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| **Name** | Rachel Sacks-Davis |
| **Title** | Doctor |
| **Supervisors** | Margaret Hellard, Campbell Aitken, Jason Grebely |
| **Summary** | *Background:* Structural and pharmacological interventions (for example, needle syringe programs and opioid substitution therapy) are partially effective for preventing hepatitis C virus (HCV) in people who inject drugs (PWID) but additional strategies are required. Individual behavioural interventions (counselling and education) are common, but little is known about their effectiveness. Prophylactic vaccines are the gold standard for infectious disease prevention, but there is no HCV vaccine. Research on correlates of successful naturally acquired immune responses to HCV can help to inform HCV vaccine development. Interventions that take the injecting social network structure into account are an area of ongoing research.<br>*Aims:* The broad aim of this research was to inform HCV prevention efforts in PWID, including vaccine development and other prevention strategies. Specific aims included synthesis of evidence on individual behavioural interventions to prevent HCV transmission; assessing whether the injecting-social network is important for HCV transmission in order to understand whether it should be a target of HCV prevention programs; and understanding the epidemiology and biological markers of HCV reinfection and spontaneous clearance of reinfection in order to inform vaccine development.<br>*Methods:* Research involved a systematic review (Chapter Two), analysis of data from the Networks 2 study (a cohort study of HCV in PWID in Melbourne, Chapters Three, Four, and Six), data from the $InC^3$ study (pooled data from nine cohort studies of incidence HCV and HIV internationally, Chapter Five), and simulated data (Chapter Six). Analysis of data from the Networks 2 study combined social network epidemiology, phylogenetics, time-to-event regression, and Bayesian post-estimation. Analysis of simulated data was undertaken using Bayesian post-estimation. Analysis of data from the $InC^3$ study involved mainly time-to-event regression.<br>*Key findings:* Few controlled trials have evaluated the effects of individual behavioural interventions on HCV incidence, and those that have done so vary in study design, outcome measures and magnitude, direction and statistical significance of findings between studies. Nonetheless, it seems unlikely that behavioural interventions can have a substantial effect on HCV transmission, at least in isolation. HCV phylogeny was associated with the social-injecting network in the Networks 2 study in Melbourne, highlighting the importance of the injecting network in HCV transmission. Collectively the studies presented in Chapters Four–Six suggest that reinfection occurs |

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| | at least as frequently as primary HCV infection, but in reinfection there is a greater propensity toward spontaneous clearance due to naturally acquired immunity. Spontaneous clearance of reinfection was predicted by female gender and *INFL3* rs860-CC genotype, indicating that these factors are associated with ongoing natural immune protection from persistent HCV infection.<br>*Conclusion:* Prevention of HCV in PWID requires a multifaceted approach. It is unlikely that individual behavioural interventions can substantially reduce HCV transmission. The injecting social network appears to be important for HCV transmission; ongoing research is required to assess its role in HCV prevention. HCV reinfection spontaneously clears more commonly than primary infection, suggesting naturally acquired immunity. Females with *INFL3* rs860-CC genotype appear to have ongoing protection from persistent HCV infection. Elucidation of the mechanism behind this may inform vaccine development. |
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