Prevention and Treatment for HCV – from modelling to evaluation - an illustration

Matt Hickman, Natasha Martin, Peter Vickerman
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Collaborators:- Sharon Hutchinson, Graham Foster, John Dillon, Sema Mandell, Mary Ramsay, Helen Harris, Ross Harris, Fiona Gordon, Javier Vilar, Matthew Cramp, Stephen Ryder, David Goldberg, Daniela De Angelis, Will Irving, Viv Hope, Noel Craine, Marion Lyons, Norah Palmateer, Esther Aspinall, Lucy Platt, Amy Master, Maria Prins, Bernd Schulte, Henrikki Bummer, Viktor Mravcik, Martin Kåberg, Anne Ovrehus, Geert Robaey, Patrizia Varreiri, Marie Jauffret, Olav Dalgard, Majca Matičič,
Overview- stages of evaluation

- Theory & Modelling shown that:
  - HCV treatment scale-up critical for HCV prevention in PWID
  - Increasing HCV case-finding in PWID cost-effective
  - Early treatment of PWID cost-effective
  - Current treatment rates unlikely to lead to measurable/observable change in HCV transmission
  - Uncertainty in measuring HCV incidence and prevalence in community surveys & Uncertainty in determining PWID prevalence
  - Phase III trial needs to resolve issues with PWID and HCV measurement
Evaluating Complex Intervention

TasP

Theory
- Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues.

Modelling
- Identify the components of the intervention and the underlying mechanisms by which they will influence outcomes to provide evidence that you can predict how they relate to and interact with each other.

Exploratory trial
- Describe the constant and variable components of a replicable intervention and a feasible protocol for comparing the intervention with an appropriate alternative.

Definitive randomised controlled trial
- Compare a fully defined intervention with an appropriate alternative using a protocol that is theoretically defensible, reproducible, and adequately controlled in a study with appropriate statistical power.

Long term implementation
- Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term.

Continuum of increasing evidence
WE HAVE MODELS – WHY HCV TREATMENT IS NEEDED FOR PREVENTION
Need Dynamic Model to Assess Intervention Impact on HCV Prevalence

Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, and Hickman M. J Hep 2011; 54:1137-44
Modeling transitions between OST and NSP & transmission of HCV

Not on OST or NSP $x_0$

On OST only $x_m$

On OST and NSP $x_{nm}$

On NSP only $x_n$

Rate of entry $\mu(X+Y)$

Rate of infection leading to chronic infection $\lambda(1-\rho)$

Rate of cessation $\mu$

Rate of spontaneous clearance $\lambda \rho$

Leaving OST $\gamma$

Leaving NSP $\delta$

Recruited on to OST $\alpha$

Recruited on to NSP $\beta$

Leaving NSP $\delta$

Leaving OST $\gamma$

Recruited on to OST $\alpha$

Recruited on to NSP $\beta$

Susceptible to HCV $X$

Chronic infected with HCV $Y$

Vickerman et al Addiction 2012
Modelling PWID and ex-PWID populations and HCV disease progression

MODELLING HCV TREATMENT AS PREVENTION
HCV RELATIVE PREVALENCE REDUCTIONS AT 10 YEARS WITH PEGIFN+RBV

Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, and Hickman M. J Hep 2011; 54:1137-44
Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, and Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modelling the impact of antiviral treatment, needle and syringe programmes, and opiate substitution therapy. Clinical Infectious Diseases 2013

COMBINATION PREVENTION SCALE-UP (OST/NSP/DAAS):
10 YEAR RELATIVE PREVALENCE REDUCTIONS WITH NO BASELINE COVERAGE OF OST/NSP AND USING DAAs

- Dark red: modest (<20%) impact, high HCV
- Orange: ~50% impact
- White: >80% impact

- >40% reduction requires HCV treatment
- OST&NSP increases benefit of HCV treatment
TREATMENT PRIORITISATION – WHO SHOULD GET NEW DAA
Projected incidence of ESLD or HCC under current treatment rates or targeted scale up.
ARE CURRENT HCV TREATMENT RATES SUFFICIENT TO ACHIEVE A MEASURABLE CHANGE IN HCV TRANSMISSION?
PHASE III – TREATMENT AS PREVENTION MEASURING OUTCOME PROBLEMS
Repeated surveys of HCV incidence and prevalence in PWID can be biased (a lot).

Mills et al. Drug and Alcohol Dependence 2012;126:324-32 & 2014; 142: 120-6
Prevost et al Addiction 2015. Relationship between the parameters and the data sources. Circles denote the unknown parameters (or functions of parameters) which are to be estimated. Squares denote the data sources.
Prevalence Estimation – data conflicts & uncertainty

- Small problem: Bristol PWID prevalence (CRC)
  - Bayesian CRC 0.9% (2770, 95%Cr-I 2570-3110) conflicts with published standard CRC estimates 0.5% (1500, 95%CI 1230-1760)

- Big problem: England PWID/opioid prevalence
  - Standard CRC analysis suggest prevalence of 1.6 million (1.2 – 2.3 million)
  - Revised analysis/non CRC method: 276,000 (249,000 – 313,000) 0.80% (0.72 - 0.91%)
CRC viewed in a Bayesian framework

- \( \pi = \text{Prevalence} \sim U(p_{\text{known}}, 1) \)
- \( P = \text{Population size} \)
- \( N = \text{number of injectors} = \pi P \)
- \( \lambda = \text{Mortality rate} \)
- \( x = \text{Number of opiate and crack related deaths in Bristol in 2011} = 15 \)
  \( x \sim P(\lambda^*N) \)

Number known PWID enforce lower bounds – covariates age, gender, homeless…

Extend to other evidence

Observed mortality rates in DDW
Prevalence Estimation – Mortality data, treatment data, crime rates

\[ \pi = \text{Prevalence} \sim U(0,1) \]

\[ P = \text{Population size} \]

\[ N = \text{Number of users} = \pi P \]

\[ n\text{miss} = N - n\text{known} \]

\[ \text{Number of offences} \sim \text{Poisson}(\delta_1 N + \delta_2 (P-N)) \]

\[ \delta_1 = \text{Offence rate in opiate users} \]

\[ \delta_2 = \text{Offence rate in non-opiate users} \]

\[ \text{Deaths not in DDW} \]

\[ \text{Mortality rate} \]

\[ \text{Number in treatment} \]

\[ \text{Proportion in treatment} \]

\[ \ldots \]
Measuring HCV among PWID

~15,000 White; 11,000 (IPB)
**HCV TAsP Evaluation issues**

- Outcome = HCV incidence & chronic prevalence in PWID in the community
  - Phase II will assess SVR and re-infection rates (but not surrogate markers of TAsP effectiveness)
  - Multiple samples and sources of evidence to account for uncertainty
  - Large HCV treatment scale-up in discrete low prevalence setting
- PWID prevalence
  - Combine evidence and data sources
  - Needed for treatment scale-up targets & phase IV evaluation