International Journal of Drug Policy 47 (2017) 117–125

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research paper

Effectiveness and cost-effectiveness of nationwide campaigns for awareness and case finding of hepatitis C targeted at people who inject drugs and the general population in the Netherlands

Charles W. Helsper[a,*], Mart P. Janssen[a], Gerrit A. van Essen[a], Esther A. Croes[b], Clary van der Veen[b], Ardine G. de Wit[a,c], Niek J. de Wit[a]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[b] Netherlands Institute of Mental Health and Addiction (Trimbos Institute), The Netherlands
[c] Centre for Nutrition, Prevention and Health Services, National Institute of Public Health and the Environment, Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, The Netherlands

ARTICLE INFO

Article history:
Received 20 December 2016
Received in revised form 5 July 2017
Accepted 21 July 2017

Keywords:
Cost-effectiveness
Hepatitis C
Case finding
Primary prevention
Campaign

ABSTRACT

Background: Hepatitis C virus infection (HCV) is a serious, but underdiagnosed disease that can generally be treated successfully. Therefore, a nationwide HCV awareness campaign was implemented in the Netherlands targeting people who inject drugs (PWID) in addiction care ('PWID intervention') and high-risk groups in the general population ('public intervention'). The objective of this study is to assess the effectiveness and cost-effectiveness of the interventions used in this campaign.
Methods: For the 'PWID' intervention, all addiction care centres in the Netherlands provided proactive individual HCV consultation and testing. The 'public intervention' consisted of health education through mass media and instruction of health care professionals. A Markov chain model was used to estimate incremental cost-effectiveness ratios (ICER, cost per QALY gained). We included a 'DAA treatment' scenario to estimate the effect of these treatment strategies on cost-effectiveness.
Results: The 'PWID intervention' identified 257 additional HCV-carriers. The ICER was €9056 (95% CI: €6043–€13,523) when compared to 'no intervention'. The 'public intervention' identified 38 additional HCV-carriers. The ICER was €18,421 (95% CI: €7376–€25,490,119) when compared to 'no intervention'. Probabilistic sensitivity analysis showed that the probability that the 'PWID intervention' was cost-effective was 100%. It also showed a probability of 34% that the 'public intervention' did not exceed the Dutch threshold for cost-effectiveness (€20,000). New treatment regimens are likely to improve cost-effectiveness of this strategy.
Conclusion: In a nationwide HCV awareness and case finding campaign, the intervention targeting PWID was effective and cost-effective. An intervention targeting risk groups in the general population showed only a modest effect and is therefore less likely to be cost-effective.

Introduction

Hepatitis C virus infection (HCV) is an infectious liver disease that can lead to serious long-term complications. Even though an estimated 71 million people are infected worldwide, the disease remains relatively unknown among the general public and medical professionals (Polaris Observatory HCV Collaborators, 2017). HCV infection generally does not cause clinical symptoms before its complications occur. Therefore identification of those infected is often delayed. After 20–30 years, approximately 25% of those chronically infected will develop liver cirrhosis, resulting in hepatocellular carcinoma in 5% of these cases (Lauer & Walker, 2001). As a consequence, HCV is responsible for 50–76% of all liver cancer cases and two-thirds of all liver transplants in the Western world (World Health Organization, 2011). In Europe (including Russia) 11.3–14.7 million people are infected with HCV. Prevalence rates (anti-HCV) in the population vary from approximately 0.5% in

* Corresponding author at: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.
E-mail addresses: C.W.Helsper-2@umcutrecht.nl (C.W. Helsper), m.p.janssen@umcutrecht.nl (M.P. Janssen), g.a.vanessen@umcutrecht.nl (G.A. van Essen), ECroes@trimbos.nl (E.A. Croes), cveen@trimbos.nl (C. van der Veen), g.a.dewit@umcutrecht.nl (A.G. de Wit), n.j.dewit@umcutrecht.nl (N.J. de Wit).

http://dx.doi.org/10.1016/j.drugpo.2017.07.022

North-West Europe to over 7% in parts of South-East Europe (Cornberg et al., 2011). In the Netherlands the prevalence is estimated at 0.1–0.4% (16,000–64,000 persons) and up to 0.6% in highly urbanized areas (Baaten, Sonder, Dukers, Coutinho, & Van den Hoek, 2007; Slavenburg et al., 2008). So far only a minority of those infected has been diagnosed (Kok, Zuure, Weegink, Coutinho, & Prins, 2007). The estimated detection rates of HCV in the population, for which the reliability and comparability is only moderate, vary across Europe from 2.7% in Poland to 80% in Sweden (Cornberg et al., 2011). High HCV prevalence rates are generally found in several risk groups. The most important risk group are people who inject drugs (PWID) with estimated prevalence rates of 60–80%. Within the Netherlands and other countries, prevalence rates among PWID differ regionally and are associated with multiple factors, such as living environment, co-infections, current and previous lifestyle and method and frequency of drug use (Nelson et al., 2011).

Other risk groups for HCV infection in the Western world are those who received blood-products before 1991 and first generation immigrants from endemic countries. HIV-positive men who have sex with men (MSM), children of HCV infected mothers and those with occupational risks of blood contact are also considered at risk for HCV infection (Cornberg et al., 2011; Health Council of the Netherlands, 2016; Vriend et al., 2013). At the time of the HCV campaign, relatively high prevalence rates made PWID, including prior PWID in methadone treatment, likely to be the most efficient population to target in the Netherlands. Furthermore, relatively high absolute numbers of unidentified HCV were anticipated among immigrants. Also, HIV-positive MSM were an emerging risk group (Kok et al., 2007; Urbanus et al., 2009; Vriend et al., 2013).

Sustained viral response (SVR) rates for HCV treatment have improved rapidly in recent years. Previously, 50% of those infected with HCV genotype 1 and 4 and 80% of those with genotype 2 or 3 could be treated successfully (Manns et al., 2007). The recently introduced DAA treatment regiments can potentially achieve SVR in over 90% of patients (Afdhal et al., 2014; Lawitz et al., 2013; Sulkowski et al., 2014; Wyles et al., 2015). These increased treatment SVR rates have converted HCV infection into a curable disease. This indicates the importance of early detection to improve HCV treatment rates, but case finding of HCV continues to be a serious challenge for health care authorities and the need to improve case finding strategies remains (Gravitz, 2011; Willemse et al., 2015; Zuure et al., 2014).

Promising developments in HCV-treatment were recognised by the Dutch Ministry of Health as generating the need for improved case finding. Therefore, the Ministry of Health initiated a national HCV case finding campaign, which was implemented from September 2009 to February 2010. This campaign consisted of two interventions, one targeting risk groups in the general population and their medical professionals and one targeting PWID in addiction care.

To determine the optimal design of the National campaign, regional pilot-campaigns using various approaches for similar populations (PWID and risk groups in the general public) were evaluated. In these pilot campaigns, increasing the awareness of HCV among risk groups in the population and medical professionals proved pivotal to improve case finding (Helsper, van Essen, Bonten, & de Wit, 2010; Helsper et al., 2012; van der Veen, Hoogenboezem, & Breemer, 2009). Therefore, increasing HCV awareness and case finding were the central aims in the national HCV campaign.

We report the effectiveness and cost-effectiveness of the two central interventions in the nationwide HCV campaign, aimed at improving case finding and increasing awareness of HCV in the Netherlands.

Methods

Interventions

Both interventions in the HCV campaign were aimed at the target populations and their healthcare workers; addiction care professionals, primary care physicians and public health workers (community workers and infectious disease- and intercultural communication experts). The campaign was implemented between September 2009 and February 2010 and included two large-scale interventions. The 'PWID intervention' was implemented in the addiction care setting. Targeted PWID mainly included people using heroin, methadone and/or cocaine. People who smoke cocaine (crack) were also considered eligible for counselling and testing. The 'Public intervention' focussed on risk groups in the general population and on medical professionals. Targeted risk groups included: PWID, first generation immigrants from countries with a HCV-prevalence rate of over 10%, HIV positive MSM, those receiving blood products before 1992, health care workers and travellers who had their skin pierced in endemic countries (>2%) and family members of HCV positive individuals.

In both interventions, risk groups were tested using an anti-HCV-ELISA test first, followed by RNA testing if the anti-HCV test was positive. Tests were performed by nurses of which the majority were addiction care nurses.

The 'PWID intervention' was implemented by all 11 Dutch addiction care institutions. In the participating methadone clinics, which are part of these organisations, local coordinators were appointed and brochures and posters targeting risk groups were distributed. The attending PWID were proactively approached by the addiction care workers and offered HCV related consultation and testing. In addition, group meetings were organized addressing the risks and treatment possibilities for HCV. Educational materials and symposia for professionals were provided to support the intervention. Testing was provided on the spot if possible or by referral to a regional laboratory where necessary.

The 'public intervention' was implemented in the six largest cities of the Netherlands; Amsterdam, Rotterdam, The Hague, Utrecht, Eindhoven and Almere. The intervention lasted six months and included the following components:

(1) The first component was aimed at increasing awareness and stimulating those at risk to visit their GP, addiction care professional or a public health service (GGD) employee. General information about HCV, its risk groups and treatment possibilities was spread through mass media such as radio advertisements, websites and internet banners. Brochures and posters were made available throughout addiction care centres, GP practices, social services and pharmacies. Informative meetings were organized at venues were high risk groups were expected to congregate such as religious venues and cultural meetings.
(2) The second component aimed to provide follow-up information for the general public and professionals. A website, which was only available during the campaign, provided elaborate information on risk groups, treatment possibilities, diagnostics and prognosis of HCV.
(3) The third component focussed on training professionals. Addiction care professionals and public health service (GGD) employees were trained on advising their target populations. GP practice staff was systematically trained by regional GP support organisations. Training included information about HCV risk, testing and communicating the need for testing. Educational materials were developed and spread among all GP practices by the Dutch college of General Practitioners (NHG).

(4) The final component was aimed at efficiently testing risk groups. This included facilitating testing in addiction care centres, regional public health services and stimulating adequate referral for testing by GPs. If tested positive, referral for treatment was advocated.

Outcome

The primary aim of the nationwide HCV campaign was to increase the number of HCV carriers identified. The change in number of anti-HCV tests performed was used as the primary outcome to assess the effectiveness of the campaign. Cost-effectiveness, the secondary outcome of this evaluation, is expressed as cost per quality adjusted life year (QALY) gained. Future (averted) healthcare costs are discounted at 4% and health outcomes (QALYs) are discounted at 1.5% (Rodenburg-van Dieten, 2006). A lifelong time horizon was considered for HCV infections as complications of such infections occur decades after the actual infection. All costs were converted to a 2016 price level. Discounting of future costs and QALYs was performed in agreement with Dutch Guidelines for health care evaluation (Zorginstituut Nederland, 2016).

Data collection

The anti-HCV test is used for primary identification of those ever infected with HCV. In case this test is positive, an HCV-RNA test is performed to test for chronic infection. Since the HCV-RNA test is also used for additional purposes, such as genotyping and assessment of the effect of treatment, the change in the number of anti-HCV tests performed was considered as the most reliable parameter to measure the campaign effect. Collection of test-data was performed separately for the two interventions.

For the 'PWID-intervention' the number of HCV related consultations, anti-HCV tests and positive tests were registered in the addiction care centres and methadone clinics. Registration was performed by the Netherlands Institute of Mental Health and Addiction ('Trimbos Institute') using standardized procedures. Because all addiction care institutions were invited to participate in the 'PWID-intervention', there was no control region available. Before the intervention, anti-HCV tests were very rarely performed in the addiction care setting which was now subject to intervention (van der Veen et al., 2009). Therefore, we assumed that all tests performed in the targeted addiction care centres and methadone clinics in the intervention period were due to the intervention only.

To assess the change in the number of anti-HCV tests resulting from the 'public intervention', we aimed to collect data from all 25 laboratories managing the diagnostic testing for the six large Dutch cities. Data were collected from three time periods; the intervention period (September 2009 to February 2010) and the same six month periods in the two preceding years (2007/2008 and 2008/2009). The number of tests during the six month intervention period was compared to the mean number of tests per six month period in the two preceding years. To adjust for changes in the number of anti-HCV test not related to the 'public intervention', similar data from four large laboratories outside the 'public intervention' area (Groningen, Tilburg, Nijmegen and Breda) were collected. Anti-HCV tests performed in addiction care were excluded from this data collection by the cooperating laboratories.

For the final analyses, data from 20 of the 25 laboratories in the intervention regions and from all contacted laboratories in the control regions, were available. In the intervention regions, one laboratory only confirmed tests found positive elsewhere and was excluded to avoid double counting. Four laboratories could not deliver data because of lack of personnel or financial resources. The number of missing tests from these centres was estimated based on the increase in the number of tests performed in laboratories which were similar in characteristics and catchment area. As a result the missing HCV data was estimated to be approximately 12.6% in the intervention period, and 13.3% in the data concerning preceding years. To adjust for missing data, the number of tests performed in the intervention regions in the corresponding measurement periods were increased accordingly.

Costs

The additional costs resulting from the nationwide hepatitis C campaign were estimated based on direct, indirect and averted costs.

The direct and indirect costs were registered by all participating organizations in both interventions using standardized forms and processed in personal contact with the participating and coordinating institutions. Direct costs result from the implementation of the interventions, such as costs of meetings, training, materials and communication costs (e.g. mass media coverage). Indirect costs result from the consequences of the interventions, such as time spent on additional consultations, testing, HCV treatment (pegylated interferon and ribavirin mainly) and guidance during treatment and education.

Averted costs are medical costs prevented by early identification and treatment of HCV carriers, such as costs related to the treatment of end-stage liver disease (e.g. cirrhosis and cancer). These costs were estimated using a Markov model (see below) (Helsper et al., 2012).

Analyses

The incremental effect of the 'public intervention' was estimated using a Bayesian Poisson model. In this model the incremental campaign effect in the intervention regions was modelled as an increase on top of the general change in the number of diagnosed cases observed in both the intervention and control regions. With this model it was possible to estimate the additional campaign effect in the intervention region whilst adjusting for the increase in the observed number of HCV infections in the control region.

For the 'PWID intervention' we assumed that all tests in the intervention period are due to the intervention only, therefore the point estimate was used to estimate effectiveness.

Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) is the ratio of additional costs brought about by an intervention such as the HCV campaign and its associated additional effects – expressed in Quality-Adjusted Life Years (QALYs) – when compared to not offering the intervention (Meltzer, 2001). The ICER provides an objective outcome that can be used to quantify the cost-effectiveness of an intervention. An ICER was calculated for both interventions considered. For the calculation of the ICERs a previously-developed Markov model was updated and supplemented with information from the registrations performed for both interventions (Helsper et al., 2012). A list of all model parameters and probabilistic distribution functions used in the model are provided in the online Supplementary materials to this paper.

Sensitivity and uncertainty analyses

The ICER is influenced by the parameters that are used in the model. This pertains to all input parameters such as percentages of

carriers receiving diagnostics and treatment, but also carrier characteristics and prevalence rates.

To evaluate which of these parameters have the largest impact on the ICER, multivariate sensitivity analyses were performed for the ICERs of both interventions. These analyses provide information concerning the models' sensitivity to uncertainty in the individual model parameters, but also on the influence of possible interactions between parameters. The multivariate sensitivity outcome is expressed in standardized regression coefficients (SRC), which are the regression coefficient of a linear regression analysis performed on the standardized data, which implies that all variables have been transformed and have a mean of 0 and variance of 1. The SRC represents the proportion of variance in the outcome explained by the corresponding independent variable (Schroeder, Sjoquist, & Stephan, 1986). The SRC's are obtained from data obtained by probabilistic sensitivity analyses (PSA) using Monte Carlo simulations. Convergence of the results was obtained after 5000 iterations for both interventions.

The simulated net costs, plotted against the corresponding gain in QALYs are demonstrated in a cost-effectiveness plane. The likelihood that the interventions are cost-effective at varying thresholds for the Willingness to Pay for additional QALYs, are depicted in a cost-effectiveness acceptability curve.

Recently, new DAA treatment regimens have improved SVR rates dramatically. We added a scenario analysis estimating the influence of these new treatment regiments on the cost-effectiveness of the campaigns. This estimate is based on the currently observed SVR rates of around 95% (Afdhal et al., 2014; Lawitz et al., 2013; Sulkowski et al., 2014; Wyles et al., 2015). We included approximated costs of the new treatment regimens, at €40,000 (The National Health Care Institute, 2016). Because treatment burden is decreased substantially with the DAA regimens, we also included a 25% increase in the percentage (wanting to be) treated (e.g. from 37.1% treated to 46.4% treated). This provides a rough indication of the expected cost-effectiveness using the latest treatment options. The updated calculations take into account the higher costs, improved SVR rates and an estimated increase in proportion of individuals treated only, since sufficient data on long-term consequences of the new treatment regimens are not yet available.

Results

The effects of both interventions are shown in Table 1, the costs of both interventions are shown in Table 2. The expected course of events was based on observations in our registrations and on previous studies and is depicted in Fig. 1.

PWID intervention

Effects

Data were provided by all 11 Dutch addiction care centres. The number of HCV consultations registered during the intervention period in these centres was 1810, resulting in 1130 anti-HCV tests. The number of positive tests was 299 (26.5%). For PWID, the mean age at time of anti-HCV testing was 46.1 years of age. In the pilot campaign, the percentage of chronic infection among anti-HCV positives in the PWID population was 86% (van der Veen et al., 2009). Using these data as a reference results in an estimated 257 (95% CI: 219–292) chronic HCV carriers identified. Since HCV testing among PWID in addiction care in the Netherlands was demonstrated to be very scarce before the intervention period, the identification of these 257 HCV carriers was considered a direct consequence of the campaign (van der Veen et al., 2009). Of the PWID tested positive, 57% was infected with genotype 1 or 4 and 43% with genotype 2 or 3. Registration data demonstrated that

Table 1
Effects of two HCV case finding interventions on number of tests and consultations.

Anti-HCV tests, positive anti-HCV tests and consultations	
Intervention for people who inject drugs ('PWID-intervention')	
Additional HCV related consultations resulting from the intervention	1,810
Additional anti-HCV tests resulting from the intervention	1,130
Additional positive anti-HCV tests resulting from the intervention	299
Additional identifications of chronic HCV resulting from the intervention — *86% of positive tests*	257
Public intervention	
Intervention regions — mean number of anti-HCV tests in control periods	22,815
Intervention regions — number of anti-HCV tests in intervention period	25,750
	12.9% increase
Control regions — mean number of anti-HCV tests in control periods	11,933
Control regions — number of anti-HCV tests in intervention period	12,655
	6.1% increase
Additional anti-HCV tests resulting from the intervention	1,554
- *corrected for increase in control region*	
Intervention regions — mean number of positive anti-HCV tests in control periods	864
Intervention regions — number of positive anti-HCV tests in intervention period	1,091
	26.3% increase
Control regions — mean number of positive anti-HCV tests in control periods	280
Control regions — number of positive anti-HCV tests in intervention period	337
	20.4% increase
Additional positive anti-HCV tests resulting from the intervention	49
- *calculated based on the before mentioned increase in tests*	
- *calculated based on Bayesian Poisson model — used in Markov model*	47
Additionally identified HCV carriers resulting from the intervention	38
- *80% of positive tests as calculated by the Bayesian Poisson model*	

Table 2
Direct and indirect costs of two HCV case finding interventions.

Costs	Costs in Euro (*95% CI*)
Intervention for people who inject drugs ('PWID-intervention')	
Direct costs, resulting from organisation, campaign execution and materials	€ 398,704 (*€ 233,596–€ 627,839*)
Indirect costs, resulting from additional consultations, testing and treatment	€ 1,893,754 (*€ 1,298,984–€ 2,606,673*)
Total costs of the 'PWID-intervention'	€ 2,292,458 (*€ 1,664,711–€ 3,021,433*)
Public intervention	
Direct costs, resulting from organisation, campaign execution and materials	€ 688,444 (*€ 398,975–€ 1,083,220*)
Indirect costs, resulting from additional consultations, testing and treatment	€ 370,669 (*€ 79,298–€ 1,425,111*)
Total costs of the 'public intervention'	€ 1,059,113 (*€ 518,709–€ 2,174,499*)

76.8% of these carriers were referred to a treatment centre. Because care for PWID in the Netherlands facilitates optimal compliance to therapy, we assumed the same SVR rate for PWID as for the general population.

Costs

Table 2 shows the direct and indirect costs including 95% confidence intervals. The direct costs of the 'PWID-intervention' were approximately €398,704 and the indirect costs were €1,893,754. Consequently, the total cost were approximately €2,292,458 (95% CI: €1,664,711–€3,021,433) leading to an estimated cost of €8919 per identified chronic HCV carrier.

Public intervention

Effects

In the 'public intervention' regions, the number of tests increased by 12.9%, from a mean of 22,815 tests in the control period (i.e. September to February in the two preceding years) to 25,750 in the six-month intervention period. In the control regions the number of anti-HCV tests increased by 6.1%, from a mean of 11,933 in the control period, to 12,655 tests during the intervention period (Table 1). Consequently, the net increase caused by the intervention is estimated at 6.8% (95% CI 6.2–7.4%), which corresponds to 1554 HCV tests attributable to the HCV campaign.

In the intervention regions the number of positive anti-HCV tests increased by 26.3%, from a mean of 864 in the control period to 1091 in the intervention period. In the control regions this number increased by 20.4%, from a mean of 280 in the control period to 337 tests in the intervention period. The additional 5.9% increase (95% CI 0.4–11.5%) in positive tests in the intervention regions represents 49 additional positive anti-HCV tests in the intervention period. The percentage of HCV positive tests increased from 3.8 to 4.2% in the intervention region and from 2.4 to 2.7% in the control region. The repeated calculation using the Bayesian Poisson model demonstrated a similar outcome at 47 positive tests. Since 80% of the anti-HCV positive tests is expected to lead to a chronic infection, approximately 38 additional chronic HCV carriers have been identified by the 'public intervention' (Alter et al., 1999; Conry-Cantilena et al., 1996). The data registration demonstrated that 65.1% of these carriers were infected with genotype 1 or 4 (the rest was genotype 2/3). These numbers were used to calculate the ICER.

Costs

Table 2 shows the direct and indirect costs of the campaigns, including 95% confidence intervals. The direct costs of the implementation of the 'public intervention' were €688,444. The indirect costs were estimated at €370,669. The total costs for the 'public intervention' were approximately €1,059,113 (95%

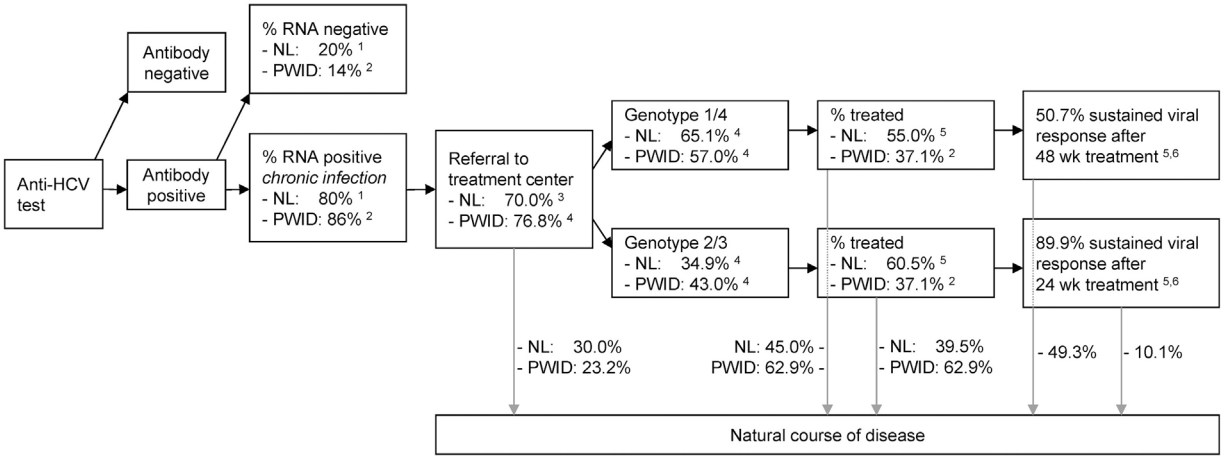

Fig. 1. Course of events after identification.
NL: general population, used for 'public intervention'. PWID: people who inject drugs, used for 'PWID-intervention'.
References (1. Lauer & Walker, 2001; 2. van der Veen et al., 2009; 3. De Jong, de Vries, Boonman-de Winter, & van Wijngaarden, 2008; 4. Observed in current campaign; 5. Thompson-Coon et al., 2006; 6. Foster et al., 1997).

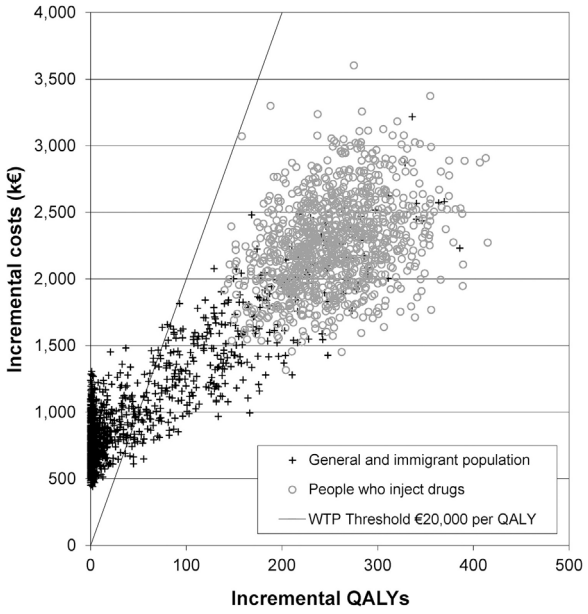

Fig. 2. Cost-effectiveness plane — simulated net costs and corresponding gain in QALYs.
(Note that all incremental QALYs are positive)

CI: €518,709–€2,174,499). The estimated costs per identified HCV carrier were €27,018.

Cost-effectiveness of the campaigns

The 'PWID-intervention' yielded discounted incremental cost of €2029 (95% CI: €1466–2703) per tested person with an associated gain of 0.22 QALYs (95% CI: 0.15–0.32). As a result, the ICER of the 'PWID-intervention' is €9056 per QALY (95% CI: €6034–13,523), when compared to 'care as usual'.

For the 'public intervention', the Markov model calculated discounted incremental cost of €683 (95% CI: €336–1405) per tested person with an associated gain of 0.037 QALYs (95% CI: 0.000–0.16). Consequently, the ICER is €18,421 (95% CI: €7376–25,490,119) per QALY, when compared to 'care as usual'.

Uncertainty and sensitivity analyses

The cost-effectiveness plane and the cost-effectiveness acceptability curve are provided as Figs. 2 and 3.

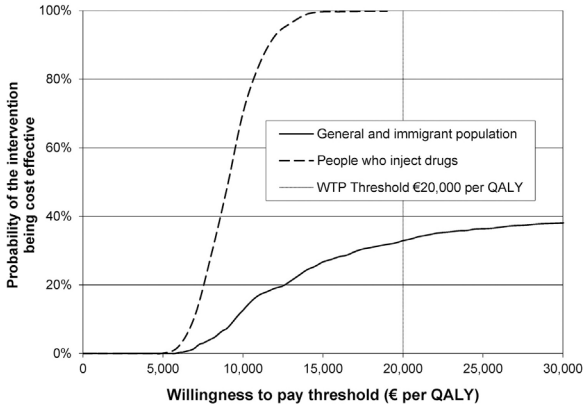

Fig. 3. Cost-effectiveness acceptability curve — probability of the interventions being cost effective.

In the Netherlands, a threshold of €20,000 is generally used as a cut-off point for cost-effectiveness (Van den Berg, de Wit, Vijgen, Busch, & Schuit, 2008). For the 'PWID-intervention', the 95% upper limit for the ICER is €13,523 (the 99.9 percentile value is €17,680). Therefore, the chance that this ICER will exceed the €20,000 threshold is negligible.

The uncertainty analysis of the 'public intervention' demonstrates that the probability that the ICER remains below this threshold is 34%. Therefore, the public intervention was not cost-effective at this threshold value for acceptable cost per QALY.

The multivariate sensitivity analysis demonstrates that, for the 'PWID-intervention', the ICER is primarily sensitive to changes in the percentage of carriers that chooses to be treated. The corresponding SRCs are −53% for carriers with genotype 2/3 and −25% for carriers with genotype 1/4. The ICER is also influenced by the cost of treatment: the SRC equals 45% of treatment of genotype 1/4 patients and 25% for genotype 2/3. Also the cost of the drug campaign influences the cost effectiveness with an SRC of 23%. The R^2 values for these sensitivity analyses were 95% or more.

The lack of a control region for the 'PWID-intervention' could have led to an overestimation of its effect. The additional sensitivity analyses performed to quantify the potential effect of such an overestimation demonstrated that a reduction of the effect on case finding by 50% would result in an ICER of €11,385. The threshold of €20,000 was reached at a reduction in effect of 82.5% (point estimate). This indicates that if an overestimation of the effect occurred, it is not likely to have influenced the resulting ICER substantially.

The ICER for the 'public intervention' showed primarily sensitive to changes in the number of identified HCV carriers (SRC = −100%). The second most influential parameter was the cost of the campaign with an SRC of 10%. The nett costs were also dominated by the number of HCV carriers identified (SRC = 87%) and the cost of the campaign (SRC = 41%). The total variance explained (R^2) by the regression model that was fitted for these sensitivity analyses was 97% or more.

The scenario analysis estimating the effect of new DAA treatment regiments (SVR12: 95%, treatment costs: €40,000, increased treatment uptake: 25%) affected the expected cost-effectiveness of the interventions.

For the 'PWID-intervention', the indirect costs increased from approximately €1,893,754 to €4,222,819. The estimated costs per identified HCV carrier increase from approximately €8919 to €17,980. The associated gain in QALYs per tested person rises from 0.22 to 0.37, leading to a new ICER of €11,035 per QALY.

For the 'public intervention', the indirect costs increased from approximately €370,669 to €754,117. The estimated costs per identified HCV carrier increased from approximately €683 to €930. The associated gain in QALYs per tested person rises from 0.037 to 0.064, leading to a new ICER of €14,471 per QALY.

Discussion

The nationwide hepatitis C campaign in the Netherlands resulted in an increase in the number of HCV tests performed, both in the intervention targeting PWID and in the 'public intervention'. The number of chronic HCV carriers identified increased as well, resulting in a net yield of 257 PWID and 38 (public) additional chronic HCV carriers diagnosed. The estimated ICER for the 'PWID intervention' is €9056 with a maximum estimated ICER of €17,680. The estimated ICER of the 'public intervention' is €18,421. However, the probability that this ICER remains below the Dutch threshold for cost-effectiveness of €20,000 in a similar situation is only 34%. Accepted cost-effectiveness thresholds differ substantially per country (World

Health Organization, 2016). In the Netherlands, this threshold is relatively low (Van den Berg et al., 2008).

The cost-effectiveness analyses of the pilot-campaigns preceding the National campaign, evaluating comparable interventions on a smaller scale, found an ICER of €7321 for a comparable 'PWID intervention' and an ICER of €11,297 for a strategy comparable to the 'public intervention' (Helsper et al., 2012). Especially, the result of the pilot campaign targeting the general population was more favourable. The comparatively modest cost-effectiveness of the 'PWID intervention' is likely to be related to the participation rates of the methadone clinics which are part of the addiction care institutions, which were lower than expected. The relatively smaller effect for the 'public intervention' examined in this paper may, at least partially, be explained by the co-occurrence of the H1N1 influenza virus pandemic during the intervention period in 2009. The H1N1-pandemic emerged in the Netherlands one month after the start of the nationwide hepatitis C campaign. It dominated the media and caused heavy workload for general practitioners due to increased GP consultations and the influenza vaccination of risk groups, which was offered in GP practices. Since GP awareness previously proved pivotal for effectiveness of a similar pilot-campaign (Helsper et al., 2010), the resulting reduction in attention and involvement of GPs and risk groups may have reduced the effectiveness of the 'public intervention'. Relatively modest attention for HCV related education may also explain why the expected enhancement of targeted testing, indicated by an increased proportion of positive anti-HCV tests, was not observed.

The main strength of this study is that it is based on the evaluation of a 'real-life' nationwide hepatitis C campaign implementing large scale interventions. In contrast to most cost-effectiveness analyses of HCV campaigns, this study provides a realistic rather than a theoretical estimation of the effects and cost-effectiveness of nationwide interventions (Coward, Leggett, Kaplan, & Clement, 2016).

Interpretation of the results is limited by imperfections in the dataset such as the possibility of missing observations in reported data and possible flaws in the registrations, and also the lack of a proper control region for the intervention targeting PWID. This may have caused increased uncertainty in the effect estimates, which we tried to compensate for by uncertainty analyses. The lack of a control region for the 'PWID-intervention' could have led to an overestimation of the effect. However, the pilot campaign indicated that HCV case finding in routine addiction care was rare before the intervention. Therefore, the assumption that HCV tests performed during the intervention can be considered as direct consequence of the 'PWID-intervention' seems justifiable (van der Veen et al., 2009). In addition, the sensitivity analysis demonstrated that the threshold for cost-effectiveness would only be exceeded if the effect is overestimated by 85%. Therefore, it is very unlikely that a potential overestimation of the effectiveness of the PWID campaign has substantially influenced the estimated cost-effectiveness of this intervention. In the registrations for the intervention and control regions of the 'public intervention', there was no reason to expect differences in the nature of missing data and possible flaws. Therefore, this is not expected to have substantially affected the estimations of the effect. The control region for the public intervention included Groningen, Tilburg, Nijmegen and Breda. Even though these are also large cities, they are not as metropolitan as Amsterdam and Rotterdam. Therefore, even though such differences were not observed, the natural progression of HCV incidence in the control region may be subject to different influences, which may lead to both under- or overestimation of the intervention effect.

The measurements of the campaign effect were limited to the active intervention periods for both interventions. Long-term effects of the campaign could not be included in the analyses. Considering the attention paid to structural incorporation of HCV in case finding protocols and the increased awareness among medical professionals and risk groups, it is likely that a longer follow through would lead to a more favourable ICER because of an increase in the campaign effect (Croes & van der Veen, 2011).

A qualitative evaluation by the 'Trimbos Institute' described additional health improvements resulting from the 'PWID-intervention'. This includes life-style improvements among consulting PWID as a consequence of increased awareness of the dangers of a lack of hygiene and risk behaviour. This effect is even larger in HCV infected PWID who undergo HCV-treatment (De Jong, Dijkstra, & van der Poel, 2011). Consequently, improved overall health resulting in an increase of quality of life would most likely lead to a more favourable ICER.

Reviews on the cost-effectiveness of HCV screening, performed at the time of our campaign interventions and more recently, demonstrate that HCV screening is likely to be cost-effective in populations with relatively high prevalence, whereas cost-effective screening in populations with lower prevalence is hard to attain (Coward et al., 2016; van Santen et al., 2016). This is consistent with the finding in our study that only the intervention targeting the group with the highest risk is clearly cost-effective. The comparatively positive outcome in our study is likely to be due to the relatively low costs and high gain in effect in the PWID population. In part, this can be explained by the high uptake of testing in our study. In a different setting, Castelnuovo et al. found an uptake among PWID of 49% for anti-HCV testing. Of those tested positive only 39% underwent the necessary PCR testing (Castelnuovo et al., 2006). In the Dutch 'PWID intervention', the uptake among PWID was 62% and PCR was generally performed automatically if the anti-HCV test was positive. This difference may be explained by the fact that addiction care in the Netherlands is well organized, with close monitoring and regular contact with the majority of the PWID.

The ICERs based on the latest SVR rates and treatment costs suggested cost-effectiveness of both interventions. Due to the lack of availability of long-term quality of life data during and after the new treatment regimens, these favourable ICERs are likely to be overestimated. Unlike the older interferon-based treatments quality of life during new treatments is uncompromised, which may improve cost-effectiveness even further.

On the other hand, injecting drug use is rapidly losing popularity and public health interventions have reduced HCV transmission rates among PWID (Health Council of the Netherlands, 2016). In addition, the implementation of HCV screening in protocols for PWID is expected to be most effective at the beginning because of the initial 'catch-up' in identification of HCV carriers susceptible to this strategy. In the longer term, the effect of the 'PWID-intervention' strategy is expected to diminish.

Finally, given the overlap in modes of transmission and risk groups, a combined approach with HBV, HIV and HCV should be considered in future campaigns. A combined campaign is and likely to be more efficient and to increase participation by risk groups and health care professionals.

This is supported by a recent report of the Health Council of the Netherlands; 'Screening risk groups for hepatitis B and C'. This report expedites important steps towards improving the efficiency of HCV case finding by specifying those at high risk and by facilitating a structured and professional approach to HCV case finding (Health Council of the Netherlands, 2016). This report includes elements of the strategies used in our campaign, such as case finding by GPs, screening of migrants from endemic countries (prevalence >2%) and testing of PWID in addiction care.

Conclusions

In a national campaign aimed at improving case finding and increasing awareness of hepatitis C, the intervention targeting people who inject drugs was shown to be cost-effective. An intervention targeting risk groups in the general population showed only a modest effect on case finding and is less likely to be cost-effective. HCV case finding campaigns are most likely to be cost-effective if focused on those with the highest risk of infection.

Funding and role of the funding source

This work was supported by ZonMw, The Netherlands Organisation for Health Research and Development [Grant number: 86000001], which is the funding body of the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research. This organisation funded the national HCV awareness campaign as well as this evaluation of its results. The sponsor had no role in the study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers are all independent from the funder and all authors had access to the data.

Conflict of interest

All authors declare that (1) all authors have support from the UMC Utrecht for the submitted work; (2) all authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have non-financial interests that may be relevant to the submitted work.

In summary, there are no competing interests.

Acknowledgements

This evaluation of the nationwide HCV campaign was funded by the Netherlands Organisation for Health Research and Development (ZonMw). The cooperation of the Netherlands Institute of Mental Health and Addiction 'Trimbos', the addiction care institutions, the Public health services (GGD) and the laboratories providing the test data were vital to the campaign and this evaluation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugpo.2017.07.022.

References

Afdhal, N., Zeuzem, S., Kwo, P., Chojkier, M., Gitlin, N., Puoti, M., et al. (2014). Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *New England Journal of Medicine*, *370*(20), 1889–1898. http://dx.doi.org/10.1056/NEJMoa1402454.

Alter, M. J., Kruszon-Moran, D., Nainan, O. V., McQuillan, G. M., Gao, F., Moyer, L. A., et al. (1999). The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *New England Journal of Medicine*, *341*, 556–562. http://dx.doi.org/10.1056/NEJM199908193410802.

Baaten, G. G., Sonder, G. J., Dukers, N. H., Coutinho, R. A., & Van den Hoek, J. A. (2007). Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. *Journal of Medical Virology*, *79*, 1802–1810. http://dx.doi.org/10.1002/jmv.21009.

Castelnuovo, E., Thompson-Coon, J., Pitt, M., Cramp, M., Siebert, U., Price, A., et al. (2006). The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health Technology Assessment*, *10*, iii–xii.

Conry-Cantilena, C., VanRaden, M., Gibble, J., Melpolder, J., Shakil, A. O., Viladomiu, L., et al. (1996). Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *New England Journal of Medicine*, *334*, 1691–1696. http://dx.doi.org/10.1056/NEJM199606273342602.

Cornberg, M., Razavi, H. A., Alberti, A., Bernasconi, E., Buti, M., Cooper, C., et al. (2011). A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. *Liver International*, *31*(Suppl. 2), 30–60. http://dx.doi.org/10.1111/j.1478-3231.2011.02539.x.

Coward, S., Leggett, L., Kaplan, G. G., & Clement, F. (2016). Cost-effectiveness of screening for hepatitis C virus: A systematic review of economic evaluations. *BMJ Open*, *6*(9), e011821. http://dx.doi.org/10.1136/bmjopen-2016-011821.

Croes, E., & van der Veen, C. (2011). Factors influencing the implementation of a hepatitis C campaign for hard drug users [in Dutch: Beinvloedende factoren bij de implementatie van de hepatitis C informatiecampagne voor drugsgebruikers]. ZonMW report number: 12500095001.

De Jong, D. J., de Vries, M. J., Boonman-de Winter, L. J., & van Wijngaarden, P. (2008). Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. *Netherlands Journal of Medicine*, *66*, 42–43.

De Jong, I., Dijkstra, M., & van der Poel, A. (2011). *Care for hard drug users after treatment for hepatitis C [in Dutch 'Nazorg voor harddrugsgebruikers na behandeling van hepatitis C']*. Trimbos Institute. ISBN: 978-90-5253-666-8.

Foster, G. R., Goldin, R. D., Main, J., Murray-Lyon, I., Hargreaves, S., & Thomas, H. C. (1997). Management of chronic hepatitis C: Clinical audit of biopsy based management algorithm. *British Medical Journal*, *315*, 453–458.

Gravitz, L. (2011). Introduction: A smouldering public-health crisis. *Nature*, *474*, S2–S4. http://dx.doi.org/10.1038/474S2a.

Health Council of the Netherlands (2016). *Screening risk groups for hepatitis B and C*. The Hague: Health Council of the Netherlands. Publication no. 2016/16. ISBN 978-94-6281-091-4.

Helsper, C. W., van Essen, G. A., Bonten, M. J., & de Wit, N. J. (2010). A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign. *Family Practice*, *27*, 328–332. http://dx.doi.org/10.1093/fampra/cmq006.

Helsper, C. W., Borkent-Raven, B. A., de Wit, N. J., van Essen, G. A., Bonten, M. J., Hoepelman, A. I., et al. (2012). Cost-effectiveness of targeted screening for hepatitis C in the Netherlands. *Epidemiology and Infection*, *140*, 58–69. http://dx.doi.org/10.1017/S0950268811000112.

Kok, A., Zuure, F. R., Weegink, C. J., Coutinho, R. A., & Prins, M. (2007). Hepatitis C in the Netherlands: Sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals. *Nederlands Tijdschrift voor de Geneeskunde*, *151*, 2367–2371.

Lauer, G. M., & Walker, B. D. (2001). Hepatitis C virus infection. *New England Journal of Medicine*, *345*, 41–52. http://dx.doi.org/10.1056/NEJM200107053450107.

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., Hassanein, T., Gordon, S. C., et al. (2013). Sofosbuvir for previously untreated chronic hepatitis C infection. *New England Journal of Medicine*, *368*(20), 1878–1887. http://dx.doi.org/10.1056/NEJMoa1214853.

Manns, M. P., Foster, G. R., Rockstroh, J. K., Zeuzem, S., Zoulim, F., & Houghton, M. (2007). The way forward in HCV treatment-finding the right path. *Nature Reviews Drug Discovery*, *6*, 991–1000. http://dx.doi.org/10.1038/nrd2411.

Meltzer, M. I. (2001). Introduction to health economics for physicians. *The Lancet*, *358*, 993–998. http://dx.doi.org/10.1016/S0140-6736(01)06107-4.

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., et al. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews. *The Lancet*, *378*, 571–583. http://dx.doi.org/10.1016/S0140-6736(11)61097-0.

Polaris Observatory HCV Collaborators. (2017). Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *Lancet Gastroenterology and Hepatology*, *2*(3), 161–176. http://dx.doi.org/10.1016/S2468-1253(16)30181-9.

Rodenburg-van Dieten, H. (2006). Guidelines for farmaco-economic research [in Dutch: Richtlijnen voor farmaco-economisch onderzoek, geactualiseerde versie]. *College voor Zorgverzekeringen*. Diemen. 2006 Report number: 25001605.

Schroeder, L. D., Sjoquist, D. L., & Stephan, P. E. (1986). *Understanding regression analysis*. Sage Publications, 31–32. ISBN 0-8039-2758-4.

Slavenburg, S., Verduyn-Lunel, F. M., Hermsen, J. T., Melchers, W. J., te Morsche, R. H., & Drenth, J. P. (2008). Prevalence of hepatitis C in the general population in the Netherlands. *Netherlands Journal of Medicine*, *66*, 13–17.

Sulkowski, M. S., Gardiner, D. F., Rodriguez-Torres, M., Reddy, K. R., Hassanein, T., Jacobson, I., et al. (2014). Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *New England Journal of Medicine*, *370*(3), 211–221. http://dx.doi.org/10.1056/NEJMoa1306218. Erratum in: New England Journal of Medicine, 2014 April 10;370(15):1469. DOI: 10.1056/NEJMoa1306218.

The National Health Care Institute. Medication costs, Netherlands: Retrieved 2nd December 2016 from www.medicijnkosten.nl.

Thompson-Coon, J., Castelnuovo, E., Pitt, M., Cramp, M., Siebert, U., & Stein, K. (2006). Case finding for hepatitis C in primary care: A cost utility analysis. *Family Practice*, *23*, 393–406.

Urbanus, A. T., van de Laar, T. J., Stolte, I. G., Schinkel, J., Heijman, T., Coutinho, R. A., et al. (2009). Hepatitis C virus infections among HIV-infected men who have sex with men: An expanding epidemic. *AIDS*, *12*, 1–7. http://dx.doi.org/10.1097/QAD.0b013e32832e5631.

Van den Berg, M., de Wit, G. A., Vijgen, S. M., Busch, M. C., & Schuit, A. J. (2008). Cost-effectiveness of prevention: Opportunities for public health policy in the Netherlands. *Nederlands Tijdschrift voor de Geneeskunde*, *152*, 1329–1334.

van der Veen, C., Hoogenboezem, G., & Breemer, J. (2009). Education campaign for hepatitis C aimed at hard drug users. Results of a pilot study [in Dutch: Voorlichtingscampagne rond hepatitis C gericht op drugsgebruikers. Resultaten van een pilotstudie]. *Verslaving: Tijdschrift over Verslavingsproblematiek*, *5*, 61–71.

van Santen, D. K., de Vos, A. S., Matser, A., Willemse, S. B., Lindenburg, K., Kretzschmar, M. E., et al. (2016). Cost-effectiveness of hepatitis C treatment for people who inject drugs and the impact of the type of epidemic; extrapolating from Amsterdam, the Netherlands. *PLoS One*, *11*(10), e0163488.

Vriend, H. J., Van Veen, M. G., Prins, M., Urbanus, A. T., Boot, H. J., & Op de Coul, E. L. (2013). Hepatitis C virus prevalence in The Netherlands: Migrants account for most infections. *Epidemiology and Infection*, *141*(6), 1310–1317.

Willemse, S. B., Razavi-Shearer, D., Zuure, F. R., Veldhuijzen, I. K., Croes, E. A., van der Meer, A. J., et al. (2015). The estimated future disease burden of hepatitis C virus in the Netherlands with different treatment paradigms. *Netherlands Journal of Medicine*, *73*(9), 417–431.

World Health Organization (2011). State of the art of vaccine research and development. Report number WHO/IVB/05.XX.2011.

World Health Organization (2016). Table: Threshold values for intervention cost-effectiveness by Region. Retrieved 2nd December 2016 from http://www.who.int/choice/costs/CER_levels/en/index.html.

Wyles, D. L., Ruane, P. J., Sulkowski, M. S., Dieterich, D., Luetkemeyer, A., Morgan, T. R., et al. (2015). Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. *New England Journal of Medicine*, *373*(8), 714–725. http://dx.doi.org/10.1056/NEJMoa1503153.

Zorginstituut Nederland (2016). Guideline for economic evaluations in healthcare. https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare.

Zuure, F. R., Urbanus, A. T., Langendam, M. W., Helsper, C. W., van den Berg, C. H., Davidovich, U., et al. (2014). Outcomes of hepatitis C screening programs targeted at risk groups hidden in the general population: A systematic review. *BMC Public Health*, *22*(14), 66. http://dx.doi.org/10.1186/1471-2458-14-66.