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ORIGINAL ARTICLE

Testing to sustain hepatitis C elimination targets in people who inject drugs: A network-based model

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Abstract

Little is known about the level of testing required to sustain elimination of hepatitis C (HCV), once achieved. In this study, we model the testing coverage required to maintain HCV elimination in an injecting network of people who inject drugs (PWID). We test the hypothesis that network-based strategies are a superior approach to deliver testing. We created a dynamic injecting network structure connecting 689 PWID based on empirical data. The primary outcome was the testing coverage required per month to maintain prevalence at the elimination threshold over 5 years. We compared four testing strategies. Without any testing or treatment provision, the prevalence of HCV increased from the elimination threshold (11.68%) to a mean of 25.4% (SD 2.96%) over the 5-year period. To maintain elimination with random testing, on average, 4.96% (SD 0.83%) of the injecting network needs to be tested per month. However, with a 'bring your friends' strategy, this was reduced to 3.79% (SD 0.64%) of the network ($p < .001$). The addition of contact tracing improved the efficiency of both strategies. In conclusion, we report that network-based approaches to testing such as 'bring a friend' initiatives and contact tracing lower the level of testing coverage required to maintain elimination.

KEYWORDS
elimination, hepatitis C, model, network, treatment

1 | INTRODUCTION

The World Health Organization (WHO) has set a target of the year 2030 for the global elimination of hepatitis C virus (HCV), defined by three parameters: (1) identification of 90% of prevalent cases, (2) successful treatment of 80% of identified cases and (3) 80% reduction in incident infections.[1] In the absence of measuring trends in HCV incidence in real-time, a fall in HCV prevalence is a valid way to measure progress towards elimination.[2] Widespread provision of HCV testing services is critical to achieve elimination[3]; in some areas, this is being achieved and HCV elimination targets are likely to be met,[4–6] while others are not on track,[7] and the COVID-19 pandemic has further reduced the likelihood of success.[8]

Abbreviations: AES, ancillary equipment sharing; CI, confidence interval; CT, contact tracing; HCV, hepatitis C virus; PWID, people who inject drugs; RNS, receptive needle sharing; RT, Random testing; SIS, susceptible-infected-susceptible; WHO, World Health Organization.

Targeted testing services towards those at higher risk of infection will be needed to maintain elimination, once achieved.[9] Accordingly, where initial elimination targets are met, provision of targeted testing for populations most at risk of re-introduction of infection must continue. It is essential that sustainable testing services are developed, implemented effectively and receive long-term funding.

The individuals who will remain most at risk of incident HCV infection are people who inject drugs (PWIDs) via the sharing of injecting paraphernalia.[10] Therefore, targeted testing services must be effective in reaching this population. The development of accessible testing services for these individuals has been critical for successful micro-elimination programmes.[11] However, the level of testing activity required to maintain elimination and prevent HCV becoming re-established in injecting networks has not been quantified. Without an understanding of how much testing will be required, it will be difficult to allocate appropriate resources towards maintaining elimination within the population.

A long-term targeted testing strategy for HCV in PWID must also be efficient and effective. The value of social network-based recruitment is that it can increase engagement of otherwise 'hidden' PWID.[12] Such an approach has two main implications—firstly, it would mean testing is focused on PWID with multiple injecting partners; PWID with greater network connectivity are more likely to be a social contact of another PWID. Secondly, it would facilitate a contact tracing (CT) testing strategy within the social network of HCV-positive PWID. This is evidenced by peer referral testing for HCV in PWID in a real-world setting,[12] and its effectiveness in achieving the elimination objectives, relative to random testing, has been shown in a recent modelling study.[13] The utility of CT in PWID with HCV has been the subject of a recent review,[14] but to date there is no simulated or real-world evidence testing its potential effectiveness.

The present study will address three questions in an injecting network of 689 PWID based on real-world empirical data. Firstly, what happens after elimination is achieved if testing for HCV stops? Secondly, what testing activity is required to maintain HCV prevalence at or below the elimination threshold? Thirdly, which treatment strategy is most effective? The answers will have real-world implications for HCV care after elimination targets are met.

2 | METHODS

2.1 | Model overview

We previously developed a network-based model of HCV transmission and treatment in an injecting network of PWID in Southampton (UK) based on real-world data[15] and simulated the elimination of HCV via the random provision of DAA.[13] In the present study, we use the same dataset and model to predict outcomes following elimination.

The first timepoint is when elimination was achieved in our previous study according to the WHO definition, where 90% of prevalent cases are identified and 80% achieve SVR following treatment (a prevalence of 11.68% in our network).[13] At each subsequent timestep, PWID move in and out of the network with a fixed probability (Table 1) and have a likelihood of introducing HCV to the network that has been previously calibrated[13] and is adjusted to prevalence outside the network.

The primary outcome at 5 years is the mean proportion of PWID required to be tested per timestep to maintain elimination. The model was run using the *epydemic* framework in Python 3 (version 1.0.0).[16]

The required testing coverage is compared between four strategies: (1) random testing (RT), (2) 'bring a friend' (BF) testing, and the addition of contact tracing (CT) in the network of positive nodes to (1) and (2), henceforth abbreviated to RT + CT and BF + CT (Figure 1). A mean proportion is taken from 100 simulations in 100 networks that meet the pre-defined UK-net characteristics.[13] Mean testing coverage required to maintain elimination was compared between strategies using a paired sample *t*-test in MATLAB R2020a for Windows.

2.2 | What happens in the model—transmission of HCV?

HCV transmission is simulated using a susceptible-infected-susceptible (SIS) model (Figure 2). HCV can be transmitted from positive nodes to injecting partners according to the frequency of equipment sharing and associated transmission probabilities (Table 1). A newly infected node develops acute infection, becoming chronic with a fixed probability (Table 1 and Figure 2).

2.3 | What happens in the model—random testing strategy (RT)?

In each timestep, N nodes are randomly selected for testing. The probability that a node is correctly identified as having HCV is calculated by multiplying the sensitivity of an OraSure HCV antibody test[17] (presently used in services in the modelled population) and the sensitivity of a confirmatory RNA test (Table 1).[18,19] In all scenarios, a node can only be tested once every 3 months. Accordingly, nodes can test positive whilst still in the acute phase (Figure 2). Nodes testing positive in this period will still be treated; those previously treated go straight to RNA testing.

2.4 | What happens in the model—bring a friend testing (BF)?

In each timestep, N nodes are selected for testing, 50% at random and 50% selected from the injecting partners of these nodes; we assume each PWID attending for testing brings along on average

TABLE 1 Key parameters used in the model

Parameter	Value	Reference
Network size	689	[31]
Network structure	UK-net	[13]
Proportion of nodes with chronic HCV at baseline	0.417 × (1–0.72) = 0.1168	[31]
New nodes rate/year (as proportion of network size)	0.176	[32]
Proportion of new nodes with HCV	min(0.008, 0.116 × current network prevalence)	[33]
Node turnover/year as proportion of network size	0.176	[32]
Frequency of injection with each neighbour—proportion of nodes	6×/week—0.12, 3×/week—0.22 1×/week—0.43 0.5×/week—0.23	[15]
Probability of equipment sharing	0.4 (AES) 0.33 (RNS) (0.16–0.51)	[15]
Transmission probability when sharing	0.0023 (AES) 0.0073 (RNS)	[34]
Spontaneous clearance rate of acute infection	0.25	[34]
Minimum testing interval	3 monthly	
Oral mouth swab antibody test sensitivity	95% (95% CI 90–99)	[35]
Confirmatory point of care RNA test sensitivity	Abbott Xpert 100% (96–100) Cephiad gene drive 98.6 (95% CI 96.9–99.5)	[18,19]
Probability a partner node will be tested in CT strategy	42% (95% CI 0.19–0.86)	[20]
Positive test to commence treatment rate	0.5 (0.25–0.75)	Local data and [21]
Treatment duration (weeks)	2 months	[36,37]
Treated persons coverage per month at baseline	Unlimited	[a]
Rate of sustained virological response	0.95 (95% CI 94–100)	[36,37]

Abbreviations: AES, ancillary equipment sharing; CI, confidence interval; CT, contact tracing; HCV, hepatitis C virus; RNS, receptive needle sharing.
[a]The local treatment capacity in Southampton (UK) (the modelled PWID network) currently comfortable exceeds the number of patients with HCV RNA; this is likely to be the case in most areas that achieve HCV micro-elimination.

a single injecting partner, as shown in a real-world study.[12] An individual can bring at most three injecting partners in each timestep.

2.5 | What happens in the model—contact tracing (CT)?

If a positive node is identified, CT ensues and a proportion of that node's network is engaged with testing. In the baseline analysis, this is set at 42% (Table 1), a proportion in keeping with available literature describing CT in PWID.[20]

2.6 | What happens in the model if a node is positive for HCV RNA?

A node testing positive for HCV has a fixed probability of progressing to treatment. The value used is in keeping with published rates of engagement with treatment for PWID[21] and local experience (Table 1). A node in treatment has a fixed probability of achieving SVR (Table 1). Treatment lasts 8 weeks and nodes are non-infectious following the first 2 weeks of treatment (Figure 2).

2.7 | Sensitivity analysis

Three parameters were adjusted independently according to published 95% confidence intervals and clinical experience (Table 1) to assess the impact on results. We adjusted the rate of receptive needle sharing (RNS) as this was shown to have the greatest impact on HCV transmission in a similar model.[15] Adjusting this parameter simulates the impact of harm reduction. We adjusted treatment engagement rates as this will vary considerably depending on outreach treatment provision to PWID. Finally, we adjusted the proportion of injecting partners tested during CT, due to lack of empirical data supporting this parameter in PWID with HCV.[20]

3 | RESULTS

If testing and treatment stop after elimination, prevalence increases to 25.4% (SD 2.96%) at 5 years (Figure 3). At elimination, residual infection is concentrated in central nodes (Figure 3A). As HCV spreads through the network, incident infection is centralized, that is PWID with more injecting partnerships become (re)infected with HCV much more frequently (Figure 3B), highlighted by the high degree of newly infected nodes, 4.3 (SD 2.8), compared to all nodes, 2.7 (SD 2.4) ($p < .001$).

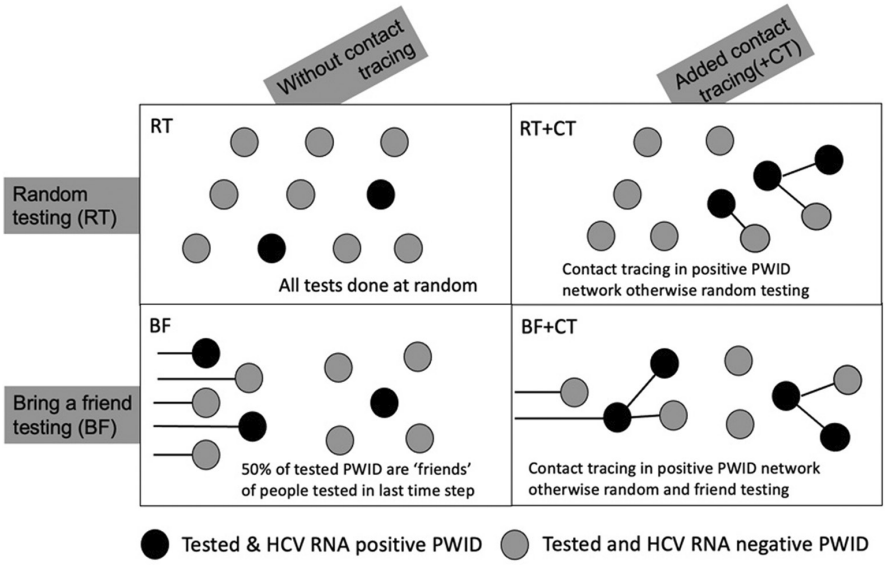

FIGURE 1 Testing strategies tested in the model. The four testing strategies tested in the model are described graphically in each box. In the random testing (RT) strategy, all PWID are randomly selected for testing. In the bring a friend (BF) strategy, 50% of tested nodes are injecting partners of nodes tested in the previous time step. In the strategies with contact tracing added (+CT), an average of 42% of an HCV-positive PWID's injecting network is tested.

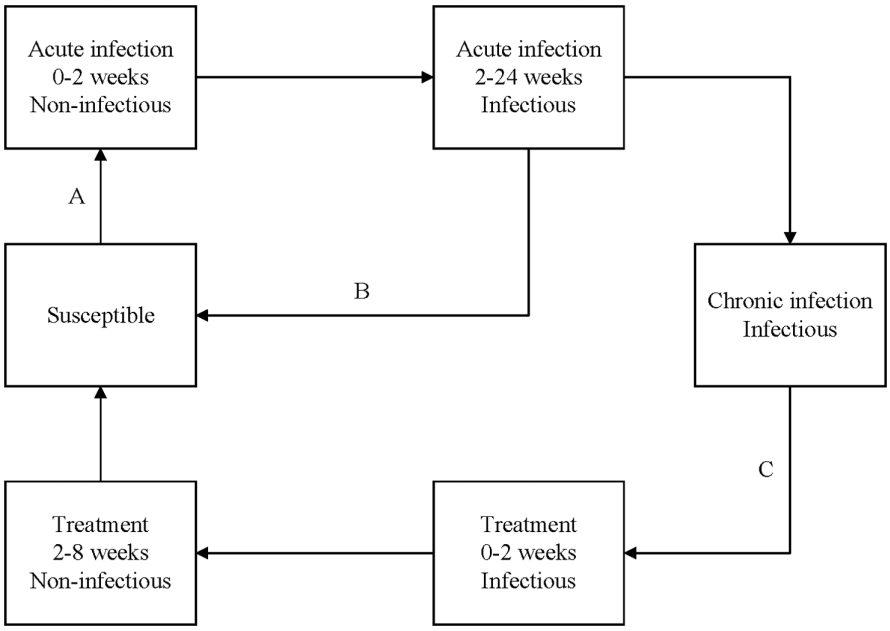

FIGURE 2 State diagram depicting the HCV transmission model. States are represented by boxes and labelled according to whether the individual in each state is infectious (can transmit HCV to injecting partners) or not. Arrows between boxes denote possible transitions between states, either deterministically at a given time point as indicated or by specific events as follows. A: Transmission via equipment sharing with an infected neighbour; B: spontaneous clearance of hepatitis C virus; C: beginning of successful course of treatment. Note that in the case of event C, treatment success is determined at transition; if treatment will fail, the individual is assumed to remain in the chronic infection state.

Figure 4 shows how increasing testing coverage within the injecting network reduces the prevalence of HCV over 5 years, and how this varies according to the four testing strategies.

3.1 | Random testing (RT)

To maintain HCV prevalence at the elimination threshold, 4.96% (SD 0.83%) of the network needed testing per month. Individuals tested had a mean degree of 2.67 (SD 0.09), and 13.5% (SD 0.98%) were infected with HCV.

3.2 | 'Bring a friend' (BF) testing

The mean proportion of PWID requiring testing monthly to maintain elimination was 3.80% (SD 0.64%), significantly lower than 4.96% for random testing ($p < .001$) (Figure 4). PWID tested in the BF strategy had higher degree (mean 3.63, SD 0.11) and were more likely to have HCV (16.3%, SD 1.16%).

3.3 | Contact tracing (CT)

The addition of CT reduced the proportion of the network requiring testing per month for both main strategies: RT+CT, 3.16% (SD 0.57) ($p < .001$) and BF+CT, 2.82% (SD 0.51) ($p < .001$) (Figure 4). CT also increased the degree of PWID and proportion of positive tests (Figure 4).

3.4 | Sensitivity analysis

Results of the sensitivity analysis are displayed in Figure 5. BF testing remained significantly more efficient than RT in all scenarios.

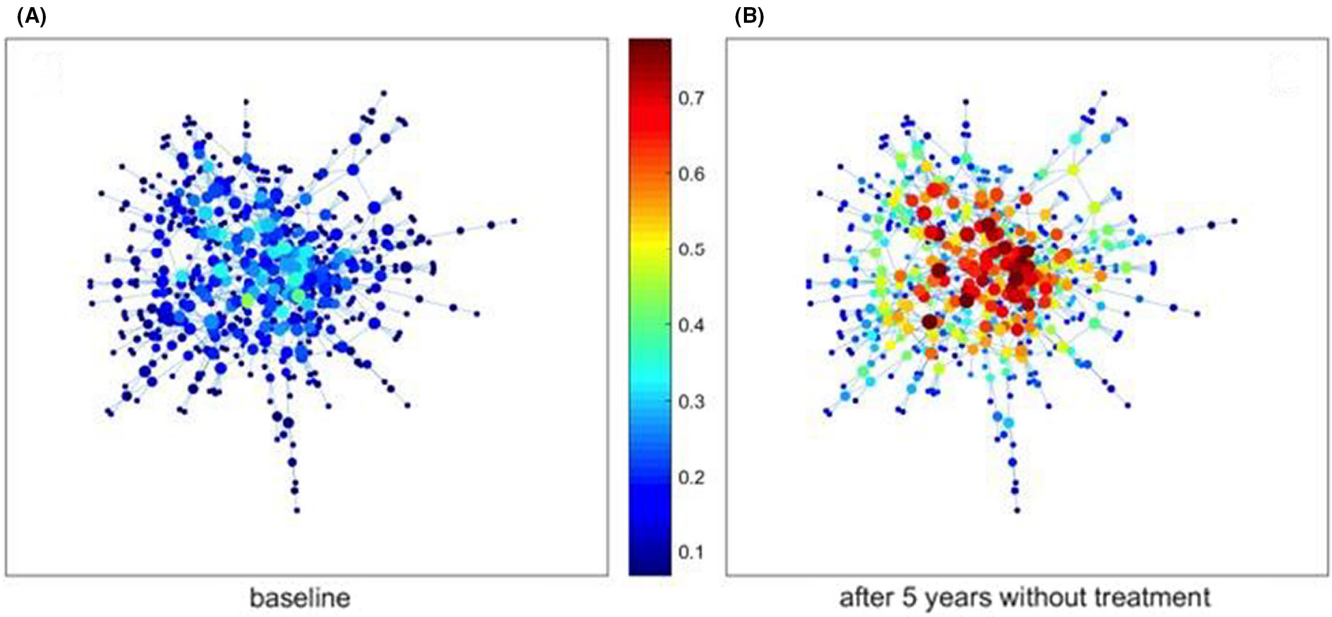

FIGURE 3 Injecting network connecting PWID at baseline and at 5 years post HCV elimination goals are achieved if testing and treatment provision stops. Nodes represent PWID and lines represent injecting partnerships. Colour scale indicates the frequency with which each node was positive for hepatitis C at (A) baseline (i.e., the point the elimination threshold was achieved) based on 100 simulations of the network and (B) 5 years after elimination was achieved if testing and treatment activity ceased. The size of the node corresponds to the number of injecting partnerships. As indicated by the colour scale, prevalent disease at 5 years is predominant in nodes with a high number of injecting partnerships.

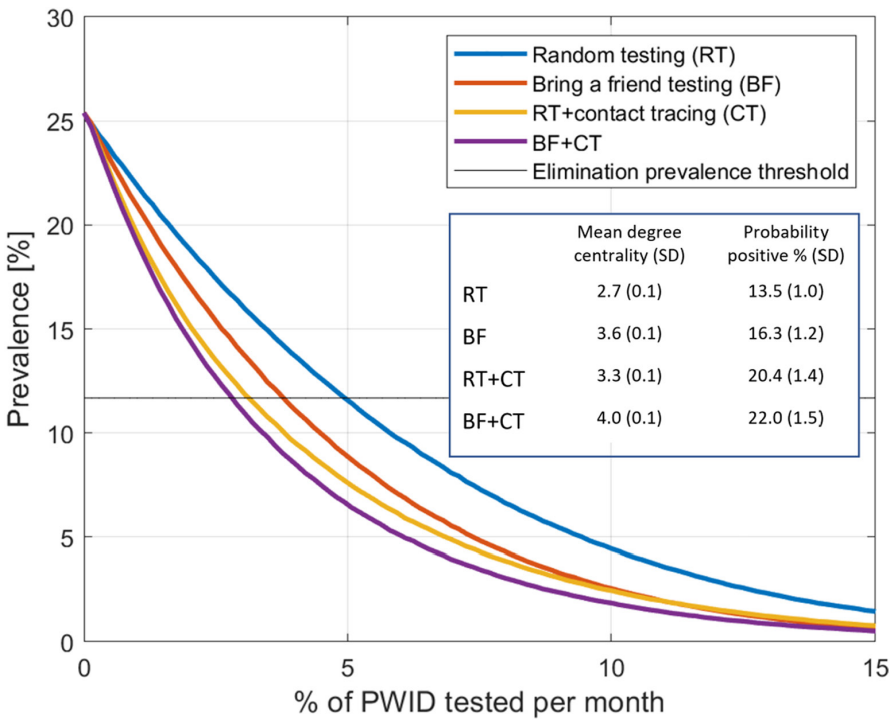

FIGURE 4 Testing coverage required per month to maintain and exceed the HCV elimination target. Line graph showing change in prevalence at 5 years (*y* axis) with increasing testing coverage in four testing scenarios. The elimination threshold for Southampton (UK) (prevalence <11.68%) is indicated. Results are from 100 simulations in 100 generated networks. Embedded table shows the degree of PWID tested in each strategy and the probability a tested PWID is positive for HCV RNA.

When CT worked well (i.e., a high proportion (86%) of an infected PWID's injecting network were tested), the additional benefit of the BF strategy was lost; the proportion of the network requiring testing per month with RT + CT was 2.28% compared to 2.20% with BF + CT (Figure 5C).

4 | DISCUSSION

To our knowledge, this is the first study to assess requirements for ongoing testing and treatment following micro-elimination of HCV in PWID. We report that network-based testing approaches lower

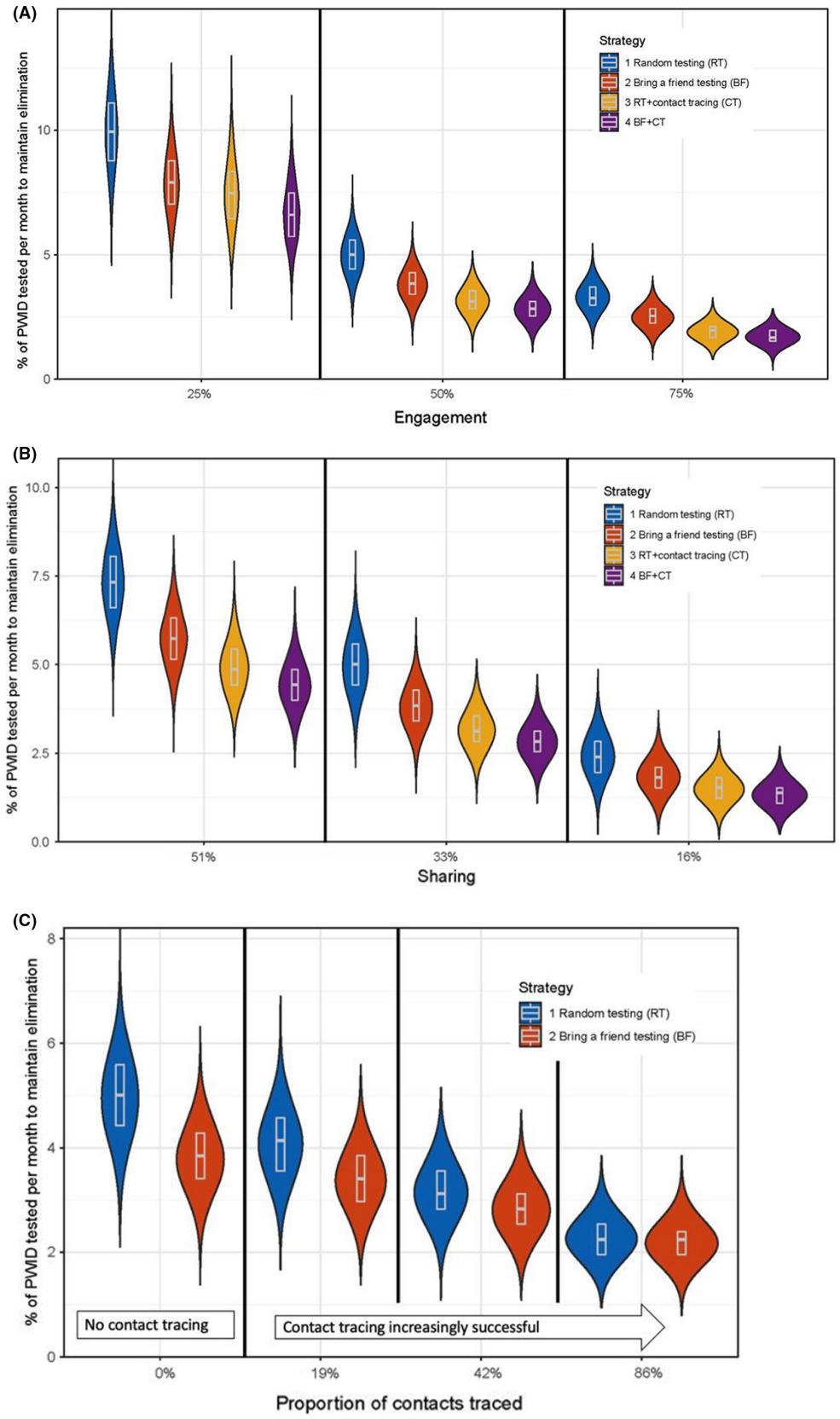

FIGURE 5 Sensitivity analyses. Violin plots comparing the proportion of PWID that need to be tested to maintain the elimination prevalence threshold for HCV in Southampton (UK) for each testing strategy under three conditions of treatment engagement 0.25, 0.5 and 0.75 (A), three conditions of receptive needle sharing rates (0.16, 0.33 and 0.51) (B), and three conditions of contact tracing effectiveness (19%, 42% and 86%) (C). In (C), contact tracing refers to the identification and testing of the injecting partners of HCV-positive PWID identified via either random testing or the 'bring a friend' strategies. Boxes indicate the median and upper and lower quartiles.

the testing coverage required to maintain elimination. Furthermore, without targeted testing and treatment, HCV recurs. We also show that HCV recurs preferentially in PWID with more injecting partnerships, showing that network-based testing approaches are more efficient as they identify PWID with more injecting partners, who are more likely to be positive and whose treatment will lead to a greater reduction in primary infection.

'Bring a friend' initiatives are feasible and have been implemented in some areas.[12] Contact tracing is a variation used effectively in other infectious diseases, but not previously assessed to identify HCV in PWID.[22] CT for HCV in PWID has previously been dismissed[23] but was recently re-proposed.[14] Katzman et al.[14] argue that after elimination conditions are favourable for CT, including low prevalence,[24] high clustering of infections and effective treatments.[25] While incentivized peer referral of injecting partners in HCV bio-behavioural surveys has become a key method to track global HCV epidemiology,[26] the acceptability of specifically asking PWID with HCV to identify injecting partners for testing needs further research.

NBMs have been used to model CT for smallpox, Ebola, SARS and more recently COVID-19[27–30]; it is considered the 'gold standard' modelling approach because it can provide sufficient detail to directly influence public health policy.[25] Our NBM has limitations. Some parameters are applied randomly across the network, for example, the equipment sharing rate was applied at random within a distribution empirically derived from a local population[15] rather than according to number of partners—when it is likely more partners would be associated with more risk taking behaviours. However, the effect of this in the model would be to decrease the relative effectiveness of network-based testing strategies, therefore underestimating the observed differences. Additionally, the proportion of partners reached through CT was taken from a single study concerning HIV in PWID.[20] To our knowledge, there are no empirical data showing the success of partner notification in HCV-positive PWID, making this an important area for further research. To account for this uncertainty, our sensitivity analysis modelled the effect of adjusting this parameter; our key findings were unaffected in this analysis.

Network-based testing strategies including 'bring a friend' initiatives and contact tracing have the potential to reduce the testing coverage and associated costs required to maintain HCV elimination by over 25%. Before implementation, the feasibility of contact tracing within injecting networks of PWID needs to be assessed. However, both contact tracing and 'bring a friend' testing strategies should be considered to help maintain elimination once WHO targets are achieved.

AUTHOR CONTRIBUTIONS

CS-B, MS-B, MW, CC, JP, SIK and RB identified the research question and designed the study. CS-B built the model, RB, MS-B and CS-B conducted the data analysis, and MS-B designed the figures. MW, CC, JP, CS-B, RS-B and SIK prepared the manuscript for submission. All authors approved the final version of this manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that relate to the content of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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