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Norwegian Institute of Public Health

Modelling hepatitis C among risk groups in Norway

- to monitor progress towards elimination

Jørgen Eriksson Midtbø, NIPH infectious disease modelling group

Outline

1. Background: Hepatitis C in Norway, elimination goals
2. Model design, technical choices and challenges
3. Results and discussion

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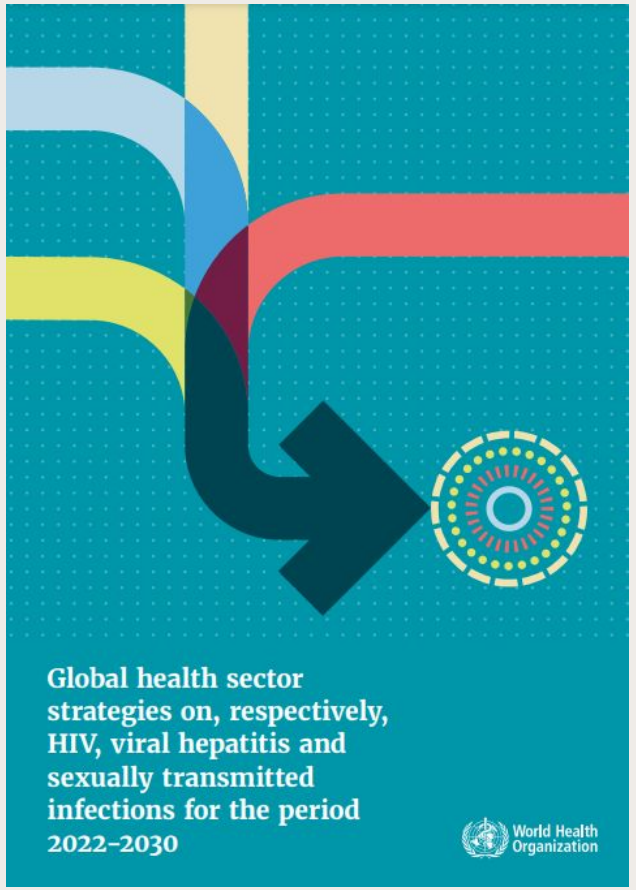
Background: Hepatitis C in Norway, elimination goals

WHO elimination goals for hepatitis C

- Chronic infection with hepatitis C virus (HCV) may cause progressive liver fibrosis
- A leading global cause of liver cirrhosis, cancer and death
- WHO estimates in 2019:
  - 58 million people lived with chronic hepatitis C
  - 1.5 million new infections/yr
  - 290 000 deaths/yr
- New oral direct-acting antivirals (DAA) are safe, effective and quick
  - Made free for everyone with HCV in Norway in February 2018
- Elimination goals by 2030:
  - 80 percent reduction in incidence from 2015
  - 5 new infections per 100 000 population, 2 per 100 000 for PWID
  - 2 deaths per 100 000
- NIPH has responsibility for monitoring progress towards elimination
  - Asked to make a model to estimate prevalence and incidence



Hepatitis C is concentrated in risk groups

- People who inject drugs (PWID) - active transmission
- Immigrants from high-prevalence countries - importers of chronic infection, little onward transmission (?)
- Other groups:
  - Persons infected through blood transfusion pre-1990
  - Men who have sex with men
  - Prevalence very low -> overshadowed by uncertainty in PWID + immigrants -> **not included**

Building on earlier work

Meijerink *et al. BMC Infectious Diseases* (2017) 17:541
DOI 10.1186/s12879-017-2631-2

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

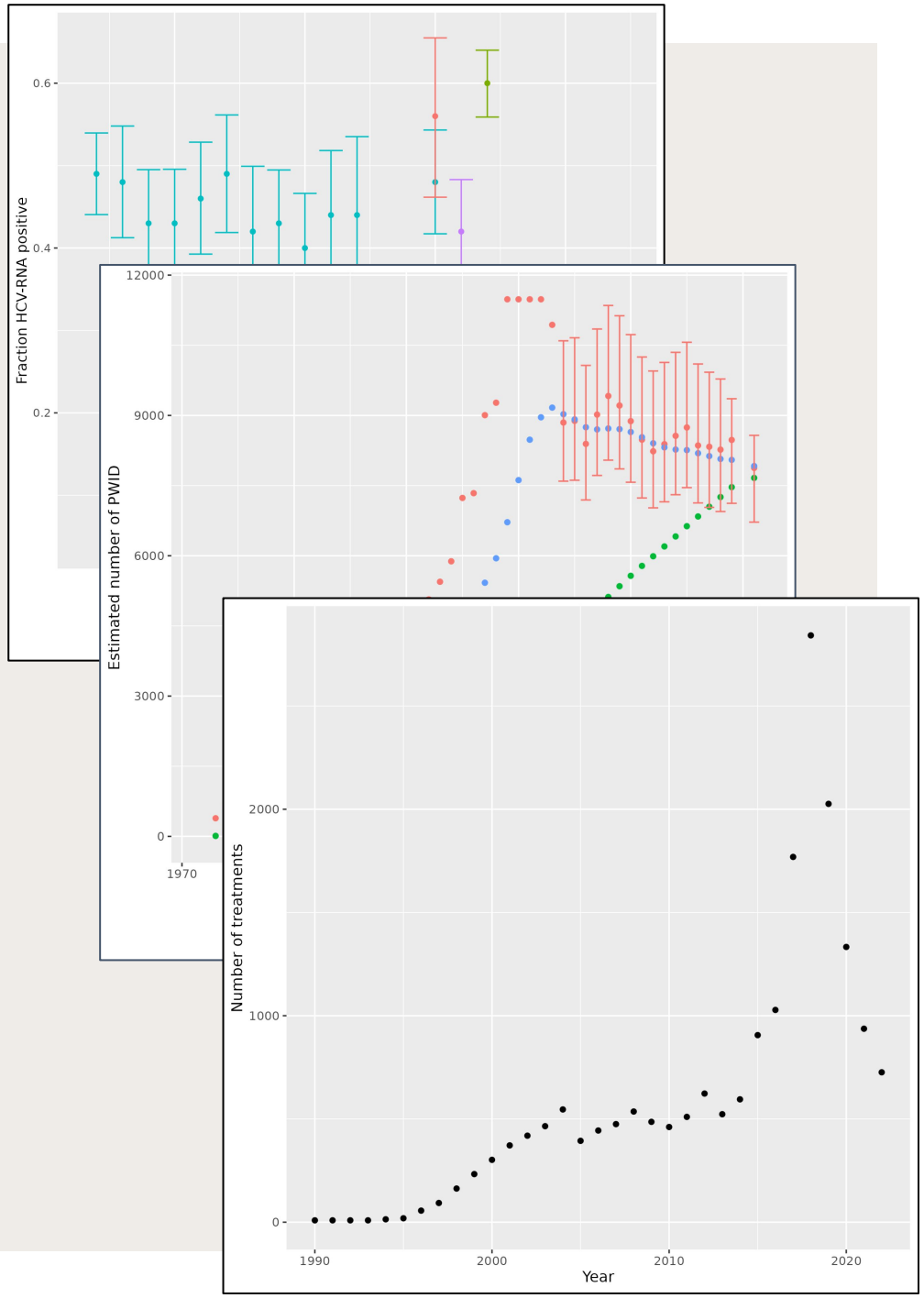
Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030

Hinta Meijerink[1,2], Richard A White[1], Astrid Løvlie[1], Birgitte Freiesleben de Blasio[1,3], Olav Dalgard[4,5], Ellen J. Amundsen[1], Espen Melum[6,7,8] and Hilde Kløvstad[1*]

- Modelling study on HCV among PWID in Norway
- 2017 - just before DAA treatments
- Main focus on severe outcomes
- Not straightforward to update and rerun their model, so we built a new one
  - However, many choices in our model inspired by this paper!

Patchy data sources

- RNA and antibody prevalence surveys - convenience sample among active PWID
- Total number of PWID - estimated from drug overdose deaths
- Number of treatments per year + estimated treatment success probability
- Immigrants: Lacking any kind of prevalence data for Norway



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Model design

Data, technical choices & challenges

A stochastic compartmental model

- Inference is performed by a particle filtered Markov Chain Monte Carlo (pMCMC) engine implemented in the *mcstate (odin/dust)* framework within R
  - Parameters are a combination of random walk in time and time-constant, inferred jointly
- All data sources are evaluated together against all parameters in a total likelihood function

https://mrc-ide.github.io/mcstate/articles/sir_models.html

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```
## Core equations for transitions between compartments:
update(S) <- S - n_SI
update(I) <- I + n_SI - n_IR
update(R) <- R + n_IR

## Individual probabilities of transition:
p_SI <- 1 - exp(-beta * I / N) # S to I
p_IR <- 1 - exp(-gamma) # I to R

## Draws from binomial distributions for numbers changing between
## compartments:
n_SI <- rbinom(S, p_SI)
n_IR <- rbinom(I, p_IR)

## Total population size
N <- S + I + R

## Initial states:
initial(S) <- S_ini
initial(I) <- I_ini
initial(R) <- 0

## User defined parameters - default in parentheses:
S_ini <- user(1000)
I_ini <- user(1)
beta <- user(0.2)
gamma <- user(0.1)
```

README.md

https://github.com/Gulfa/metapop

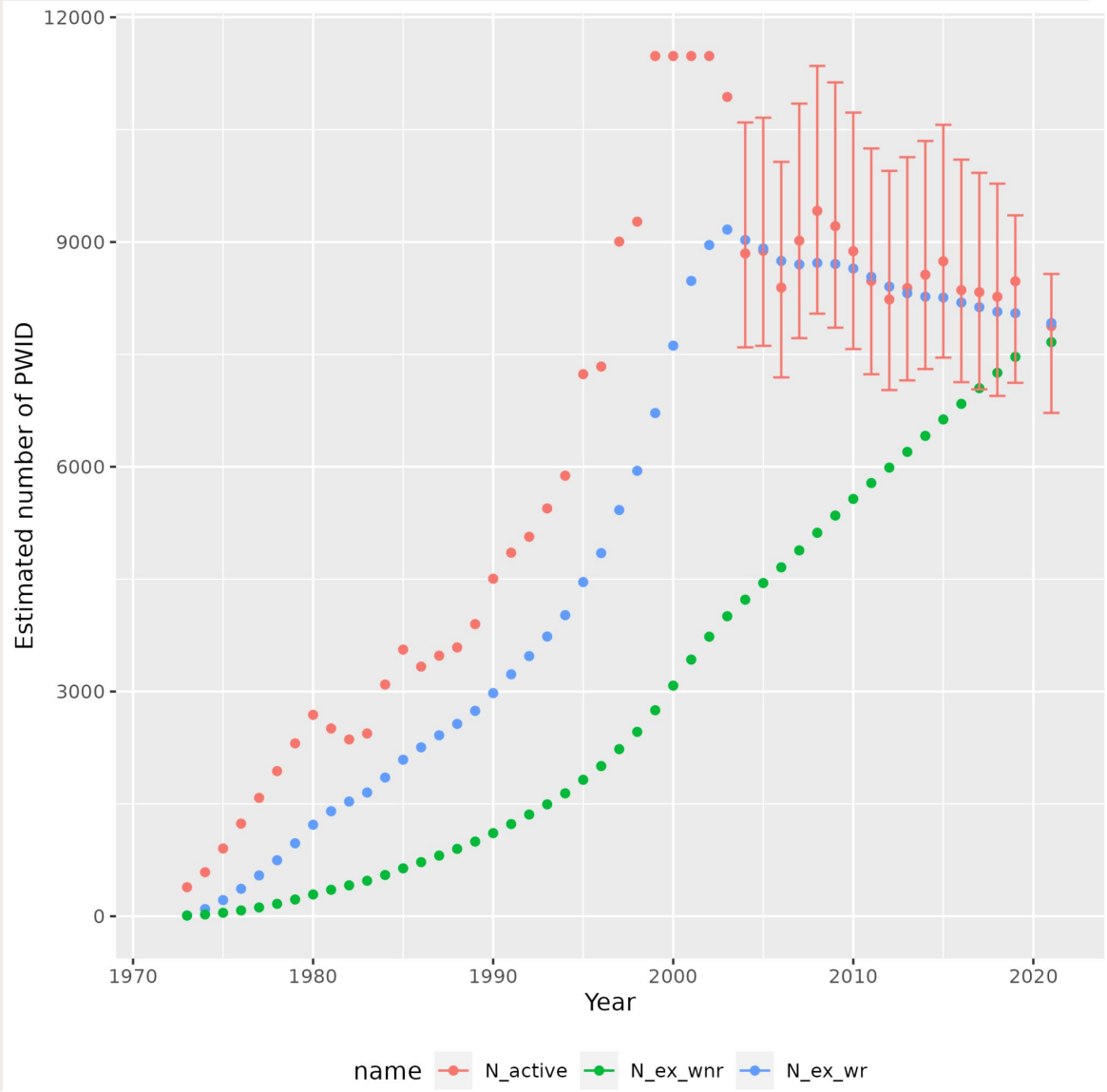
metapop

A stochastic metaopulation model with vaccination and multiple strains. Initially developed for modelling COVID-19 in Norway

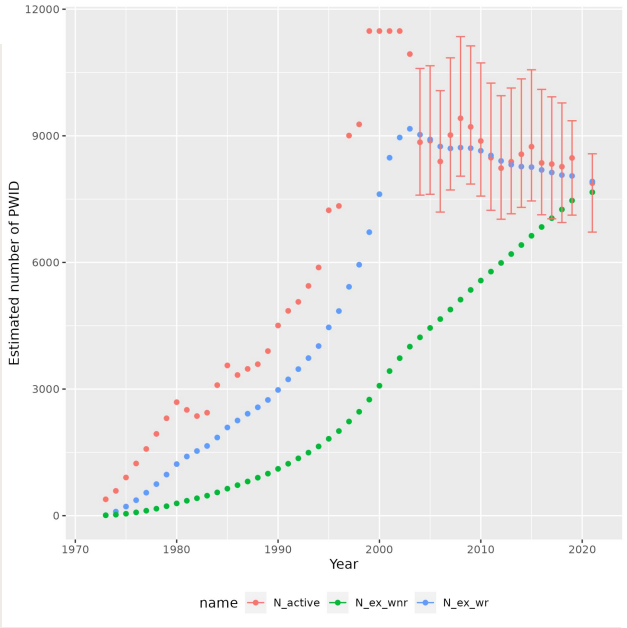
https://mrc-ide.github.io/mcstate/articles/sir_models.html

The PWID population

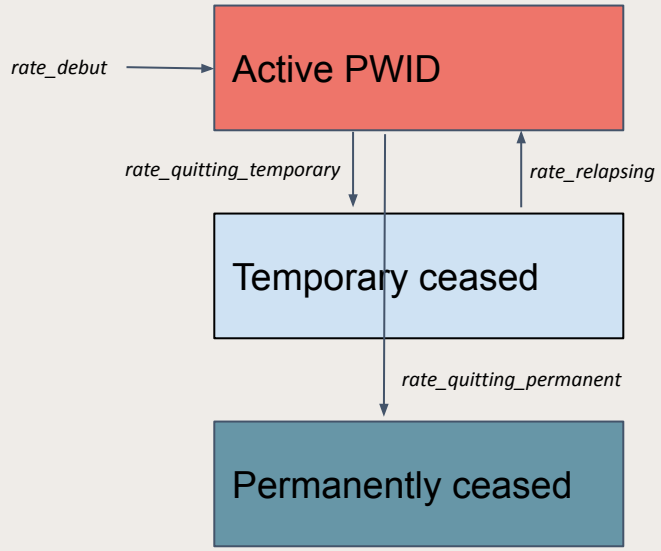
Estimated by mortality multiplier method courtesy of NIPH, Dept. of Alcohol, Tobacco and Drugs



The PWID population



- We make a model for the PWID population consisting of three groups
  - Active PWID - currently injecting
  - PWIDs temporarily ceased injecting, will relapse
  - PWIDs permanently ceased injecting
- Parametrise this by four rates
  - *rate_debut*
  - *rate_quitting_temporary*
  - *rate_relapsing*
  - *rate_quitting_permanent*
- To give model necessary flexibility, we do a random walk on *rate_debut* over time
  - The particle filter is used to filter the desired trajectories
  - The 3 other parameters are kept constant in time, inferred by MCMC



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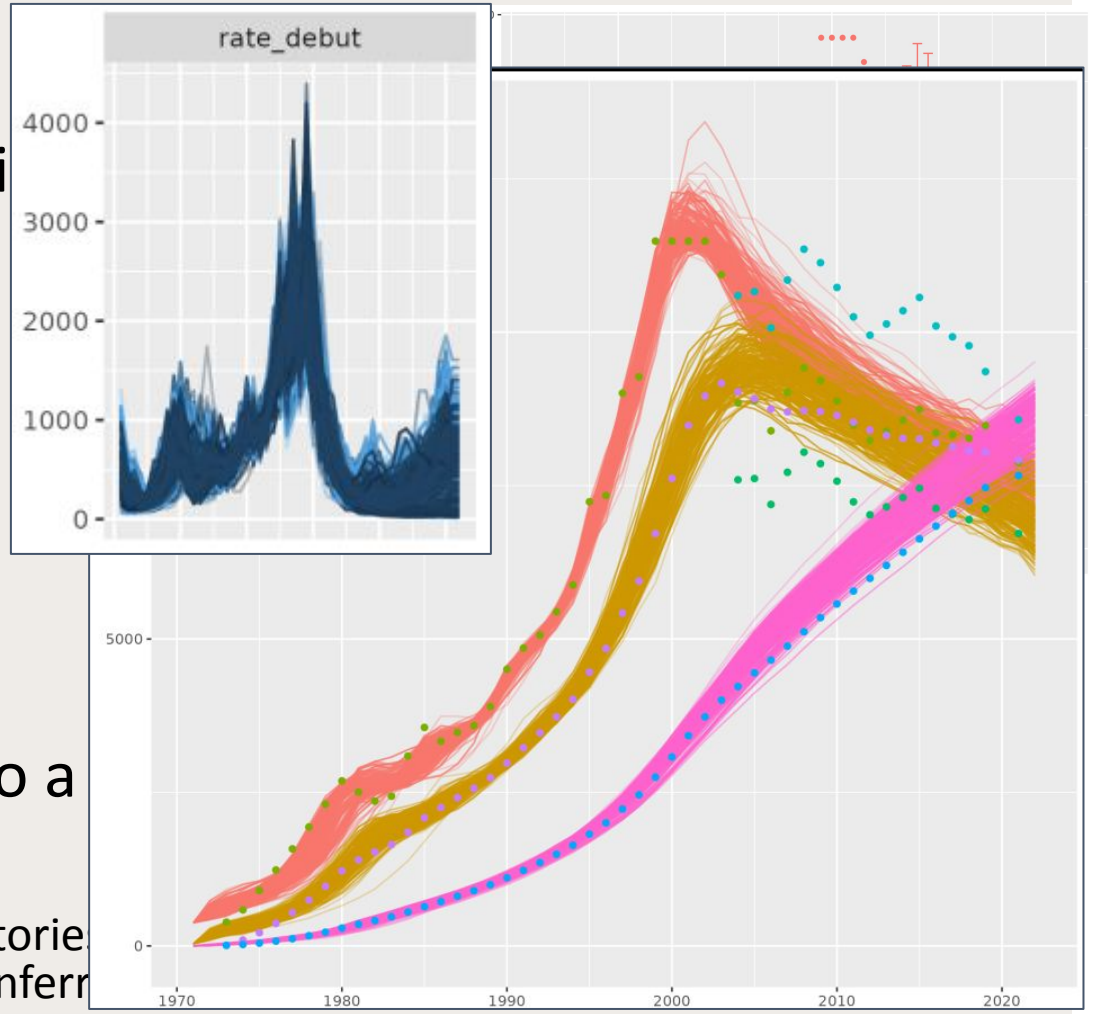


Sequential Monte Carlo (particle filter)

At each time step, the model draws a random perturbation on *rate_debut* (and on *rate_treatment*)

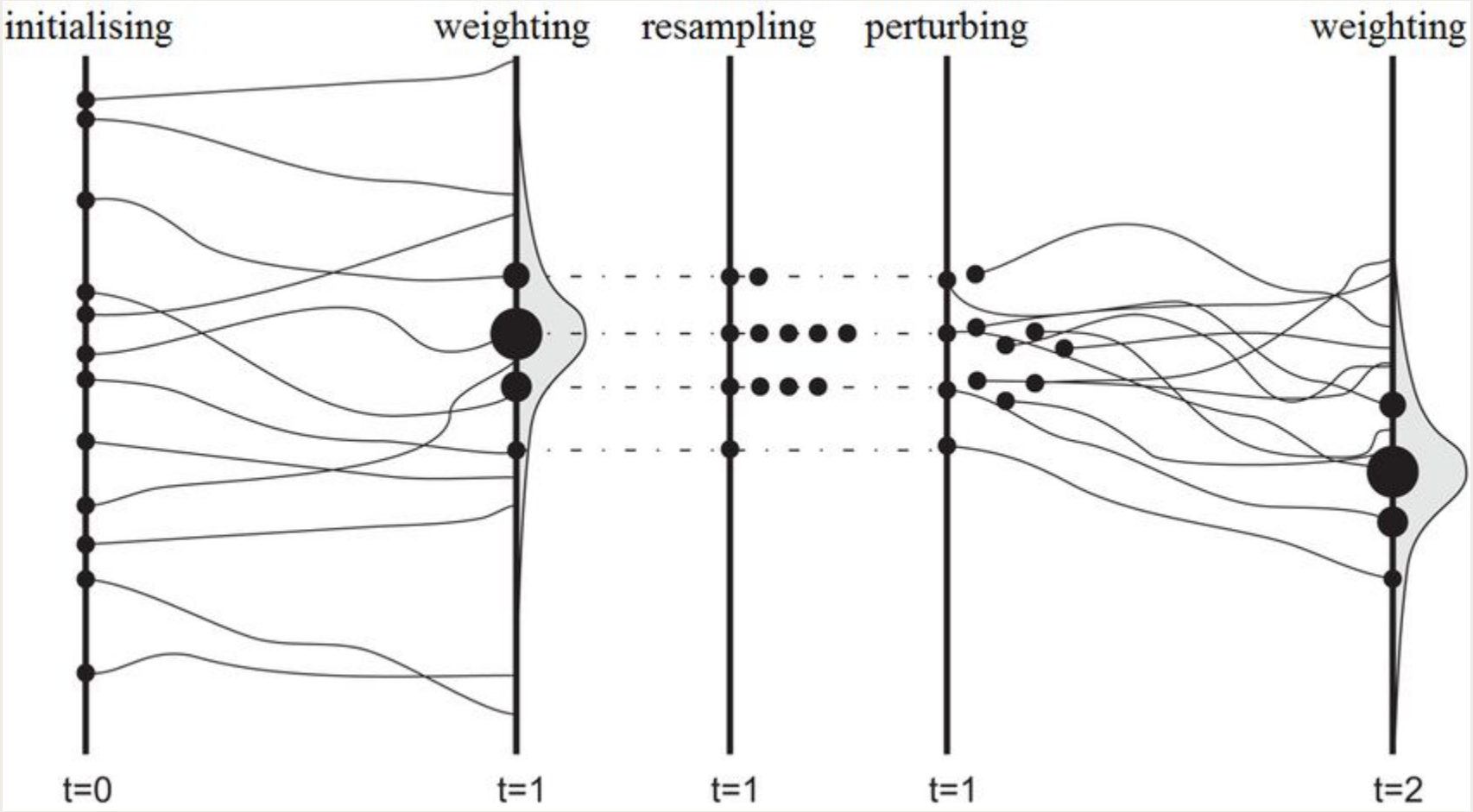
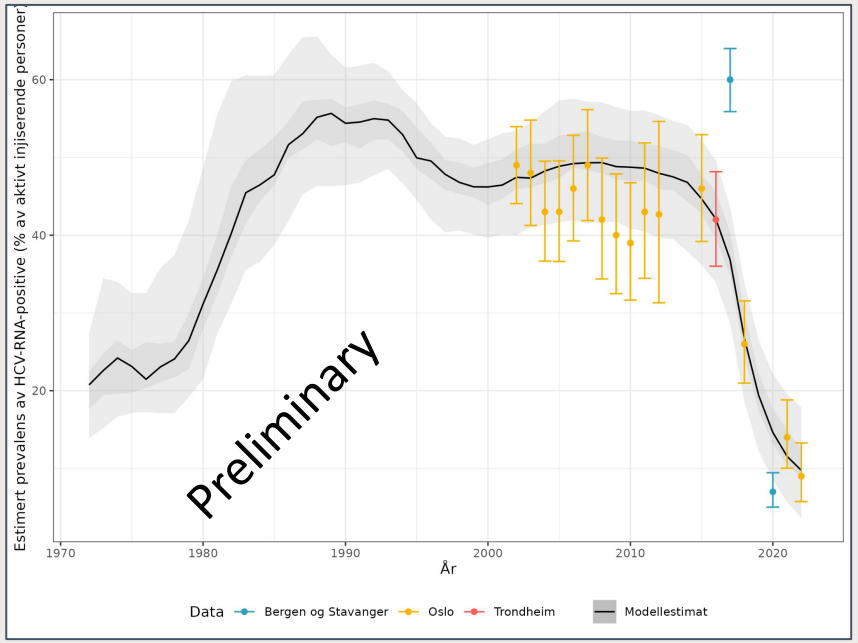
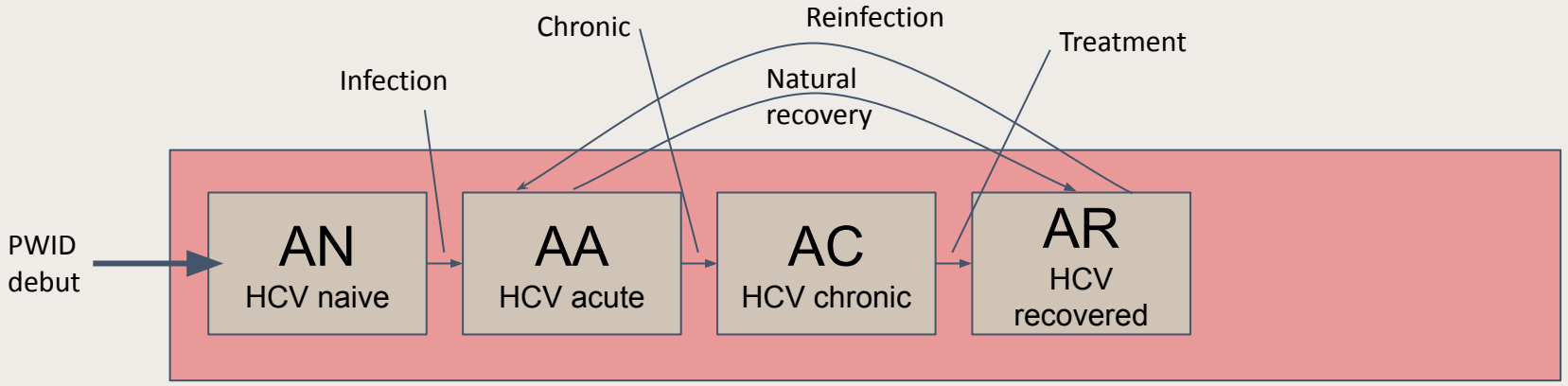


Illustration by Danilo Alvares

Spreading of HCV among active PWID

- Assume a constant underlying transmission rate β through simulation, inferred by MCMC
- Effective transmission rate lowered gradually by
  - needle and syringe and opioid substitution treatment programmes
  - geographical dispersion - GINI coefficient
- Informed by fraction active PWID who are RNA positive





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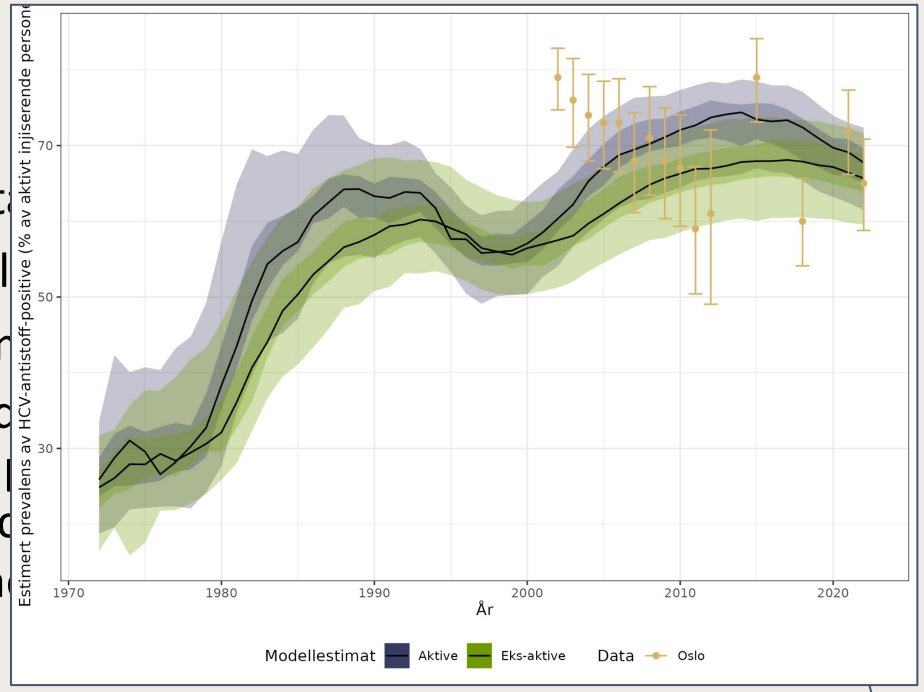
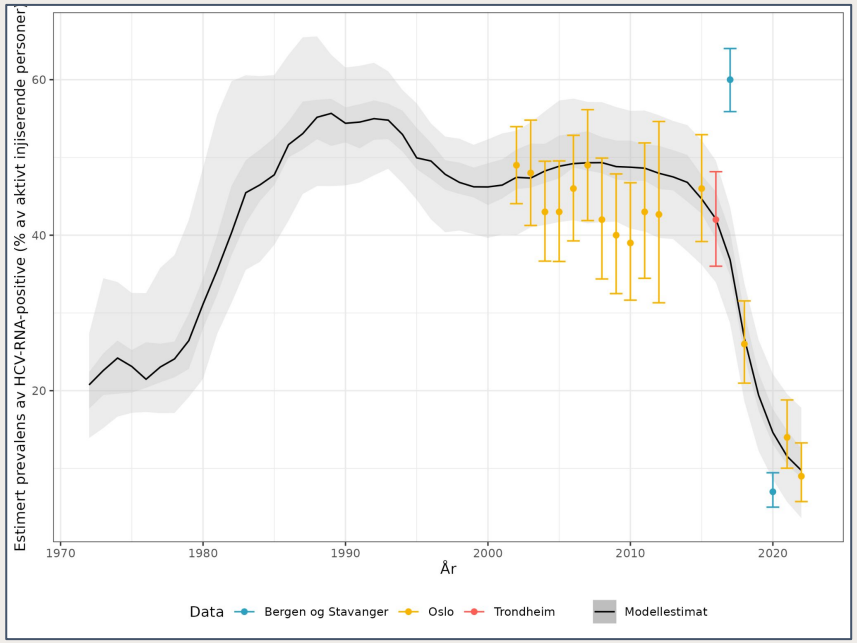
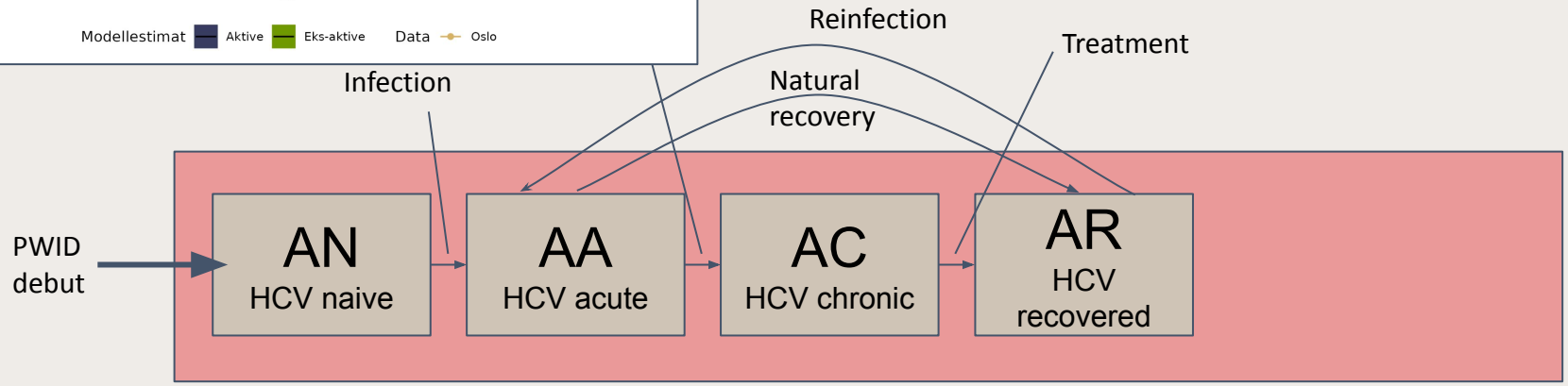
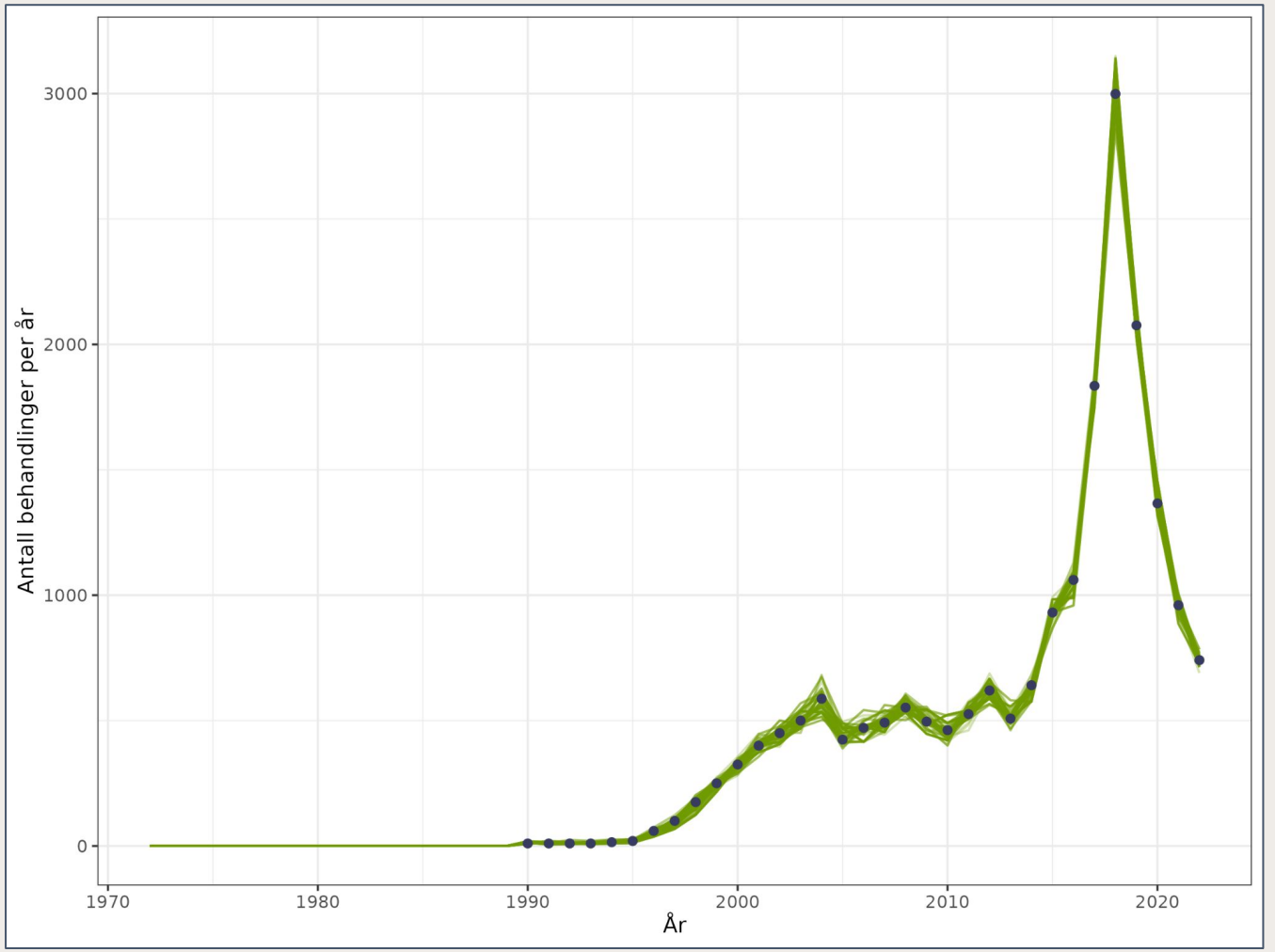






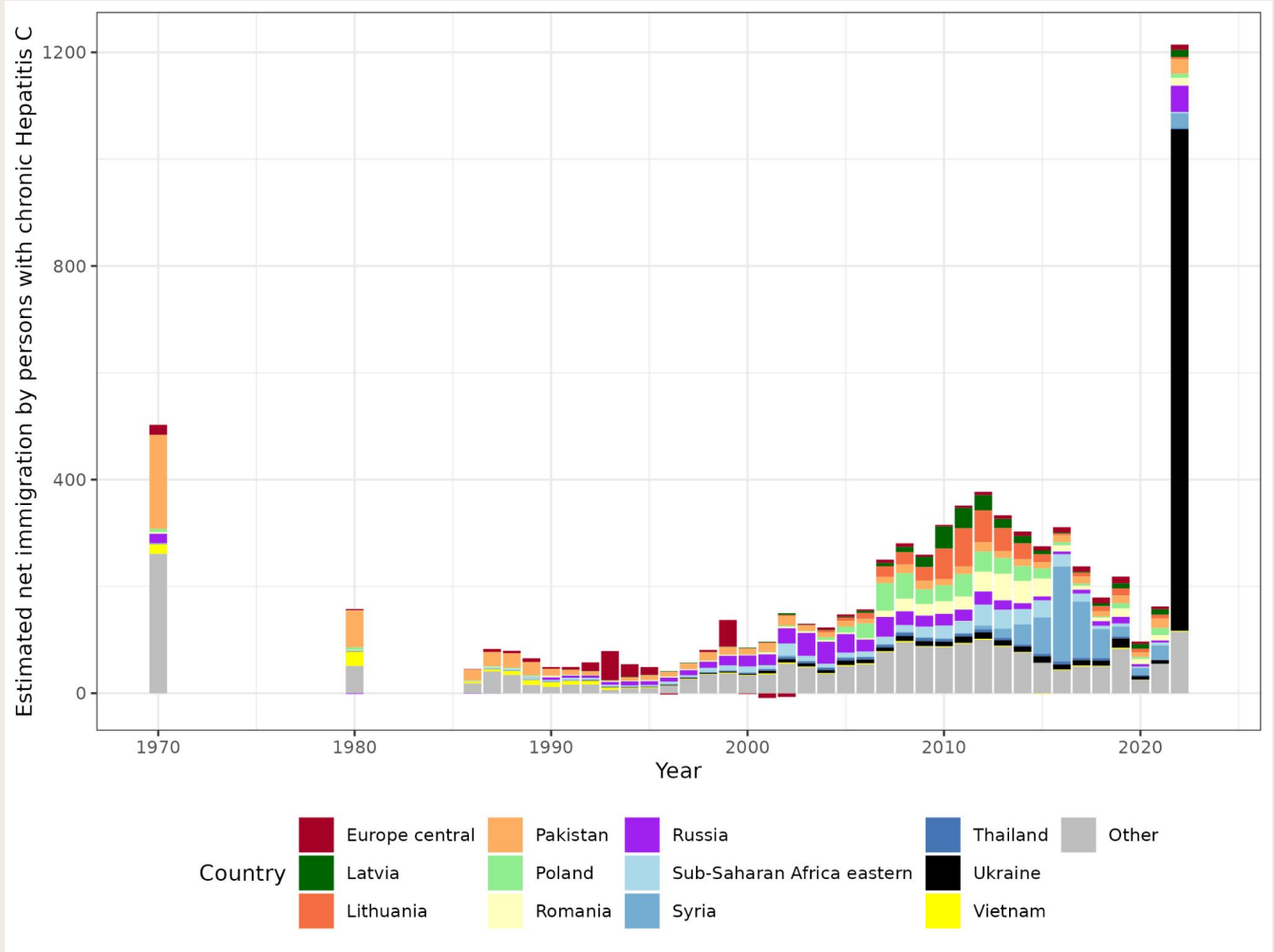
Treatments

- Treatment rate varies significantly from year to year, and thus is modelled as another random walk parameter against the particle filter.
- We assume that all groups (active and ex PWID, immigrants) have the same per-person probability of seeking treatment



Immigrants

- We have no data on Norwegian immigrant HCV prevalence
- Immigrants are however needed in the model because they couple to the PWID through treatment data
- We make a simplistic assumption:
  - yearly immigration data +
  - per-country HCV prevalence estimates



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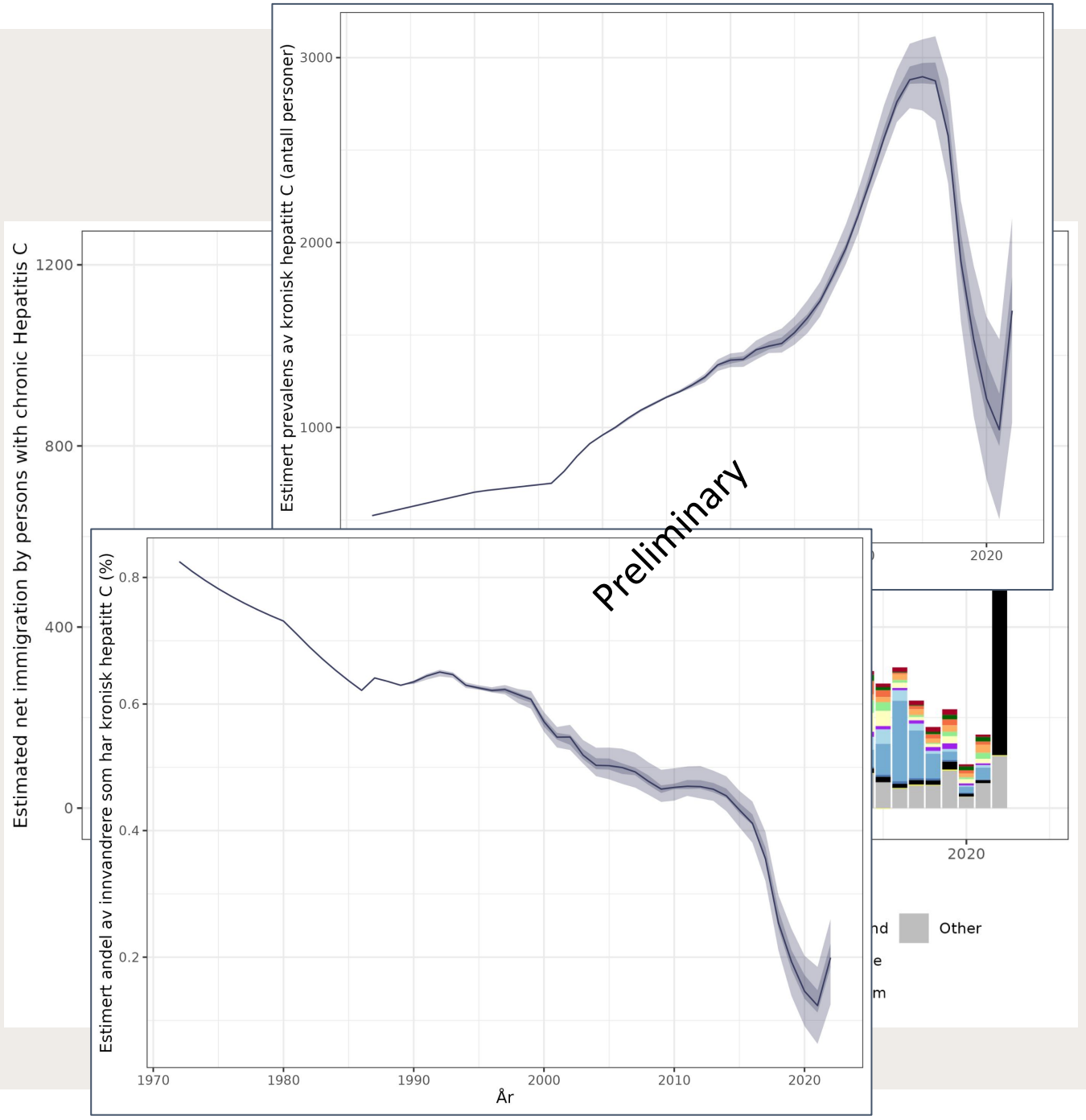

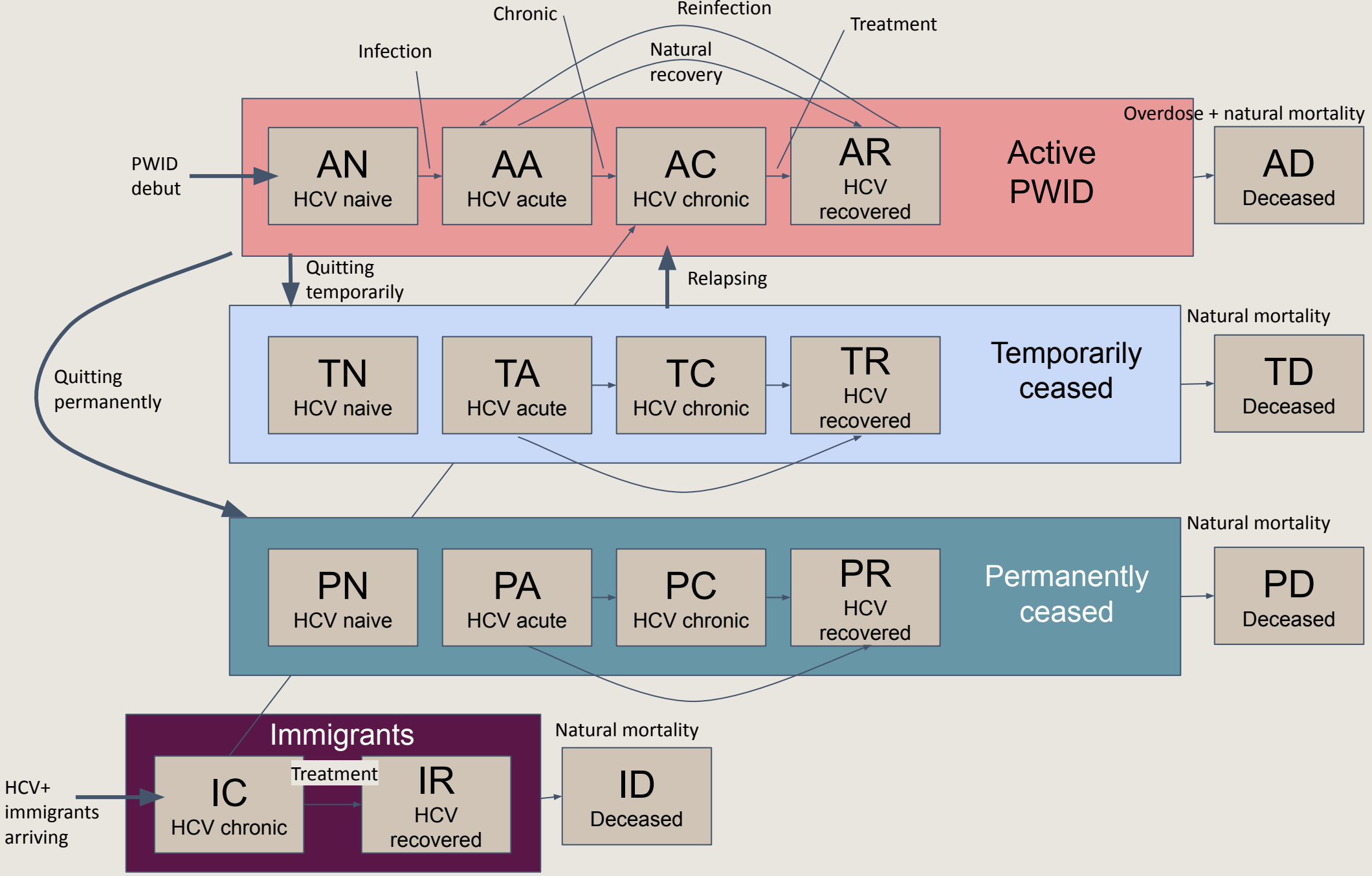
Chronic
Reinfection
Treatment
Infection
Natural recovery
Overdose + natural mortality
PWID debut
AN HCV naive
AA HCV acute
AC HCV chronic
AR HCV recovered
Active PWID
AD Deceased
Quitting temporarily
Relasping
Natural mortality
Quitting permanently
TN HCV naive
TA HCV acute
TC HCV chronic
TR HCV recovered
Temporarily ceased
TD Deceased
Natural mortality
PN HCV naive
PA HCV acute
PC HCV chronic
PR HCV recovered
Permanently ceased
PD Deceased
Immigrants
Natural mortality
HCV+ immigrants arriving
IC HCV chronic
Treatment
IR HCV recovered
ID Deceased

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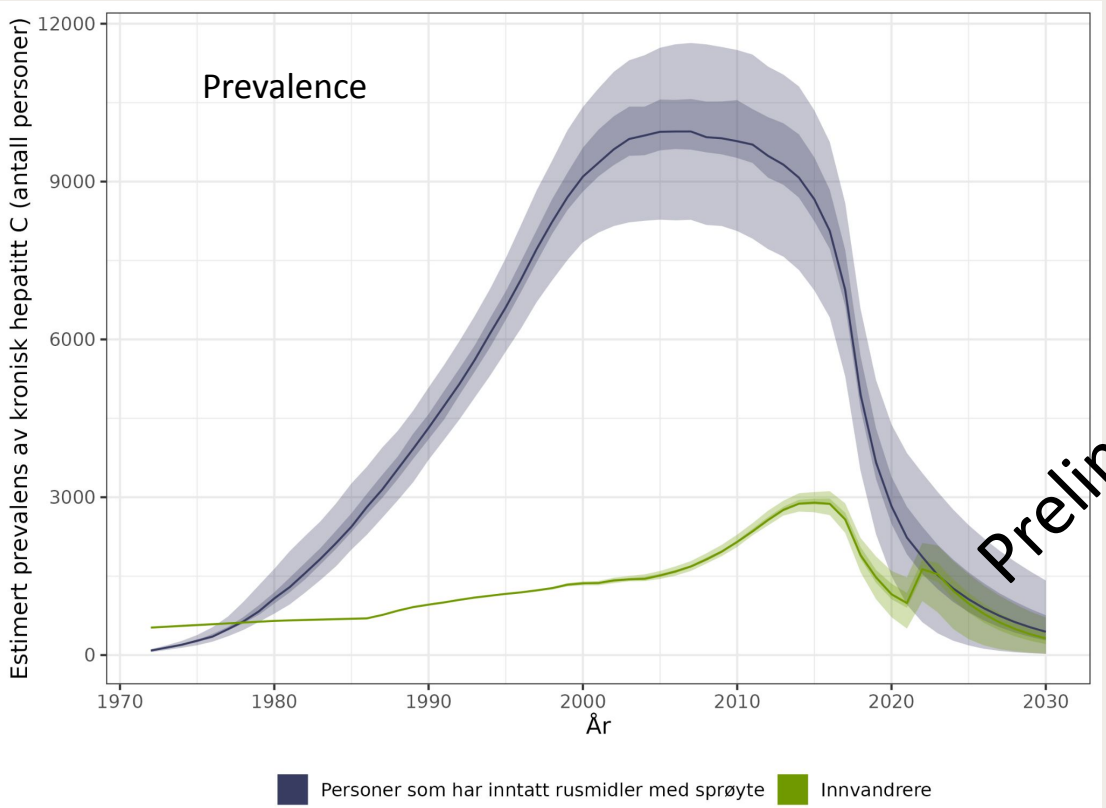
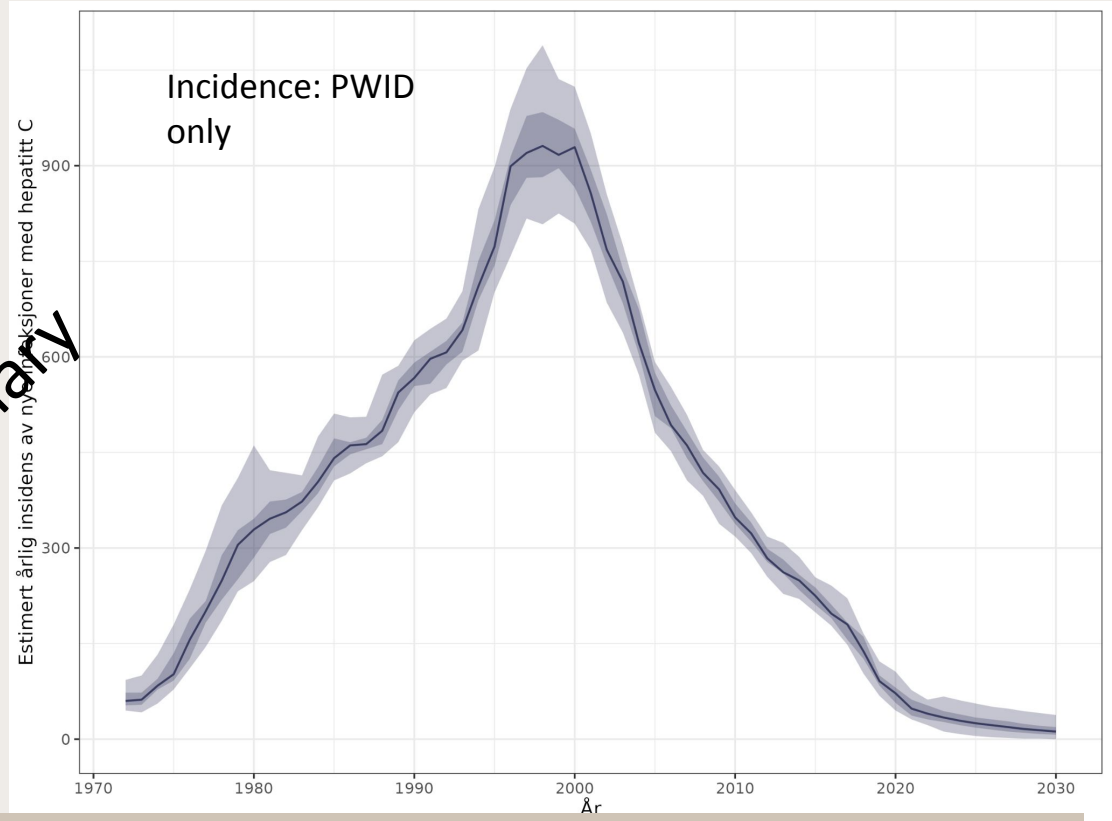
Results and conclusions

The model suggests Norway is on track to reach elimination goals

The model predicts forward in time by keeping random-walk parameters constant at last value



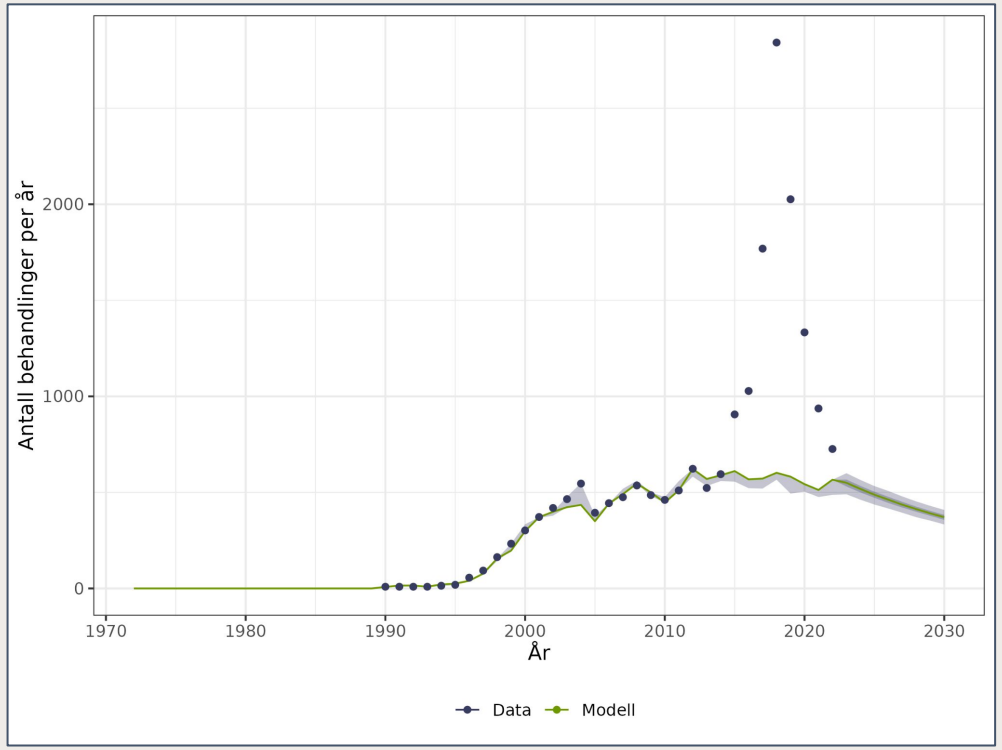
Preliminary

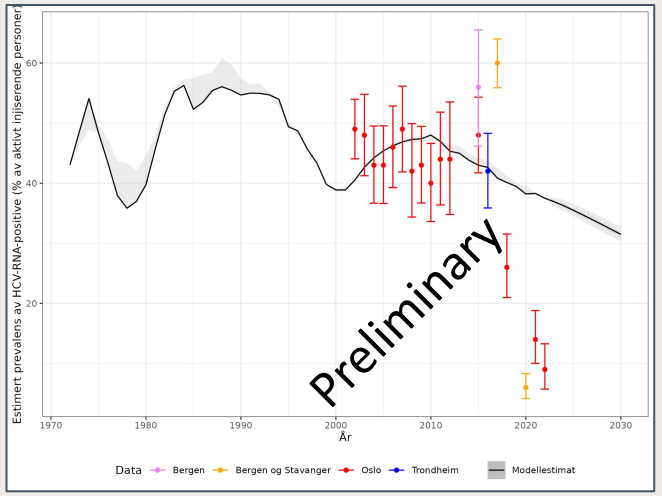


The large error bands make the case for closer monitoring of risk groups

Counterfactual: The impact of DAA treatments

Keep the transmission rate fixed at with-treatment model estimate, keep treatments at 2013 level





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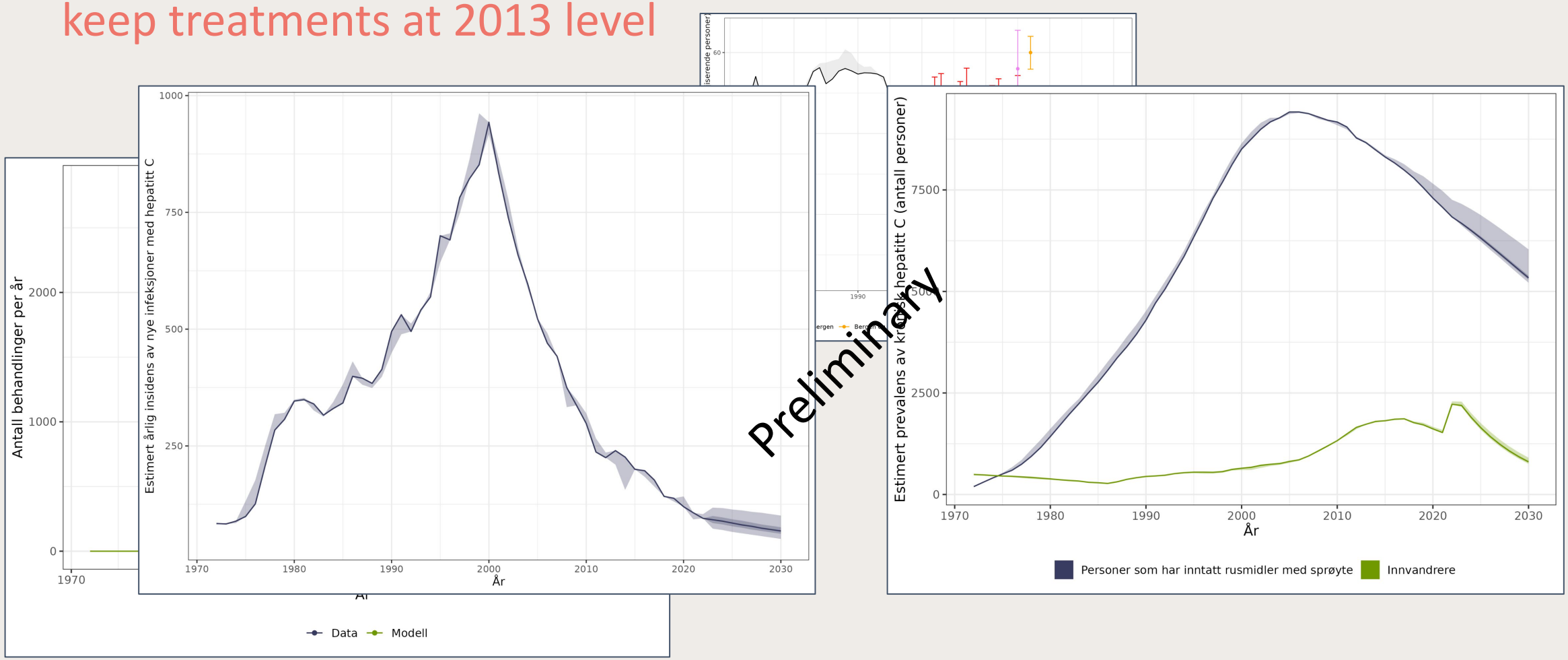

Conclusions and outlook

- The hepatitis C prevalence & incidence is estimated to be rapidly declining, and this is largely attributable to treatment
- Norway is estimated to be **on track** to reach the elimination goals, and the hepatitis C epidemic among PWID is predicted to die out
- More sensitivy analyses needed, e.g.
  - Vary assumptions on immigrant prevalence
  - Test assumption of equal treatment uptake
- Question: How to choose the “correct” number of particles in the particle filter to represent uncertainty and not overfit? (Presently 10^3-10^4)

This work is done together with **Robert Neil Whittaker**, with valuable input from Hilde Kløvstad, Sasi Kandula, Gunnar Rø, Birgitte de Blasio and others.