The potential prevention benefits of a treat-all hepatitis C treatment strategy at global, regional, and country levels: a modelling study

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Hepatitis C virus (HCV) epidemic

- Highly effective direct acting antivirals (DAAs) have been developed as treatment for hepatitis C virus (HCV) infection
- An estimated **71 million** people are infected with HCV globally
- The WHO has set targets to eliminate HCV by 2030
  - Includes **reducing incidence** by 80% from 2015 levels

- Main modes of transmission: injecting drug use, unsafe medical injections and procedures, and vertical transmission
  - Injecting drug use important in many settings[1]
  - Unsafe medical procedures important mostly in low- and middle-income settings[2]

1: The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. Trickey et al, 2019
2: Evolution of the global burden of viral infections from unsafe medical injections, 2000-2010. Pepin et al, 2014

Treatment as prevention and aims

- Many countries are developing strategies to scale-up treatment
- **Some countries have treatment guidelines excluding people with substance use issues or limit treatment to those with advanced liver disease**
- How do we treat to prevent transmission?
  - Target high risk groups?
  - What prevention gains do we achieve from a treat all strategy?

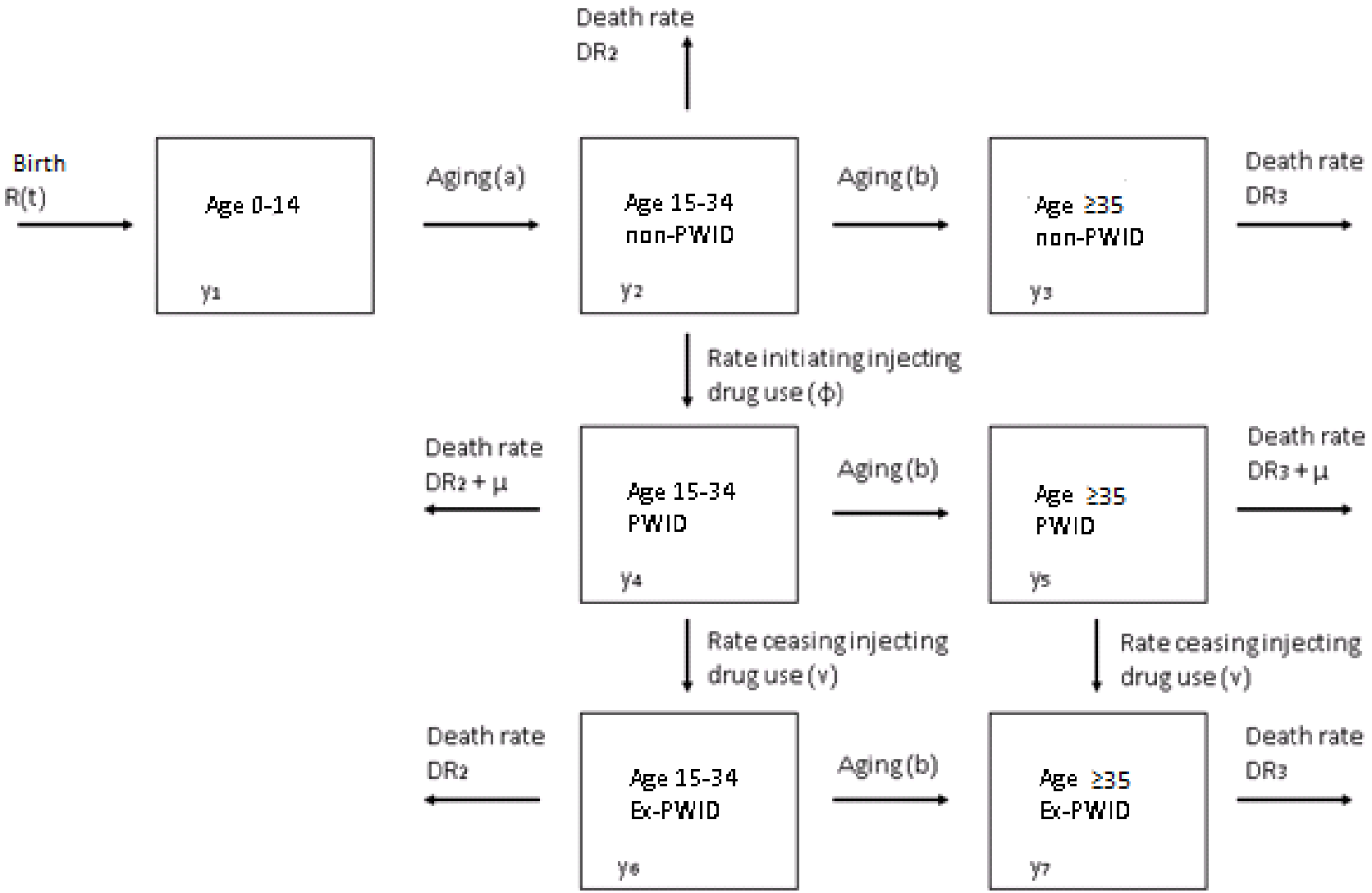
- We **aimed** to estimate the number of infections averted by treating people with chronic HCV, for several strategies:
  - Treat all
  - Treat people who inject drugs (PWID)
  - Treat older age groups
  - Treat people with advanced liver disease

Model description

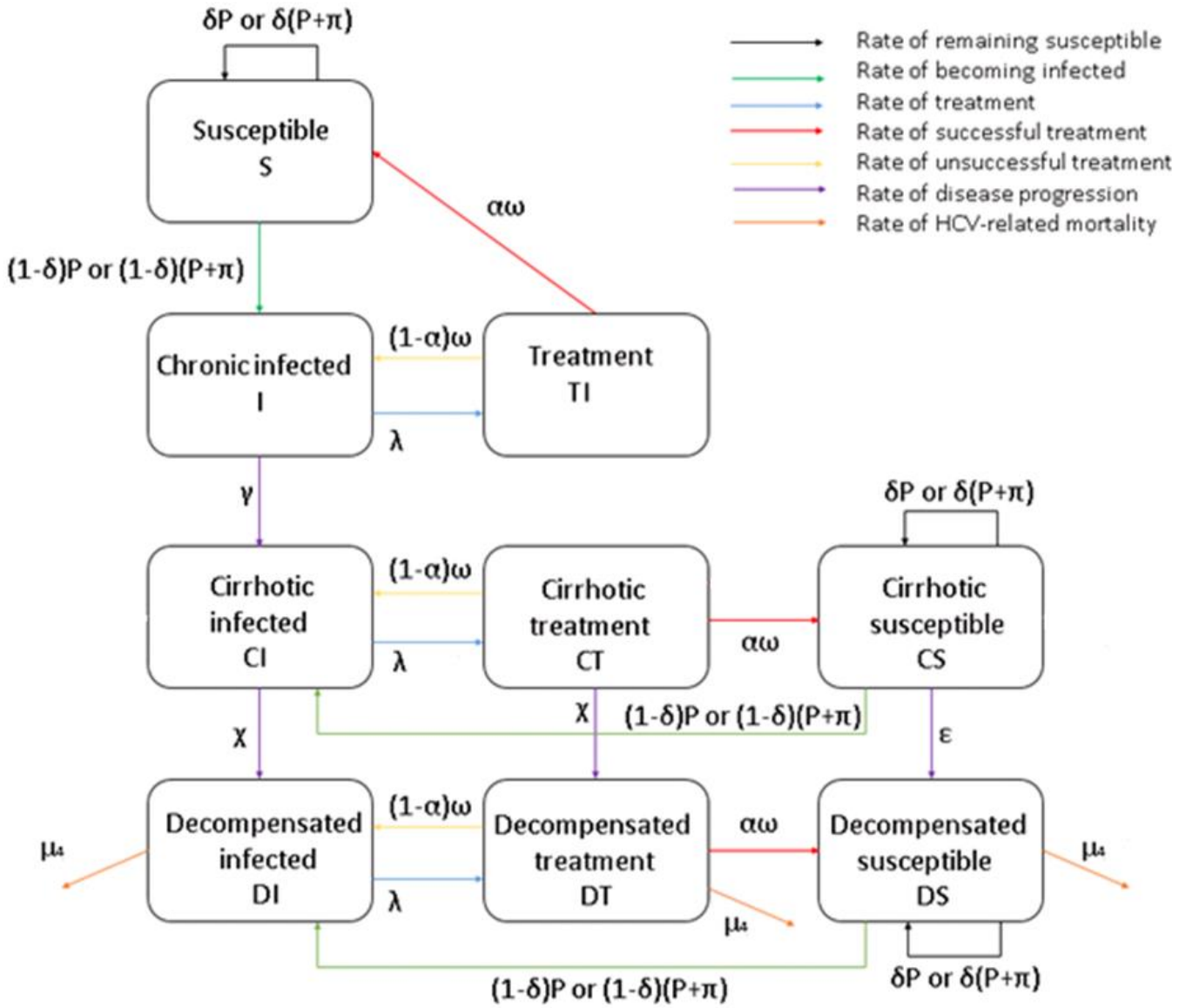
- A dynamic, deterministic model of HCV transmission for simulating country-level HCV epidemics among:
  - PWID
  - the general population

- Incorporates:
  - population growth
  - ageing
  - demographics
  - disease progression
  - injecting drug use
  - vertical HCV transmission
  - historical treatment numbers

Schematic of age and injecting status



Schematic of HCV infection, treatment and disease progression



Model parameterization

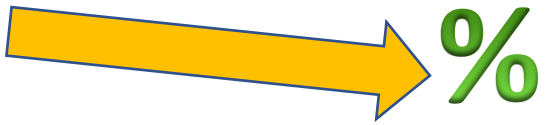
- Demographic information: UN datasets
- Key parameters and bounds from various systematic reviews:
  - HCV prevalence among general population[1]
  - HCV prevalence among PWID[2]
  - Proportion of adults that are PWID[2]
- **Countries included if data were available on all three key parameters**
- Model accounted for uncertainty in parameters for each country

- Model uses historical country-level treatment data taken from a range of sources (mostly the Center for Disease Analysis: https://cdafound.org/polaris/)

1: Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Blach et al, 2017
2: Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Degenhardt et al, 2017

Key model assumptions

- Decreasing HCV epidemics among general population (around 1% per year)[1] - due to evidence from countries with 2 surveys



- Stable HCV epidemics among PWID[2]
- Stable proportion of adults that are PWID[2]
  - except in Eastern Europe and Sub-Saharan Africa: increasing

- Assumptions investigated in many sensitivity analyses

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Mathematical model scenarios

- The model was run 2018-2038 (1000 model fits for each country)
- Firstly with that country's baseline level of treatment (counterfactual)
- And then with **50 additional individuals being treated in 2018**
  - Treat all – individuals randomly selected from all infected individuals
  - Treat PWID – selected randomly from PWID
  - Treat older age groups – selected randomly from people ≥35 years
  - Treat people advanced liver disease – selected randomly from people with cirrhosis
  - Infected individuals can overlap between categories
- Track benefits to 2038 with baseline treatments from 2018 continued
- Low number of 50 treatments chosen to give an estimate of prevention benefit without altering each country's epidemic trajectory

Determinants of infections averted

- To investigate the determinants of the number of infections averted per treatment we used **univariable and multivariable linear regression analyses** of country-level characteristics:
  - Current population growth rates
  - Population-attributable fraction of IDU to HCV transmission (from Trickey et al[1])
  - Population proportion of PWID among adults[2]
  - Average duration of IDU
  - HCV prevalence among PWID
  - HCV prevalence among the general population
- We did this for the infections averted in the treat all and PWID scenarios

1: The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. Trickey et al, 2019
2: Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Degenhardt et al, 2017

Countries included

- 88 countries were modelled that had the required data(85% of world's population)

Global results summary

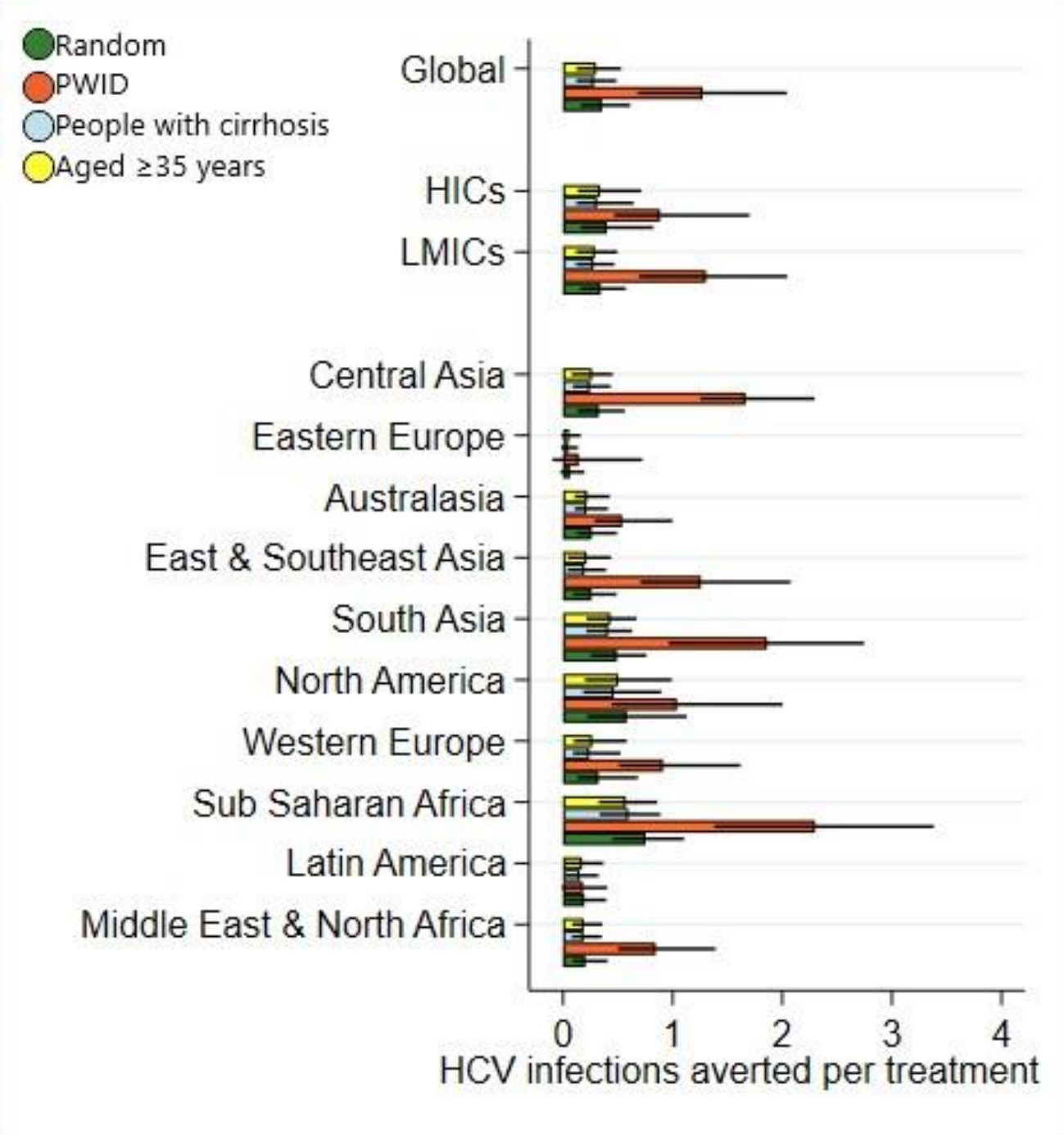
- Similar numbers of infections averted per treatment for treat all, cirrhosis, and age ≥35 years strategies – much higher for PWID

Strategy	Global average HCV infections averted 2018-2038 per treatment Median (95% credibility intervals)
Treat all (random selection)	**0.35 (0.16, 0.61)**
People aged ≥35 years	**0.30 (0.12, 0.53)**
People with cirrhosis	**0.28 (0.12, 0.49)**
PWID	**1.27 (0.68, 2.04)**

- Extra analyses (with similar methods) suggest that from the 1.5 million HCV treatment globally in 2018, **525,764 (95%CrI: 243,948-980,523)** chronic HCV infections would be averted over the next 20 years

Regional variation

- Less infections averted in high-income countries (HICs) than low- and middle-income countries (LMICs)
- Eastern Europe appears to have the least benefit of treatment as prevention, followed by Latin America
- Sub Saharan Africa and South Asia see the biggest benefit

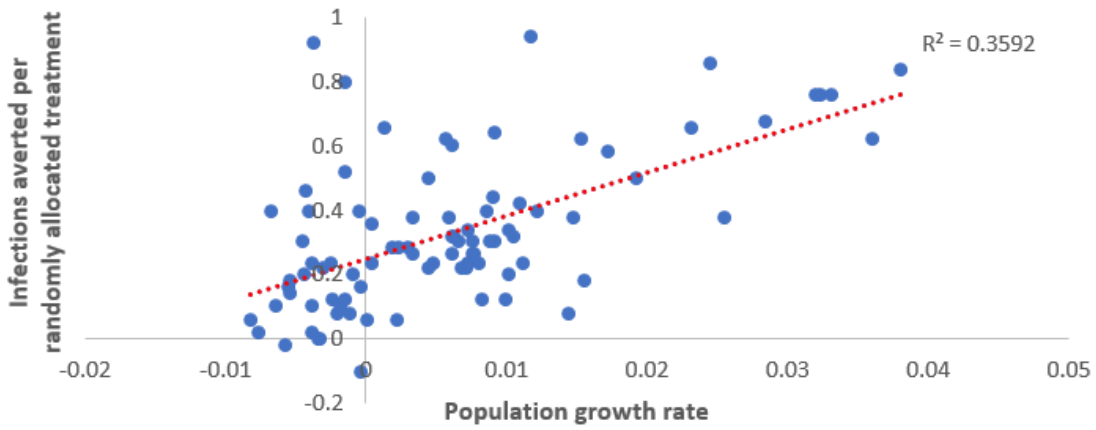


Determinants of infections averted

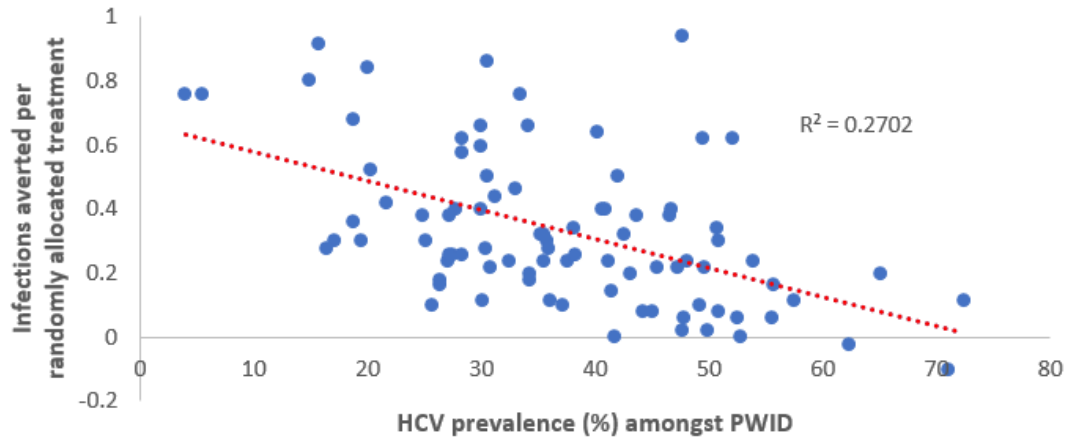
- For both the random allocation (treat all) strategy and the PWID strategy, the infections averted is associated with:
  - Increases ↑ with a country's population growth-rate
  - Increases ↑ with the proportion of adults that are PWID
  - Decreases ↓ with HCV prevalence in the general population
  - Decreases ↓ with HCV prevalence in PWID

Treat all strategy

a)

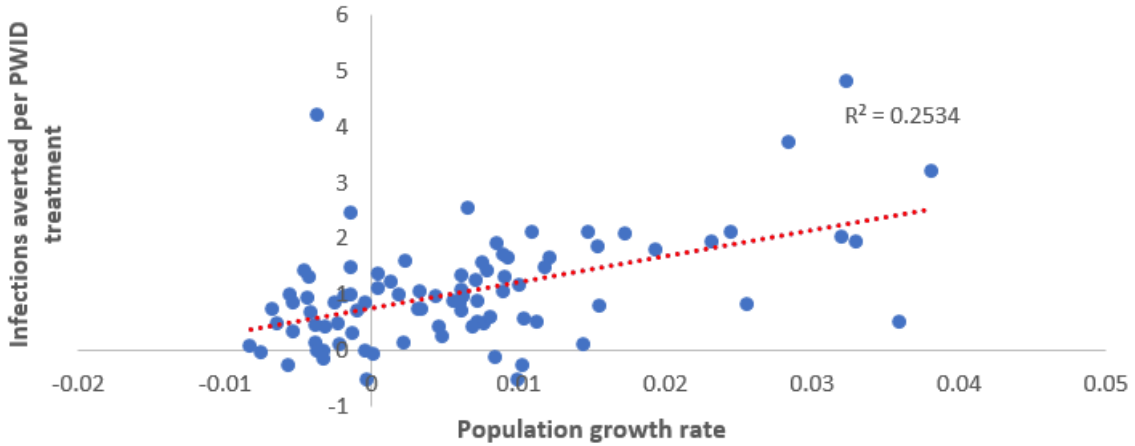


b)



PWID strategy

a)



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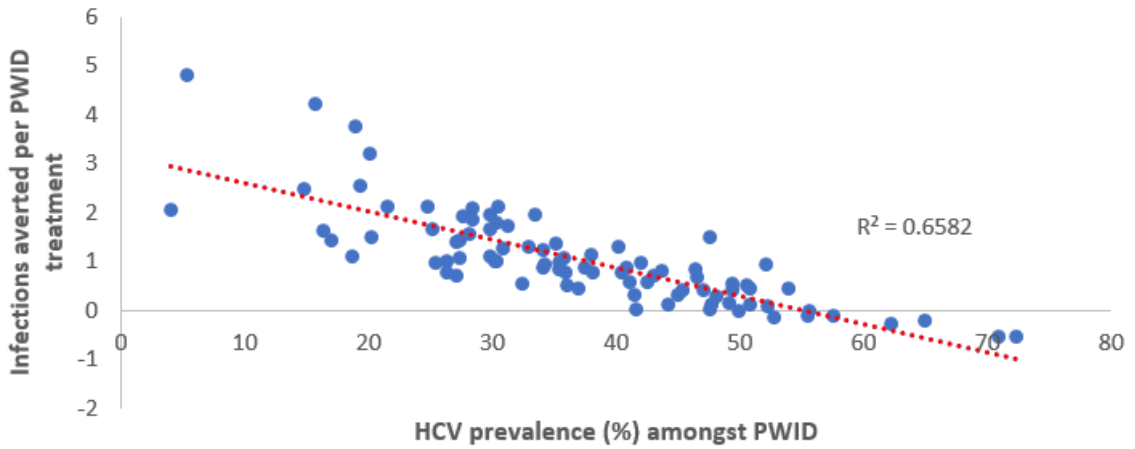

Sensitivity analyses

- Each strategy averts more infections if the gen-pop HCV prevalence is stable instead of decreasing: 0.55 (95%CrI: 0.36-0.77) (vs 0.35)
- More infections averted if we assume regional epidemic trajectories differ based on CDA analyses[1]: 0.65 (95%CrI: 0.30-1.10) (vs 0.35)
- Halving background treatment rates among PWID and doubling among people with cirrhosis produces a similar number of infections averted compared with the baseline projections
- Including only the countries with ≥2 key prevalence parameters scored as moderate or better quality, the IA per treatment was similar

1: Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Blach et al, 2017

Limitations

- Taking data from disparate sources can create imprecise results but overall trends should be robust
- **Data!**
  - Data unavailable for many countries (particularly Africa)
  - Not necessarily high quality data
- Migration not included – lack of data
- Different coverage rates of treatment may have different effects
- Assumes random mixing rather than actual networks among PWID – previous research suggests random mixing may overestimate treatment as prevention and that post-treatment behavioural changes are important[1]
- Assumptions about directions of epidemics:
  - Only 3 countries had 2 robust, comparable general population estimates
  - Investigated in sensitivity analyses

1: Impact of Hepatitis C Treatment as Prevention for People Who Inject Drugs is sensitive to contact network structure. Metzig et al, 2017

Implications

- Prevention benefits can be achieved from a random treat all strategy
- **Globally, more prevention benefits are achieved through targeting PWID (high incidence groups)**
- High incidence groups drive the impact of treatment as prevention
  - Countries should not exclude people with substance use from HCV treatment
- Treating only those with advanced disease has less impact in terms of treatment as prevention than a treat-all strategy (however, other factors also important)
- Regardless of strategy, higher impact is achieved in countries with high population growth, more PWID, and lower HCV prevalence
- WHO now advocates a treat-all strategy, partially based on the impact of treatment as prevention[1]

1: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. WHO, 2018

- Published in the Journal of Viral Hepatitis: **"Modelling the potential prevention benefits of a treat-all hepatitis C treatment strategy at global, regional and country levels: A modelling study"** by Trickey et al, 2019
- Also published as an annex to the 2018 WHO guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection
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