total population is 2,173,800
5. This gives an incarcerated HCV population percentage of 32%, which is consistent with B

Note if the percentages in 4 are changed then all population models have to be re-fitted to remain consistent.

To reduce the complexity of the overall model, incarcerated gen pop subjects are added to the former compartments of the prison population. This also reflects that incarcerated non injecting drug users probably have a higher risk of moving to a prison PWID population. On release 20% of the prisoners in the former prison compartments are assumed returned to the general population. This is a complex parameter and there are no consistent estimates in the literature.

In terms of modeling the most important parameter within the prison model is the relative increase in the risk of being infected with HCV compared to the PWID population and this is estimated as 2.8 [6]. The key fitting points are the number of the 3,5000,000 subjects with HCV in 2016. The split (section 1) is gen pop:PWID:prison pop = 20%:60%:20%. Figure 13 shows the # of HCV subjects in 2016.

Figure 13 2016 split of the HCV subjects between the three populations

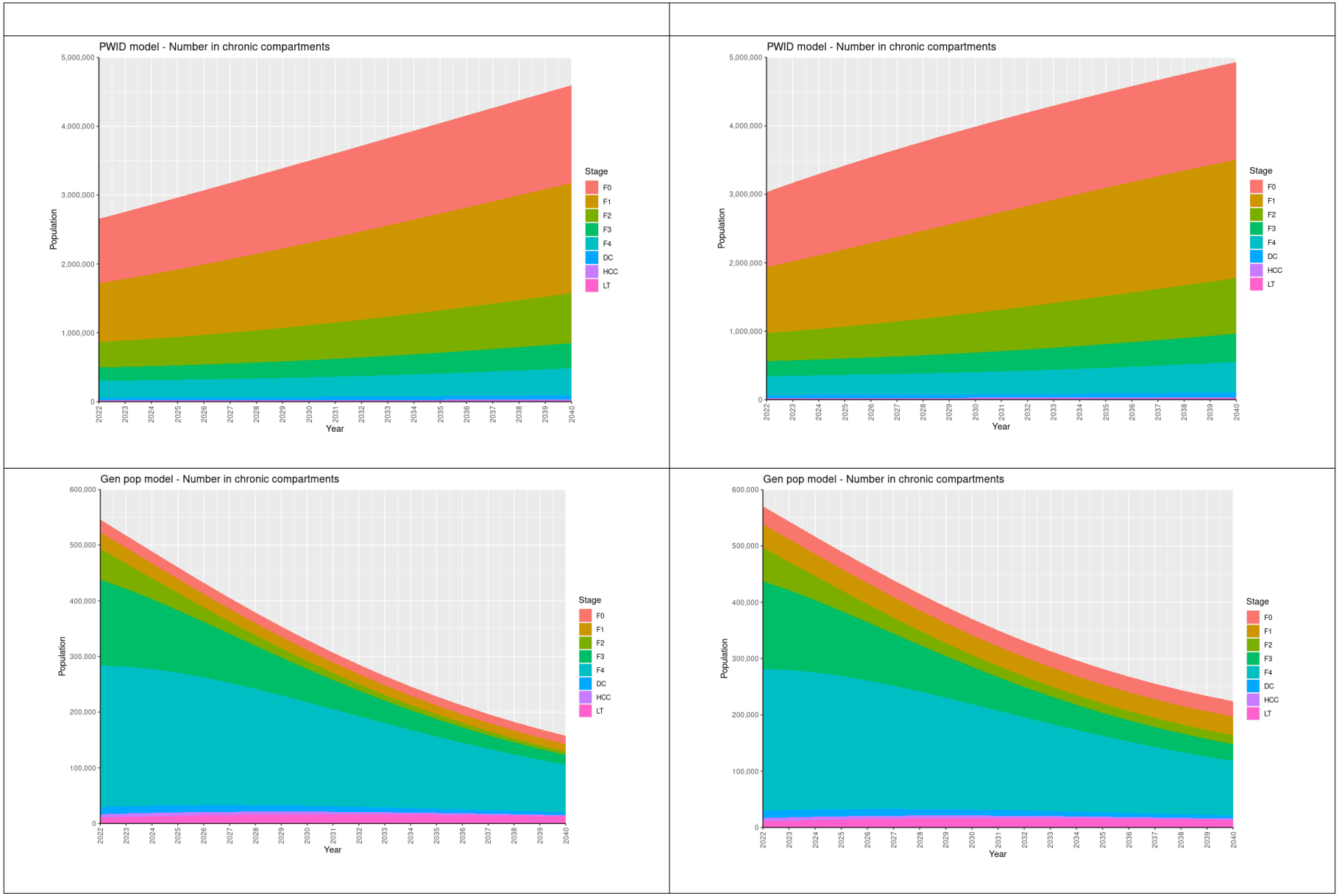


The total HCV subjects in 2016 is 3,500,000. Note that the model can't sustain the 20% estimate for the HCV proportion in the prison population. This trend could be changed by performing a parameter fitting to a subset of prison model parameters, except there is no data to base this fitting on.

Comparison of models with and without the fitting population

Turning off the flows to and from the prison population allows the effect on the general and PWID population to be characterized – see Figure 14. Given that the prison population has a higher infectiousness rate than the PWID population, it would be expected that the number of HCV cases in the PWID population would increase. As HCV is not modeled as an infectious disease in the general population, returning prisoners to the general population will have a large effect on the decline (as ‘baby boomers’ die) of HCV in the general population.

Figure 14 Comparison of PWID and gene pop without and with flows to and from prison population



1. Danielle Kaeble and Lauren Glaze, BJS Statisticians,Bureau of Justice Statistics. Correctional Populations in the United States, 2015. December 2016, NCJ 250374 https://bjs.ojp.gov/content/pub/pdf/cpus15.pdf Accessed Sept 2021

2. Stone J, Fraser H, et al, Vickerman P. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2018 Dec;18(12):1397-1409. doi: 10.1016/S1473-3099(18)30469-9. Epub 2018 Oct 29. PMID: 30385157; PMCID: PMC6280039.

3. Weinbaum C, Lyerla R, Margolis HS. Prevention and control of infections with hepatitis viruses in correctional settings. MMWR Recomm Rep. 2003;52(RR01):1-33 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5201a1.htm Accessed Sept 2021

4. Dolan K, Moazen B, Noori A, Rahimzadeh S, Farzadfar F, Hariga F. People who inject drugs in prison: HIV prevalence, transmission and prevention. Int J Drug Policy. 2015 Feb;26 Suppl 1:S12-5. doi: 10.1016/j.drugpo.2014.10.012. Epub 2014 Dec 1. PMID: 25727258.

5. Wikipedia. https://en.wikipedia.org/wiki/Incarceration_in_the_United_States Accessed Sept 2021

6. Stone J, Fraser H, Young AM, Havens JR, Vickerman P. Modeling the role of incarceration in HCV transmission and prevention amongst people who inject drugs in rural Kentucky. Int J Drug Policy. 2021 Feb;88:102707. doi: 10.1016/j.drugpo.2020.102707. Epub 2020 Mar 6. PMID: 32151496; PMCID: PMC7483428.

7. Tatar M, Keeshin SW, Mailliard M, Wilson FA. Cost-effectiveness of Universal and Targeted Hepatitis C Virus Screening in the United States. JAMA Netw Open. 2020 Sep 1;3(9):e2015756. doi: 10.1001/jamanetworkopen.2020.15756. PMID: 32880650; PMCID: PMC7489814.