PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons
AUTHORS	Martin, Natasha; Hickman, M; Miners, Alec; Hutchinson, Sharon; Taylor, Avril; Vickerman, Peter

VERSION 1 - REVIEW

REVIEWER	Dr Julie Parkes Senior Lecturer Public Health Primary Care and Population Sciences Faculty of Medicine University of Southampton
REVIEW RETURNED	22-May-2013

THE STUDY	There is a huge amount of detail on the economic modelling methods which seems to be overall very good, although I am not an expert modeller so cannot comment on the more mathematical aspects presented in the appendix. However there are just a few places where it is less clear and there appears to be some lack of consistency between appendix information and text in the paper. For example, (i) the appendix states 26% of acutely infected patients progress to chronic disease whereas in body of text reports 26% spontaneously clear resulting in prevalence of 35% chronic infection in PWID. (ii) chronic prevalance HCV AB in PWID is 45% with spontaneous clearance of 26% resulting in 35% seems a little confusing with lack of clarity of how this is derived and what denominators are being used. Overall the references for both the paper and the appendix are very good and appropriate. I have just one small issue which authors could clarify concerning the mean length of stay in custody which I would like to see referenced as some data from MoJ 2012 suggest it is 9 months and not 4 months as stated in the text?...Would this impact on the analysis? I would also like to see a (referenced) sentence in the DBS diagnostic test performance is reported -this which would be helpful to the general reader.
GENERAL COMMENTS	I thought this was a well written paper that addresses a very important area of clinical and public health interest. The results will be very useful for commissioners, clinicans and patients. There were just a few inconsistencies, some places where clarity coudl be improved and referencing that require attention.

REVIEWER	Prof Maarten J Postma, Prof, University of Groningen, NL
REVIEW RETURNED	22-May-2013

THE STUDY	Please explain better why a dynamic model is needed in this case, in particular in prisons population dynamics are limited Please consider the new treatments for hcv

REVIEWER	Dr Richard Gilson Head, Research Department of Infection and Population Health University College London London, UK No competing interests.
REVIEW RETURNED	31-May-2013

THE STUDY	Regarding the last point (which should be the other way around?) - it would be helpful if the authors included some more of the key parameter assumptions in the text as they are difficulty to find in the appendices. This applies particularly to the testing rates with DBS versus standard of care (they quote a fold increase but not absolute rates), which accounts for a large part of the variation in the outcomes.
REPORTING & ETHICS	No ethical issues
GENERAL COMMENTS	What was the effect of variation in testing cost - it was not clear whether variation in this was examined. Incorporating testing as a routine in prison entry screening, or in drug services assessments could reduce costs. The costs, particularly in terms of staff time appear high in the baseline case in the appendix (Table 1). Overall this is a very detailed and interesting analysis. The importance of continuity of care is particulary striking.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1, comment 1: There is a huge amount of detail on the economic modelling methods which seems to be overall very good, although I am not an expert modeller so cannot comment on the more mathematical aspects presented in the appendix. However there are just a few places where it is less clear and there appears to be some lack of consistency between appendix information and text in the paper. For example, (i) the appendix states 26% of acutely infected patients progress to chronic disease whereas in body of text reports 26% spontaneously clear resulting in prevalence of 35% chronic infection in PWID. (ii) chronic prevalance HCV AB in PWID is 45% with spontaneous clearance of 26% resulting in 35% seems a little confusing with lack of clarity of how this is derived and what denominators are being used.

Author reply: We thank the reviewer for pointing out this inconsistency and have corrected the appendix to say that 26% of acute infections spontaneously clear (Micallef et al. J Viral Hep 2006;13:34-41), with the remaining 74% proceeding to chronic infection. Accordinglywe assume that 74% of those who are antibody positive (a marker of HCV exposure) are chronically infected (RNA positive) and that if 45% of the PWID population are antibody positive then 35% will be chronically infected with HCV. We have clarified the text accordingly, and have also thoroughly checked the appendix for consistency. We have edited the following accordingly:

(Appendix) This model assumes a proportion (74%) of acutely infected PWID progress to chronic infection.

(Main text, methods) PWID HCV chronic prevalence was estimated from HCV antibody prevalence among PWID in England (45% [41-49%, 95% confidence interval (CI)][27]). As one-quarter of acute infections spontaneously clear[28], we assume three-quarters of those who are ever exposed (antibody positive) are chronically infected, resulting in an estimated 35% chronic HCV infection prevalence among PWID.

Reviewer 1, comment 2: Overall the references for both the paper and the appendix are very good and appropriate. I have just one small issue which authors could clarify concerning the mean length of stay in custody which I would like to see referenced as some data from MoJ 2012 suggest it is 9 months and not 4 months as stated in the text?...Would this impact on the analysis?

Author reply: We note that the average length of stay for ex or non-PWID in our analysis is 8 months, based on Ministry of Justice data. However, it has been documented that people who inject drugs have shorter sentence durations (Bird AG et al. AIDS 1995;9:801-808; Sutton AJ Epidemiol Infec 2008;134:231-412, Taylor A et al. Addiction 2013) likely due to shorter sentencing for drug-related crimes. In a recent study in Scotland the median sentence was 7.1 months in PWID (Taylor A et al. Addiction 2013) which given most people may expect to serve approximately half the sentence would equate to a duration of 4 months, consistent with a previous estimate of 4 months from a modeling analysis based on data from England and Wales(Sutton AJ Epidemiol Infec 2008;134:231-412). Therefore, we believe it is reasonable to assume a shorter length of stay for PWID (4 months) as compared to non- or ex-PWID (mean 8 months) for our base-case. Furthermore, this leads to conservative cost-effectiveness estimates due to the high likelihood of discontinuity/discharge before the end of treatment if treatment is initiated within prison. We note that if sentence durations were longer for PWID, then the case-finding intervention would be more cost-effective as fewer treatments would be interrupted due to release. We have edited the following accordingly:

(Methods, parameters): Incarceration duration for non-PWID and ex-PWID was age-stratified, with a mean of 8 months[29]. However, PWID have shorter durations in custody than non-PWID[29-31]. We used a 4 month PWID incarceration duration, based on a modeling estimate using data from England and Wales[29]. A recent study in Scotland reported a median sentence of 7.1 months in PWID[31] which given most prisoners serve approximately half their sentence[32] would also equate to a duration of 4 months.

Reviewer 1, comment 3: I would also like to see a (referenced) sentence in the DBS diagnostic test performance is reported -this which would be helpful to the general reader.

Author reply: We agree that the sensitivity and specificity of the DBS diagnostic test is important information, and have updated the text as follows:

(Methods, parameters) We assumed all diagnostic tests are 100% accurate
due to the high sensitivity and specificity of DBS (99.6% sensitivity, 100% specificity in a setting with 50% prevalence [29]) and venipuncture assays[30].

Reviewer 2, comment 1: Please explain better why a dynamic model is needed in this case, in particular in prisons population dynamics are limited

Author reply: Our previous work has shown that HCV antiviral treatment for people who inject drugs

could have both an individual benefit (preventing liver disease progression) and population benefit (by preventing onwards transmission and reducing HCV prevalence). A dynamic transmission model is able to account for both these individual and population benefits, and as HCV transmission and treatment occurs both in prisons and in the community, a dynamic model is necessary to capture these important dynamics. Furthermore, the high turnover rates and frequent incarceration and reincarceration of people who inject drugs necessitates a dynamic model to capture the turnover of prison populations in order to properly evaluate a case-finding and treatment intervention. We think the prison population dynamics are highly dynamic; HCV transmission occurs within prisons, frequently at high rates (Larney S et al. Hepatology 2013), and sharing of injecting equipment is also reported to occur in prison, and the frequent incarceration/reincarceration and high turnover of PWID creates a changing risk environment which can only be captured through a dynamic model. We have edited the introduction accordingly to clarify this point.

(Introduction) Unlike previous economic evaluations of HCV testing in these settings[12 13], we incorporate a dynamic mathematical model to capture the potential prevention benefits of treatment, which can substantially increase the cost-effectiveness of HCV treatment for PWID[14]. A dynamic model is able to account for both individual and population benefits of treatment, as well as the dynamic nature of incarceration, especially among people who inject drugs.

Reviewer 2, comment 2: Please consider the new treatments for hcv

Author reply: We agree that the new treatments for HCV are important, and included this as a sensitivity analysis where we examine the impact if genotype 1 patients are provided triple therapy with protease inhibitors (telaprevir or boceprevir) and pegIFN+RBV (see Methods- Sensitivity Analysis, results we state “Using telaprevir/boceprevir for genotype 1 patients minimally altered the ICER.”, and Figure 2). This base-case results presented were robust to the use of the new triple HCV therapies. Unfortunately, we are unable at this time to consider the future interferon-free direct acting antiviral treatments (which could be associated with shorter treatment duration, higher SVR, lower side effects) as treatment costs and health utilities are not available for these future regimes. We have included mention of this limitation in the discussion.

(Discussion, Limitations) Sixth, we were unable to evaluate the cost-effectiveness of future interferon-free direct-acting antiviral therapies as information on treatment costs and health utilities are unavailable. These treatments will likely have increased SVR (likely 90% for all genotypes), shorter treatment durations (12-24 weeks), lower toxicity, and simpler dosing regimes[54]. Therapies with shorter duration could increase the impact of testing and treatment in prison as more patients will be able to complete therapy prior to release, and could potentially be more cost-effective depending on the ratio of additional costs to incremental impact.

Reviewer 3, comment 1: It would be helpful if the authors included some more of the key parameter assumptions in the text as they are difficulty to find in the appendices. This applies particularly to the testing rates with DBS versus standard of care (they quote a fold increase but not absolute rates), which accounts for a large part of the variation in the outcomes.

Author reply: We agree with the reviewer’s suggestion and have included more of the key parameter assumptions in the methods section of the main text under ‘HCV prevalence’ and ‘Incarceration duration’. Additionally, we have also included baseline testing rates as detailed below. As we have expanded the details of parameterization in the main text, we have moved two of the tables (table 1 and 3) to the appendix to reduce duplication and increase clarity. We have also edited the following accordingly:

(Methods, Testing rates): The overall baseline PWID testing rate (mean value of 12% undiagnosed PWID per year) was estimated through fitting the model to the current proportion of diagnosed PWID (approximately 50%[4]). Data on the proportion of tests from different settings (29.4% from addiction services, 11.5% from prison) was used in combination with the model projected annual numbers of PWID in contact with each setting to calculate setting-specific testing rates (6% and 10% per year of undiagnosed PWID in contact with addiction services and prisons, respectively, see appendix). We assume ex-PWID are tested at equal rates to PWID in prison and in general community settings. We assumed all diagnostic tests are 100% accurate due to the high sensitivity and specificity of DBS (99.6% sensitivity, 100% specificity in a setting with 50% prevalence [33]) and venepuncture assays[34], and because those who receive an initial positive test will receive additional tests before treatment.
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Reviewer 3, comment 2: What was the effect of variation in testing cost - it was not clear whether variation in this was examined. Incorporating testing as a routine in prison entry screening, or in drug services assessments could reduce costs. The costs, particularly in terms of staff time appear high in the baseline case in the appendix

Author reply: We vary the testing cost +/- 50% (as shown in Table 1 of the appendix), to account for uncertainty in variables such as time of administration of the test, grade of health care worker etc. However, in the Ancova analysis of the multivariable uncertainty results, the variation in test cost did not contribute substantially to the variation in incremental costs. We note that the reviewer is concerned that the staff time associated with testing is high, and note that our estimates for staff time were taken from previous UK Health Technology Assessments for HCV testing. This assessment assessed testing costs using a routine prison entry screening pilot, therefore we believe the cost estimation is appropriate. However, we agree that it is likely a streamlined and experienced testing service would likely result in increased efficiency and lower costs. Unfortunately, there are insufficient data to parameterize this possibility. We have included a note in the discussion stating that reduced staff time and testing costs would increase the cost-effectiveness of the intervention.

(Discussion, Limitations) Our modelled UK treatment and HCV health care costs are within the range of those presented by recent US studies[48 49], with the exception of approximately 3-fold higher liver transplantation costs, which would increase the cost-effectiveness of case-finding in the US. Testing costs were taken from UK economic evaluations, however it is possible a streamlined and experienced testing service could lower costs associated with staff time, thus increasing cost-effectiveness.