

**Criteria Grid**  
**Best Practices and Interventions for the Prevention and Awareness of Hepatitis C**

<b>Best Practice/Intervention:</b>	Sroczynski G. et al. (2009) Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. <i>European Journal of Public Health</i> , 19(3):245-253.			
<b>Date of Review:</b>	June 16, 2015			
<b>Reviewer(s):</b>	Christine Hu			
<b>Part A</b>				
<b>Category:</b>	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
<b>Best Practice/Intervention:</b>	<b>Focus:</b> Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: _____ <b>Level:</b> Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ <b>Target Population:</b> <u>people infected with hepatitis C</u> <b>Setting:</b> Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ <b>Country of Origin:</b> <u>Austria</u> <b>Language:</b> English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
<b>Part B</b>				
	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
<i>Is the best practice/intervention a meta-analysis or primary research? <b>Please go to Comments section.</b></i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Systematic review to determine the long-term effectiveness and cost-effectiveness of Hepatitis C virus infection screening in different populations
<i>The best practice/intervention shows evidence of "scale up" ability</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>The best practice/intervention shows evidence of transferability</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>The best practice/intervention shows evidence of adaptation</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Different countries have different epidemiology, health care systems, disease management practice patterns and treatment costs. Therefore, results of this review cannot be generalized nor transferred from one country to another.
	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Only studies from USA and European countries were included in this review due to the inclusion criteria. Results of this review may not be applicable to developing countries given different costs of HCV screening.
<i>The best practice/intervention has utilized a program evaluation process</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Consultation and feedback with community has taken place</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is sensitive to gender issues</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Results showed that HCV screening in pregnant women was dominated by no screening.
<i>The best practice/intervention is sensitive to multicultural and marginalized populations</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is easily accessed/available electronically</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Free PDF download from <a href="http://eurpub.oxfordjournals.org/content/19/3/245">http://eurpub.oxfordjournals.org/content/19/3/245</a>
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say? <b>Please go to Comments section</b></i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Incremental cost-effectiveness ratios of HCV screening vs. no screening varied over the range of 18300 – 1151000 €/QALY, if screening was not dominant. Screening in blood recipients yielded an ICER over 140600 €/LYG which was considered not to be cost-effective. HCV screening was considered cost-effective (ICURs below 40000€/QALY for Peg-IFN+RBV treatment) in populations with elevated HCV prevalence.
<i>How is the best practice/intervention funded? <b>Please go to Comments section</b></i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The article was supported in part by an unrestricted educational grant from Hoffmann La-Roche Ltd.,

				Basel, Switzerland.
<i>Is the best practice/intervention dependent on external funds?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Other relevant criteria:</i> _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

# Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection

Gaby Sroczynski<sup>1</sup>, Eva Esteban<sup>1</sup>, Annette Conrads-Frank<sup>1,2</sup>, Ruth Schwarzer<sup>1</sup>, Nikolai Mühlberger<sup>1</sup>, Davene Wright<sup>2</sup>, Stefan Zeuzem<sup>3</sup>, Uwe Siebert<sup>1,2,4</sup>

**Background:** Hepatitis C virus (HCV) infection is an emerging problem in public health. In most countries, the majority of HCV infected people are yet undiagnosed. Early detection and treatment may result in better health outcomes and save costs by preventing future advanced liver disease. The evidence for long-term effectiveness and cost-effectiveness of HCV screening was systematically reviewed. **Methods:** We performed a systematic literature search on long-term health-economic effects of HCV screening and included Health Technology Assessment (HTA) reports, systematic reviews, long-term clinical trials, full health economic and decision-analytic modelling studies with a sufficiently long time horizon and patient-relevant long-term outcomes such as life-years gained (LYG) or quality-adjusted life years (QALY) gained. Economic results were converted to 2005 Euros. **Results:** Seven studies were included. Target population, HCV prevalence, study perspective, discount rate, screening and antiviral treatment mode varied. The incremental effectiveness of HCV screening and early treatment compared to no screening and standard care varied from 0.0004 to 0.066 LYG, and from 0.0001 to 0.072 QALY. Incremental cost-effectiveness and cost-utility ratios of HCV screening vs. no screening were 3900–243 700 €/LYG and 18 300–1 151 000 €/QALY. HCV screening seems to be cost-effective in populations with high HCV prevalence, but not in low HCV prevalence populations. **Conclusions:** HCV screening and early treatment have the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Further research on the long-term health-economic impact of HCV screening when combined with appropriate monitoring strategies in different European health care systems is needed.

**Keywords:** chronic hepatitis C, cost effectiveness, screening.

## Introduction

Chronic Hepatitis C (CHC) is an emerging problem in public health. In Europe, the Hepatitis C virus (HCV) infection affects > 1% of the population with a HCV-incidence of 8.6/100 000.<sup>1,2</sup> HCV prevalence differs considerably across countries and risk groups.<sup>3</sup> The highest HCV prevalence (36–81%) is currently found in intravenous drug users (IDUs).<sup>1</sup>

The majority of HCV-infected people progress to chronic disease.<sup>4</sup> Approximately 15–20% of CHC cases develop cirrhosis within 20–30 years,<sup>5–12</sup> which is associated with a high risk for advanced liver disease, quality of life impairment, reduced life expectancy and high treatment costs. CHC is considered to be the leading cause of liver cancer and liver transplantation in Europe.<sup>13</sup>

Screening for CHC clearly fulfils the general criteria for population screening<sup>14,15</sup> and may help to identify

HCV-infected patients in an early stage of the disease (e.g. mild chronic hepatitis without fibrosis), so that they can be adequately monitored and treated. Moreover, it has been reported that it may be cost-effective to treat patients diagnosed with mild disease.<sup>16,17</sup> Furthermore, for the majority of acute HCV cases, which present no symptoms, early treatment and for symptomatic acute HCV cases watchful waiting may be currently the most effective and cost-effective strategies.<sup>18</sup> Thus, early detection and early treatment may have the potential to result in better health outcomes and to save costs by preventing future advanced liver disease. Another important reason to identify unaware HCV-infected persons is to prevent further HCV-transmission using appropriate interventions to change behaviour leading to HCV transmission (e.g. needle sharing).

However, currently most European countries lack specific policies for HCV screening. Only few European countries perform HCV screening in special subpopulations with elevated HCV prevalence. But even in these cases, the recommendations and medical practices are heterogeneous.<sup>19–21</sup> In March 2007, the European Parliament called for EU-wide action on Hepatitis C by formally adopting the Written Declaration on Hepatitis C.<sup>22</sup> Specifically, the European Parliament calls for a council recommendation on Hepatitis C screening to ensure early diagnosis and wider access to treatment and care within the member states. Furthermore, the European Liver Patients Association (ELPA) strongly suggests that the European Union should encourage tailored screening campaigns that target people in at-risk groups.<sup>23</sup>

Despite all potential benefits, HCV screening may have substantial health-economic consequences and it is not clear whether it leads to improved long-term health outcomes, because not all CHC patients will develop progressive liver disease in their lifetime, and not all CHC patients benefit from antiviral treatment.<sup>16,24,25</sup> Furthermore, current antiviral

1 Department of Public Health, Information Systems and Health Technology Assessment, UMIT – University of Health Sciences, Medical Informatics and Technology, Hall i.T., Austria

2 Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

3 Department of Internal Medicine, Gastroenterology, Hepatology, Pneumology and Endocrinology, Johann Wolfgang Goethe-University, Frankfurt a.M., Germany

4 Program in Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA

**Correspondence:** Uwe Siebert, Department of Public Health, Information Systems and Health Technology Assessment, UMIT – University of Health Sciences, Medical Informatics and Technology, Eduard Wallnoefer Center I, A-6060 Hall i.T., Austria, tel: +43-50-8648-3930, fax: +43-50-8648-673930, e-mail: public-health@umit.at

treatment options are costly, and impose the burden of side effects.<sup>16,24,25</sup> Therefore, a thorough assessment of HCV screening must consider all consequences for individuals and society during a sufficiently long time horizon.

In this review, we systematically evaluated the current evidence on long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection in different populations.

## Methods

A systematic literature search was conducted using the databases Medline, Cochrane Database of Systematic Reviews, Cochrane central register of controlled trials (CENTRAL), and the NHS databases abstracts of reviews of effects (DARE), Health technology assessment (HTA) and Economic evaluation database (NHS EED) to identify studies assessing the clinical and economic long-term consequences of screening for Hepatitis C virus infection (HCV). The time horizon of the literature search was limited to March 2007. All references were imported into a literature database using a literature management software program (EndNote 9.0, Thomson ResearchSoft TM, Thomson Corporation, Stamford, CT, USA).

First, reference titles and abstracts were screened for relevant articles. In a second step, studies were selected based on *a priori* inclusion and exclusion criteria after reading the full text document. We included health technology assessment (HTA) reports, systematic reviews, long-term clinical trials, full health economic studies and decision-analytic modelling studies assessing the impact of screening for Hepatitis C virus infections. As clinical and economic consequences of screening occur over a long time horizon, we only included studies that reported both long-term effectiveness and cost effectiveness in terms of life-years gained (LYG), quality-adjusted life-years gained (QALY), lifetime cost per life-year gained (Cost/LYG) or cost per quality-adjusted life-year gained (Cost/QALY). We excluded studies in languages other than English or German, editorials, letters, abstracts, unsystematic reviews, studies reporting only short-term effectiveness data (e.g. sustained virological response, SVR), studies assessing screening of blood donations or serological testing during antiviral treatment. We also excluded studies that did not report sufficient data to derive incremental effectiveness and cost-effectiveness ratios or cost-effectiveness studies reporting only costs per HCV case detected.

We systematically extracted the results from the publications and summarized the information in evidence tables reporting clinical and economic outcomes.

If necessary and possible, we recalculated the incremental cost-effectiveness ratios (ICER) or incremental cost-utility ratios (ICUR) from the data reported in the publication. To facilitate comparison across countries and to enable other countries to transfer our results into their currencies, all costs were converted to 2005 Euro (€) using gross domestic product purchasing power parities (GDPPP) (conversion to Euro of the index year) and the German Consumer Price Index (CPI) (inflation to the year 2005).<sup>26,27</sup> Germany was used as the reference country for the cost conversion, because it is the country with the largest population in Europe.<sup>28</sup>

## Results

### Literature search

A total of 127 unique references were retrieved. Ten publications,<sup>20,29–37</sup> including two HTA reports<sup>20,36</sup> assessing

lifetime health effects and costs of screening for Hepatitis C met the inclusion criteria. No long-term clinical trial assessing the long-term effectiveness (e.g. mortality) of screening for Hepatitis C virus infection and early HCV-treatment was identified.

Two publications by Stein *et al.*<sup>33,34</sup> reported the cost-effectiveness results of a decision-analytic model performed within an HTA report conducted by the National Institute for Health and Clinical Excellence (NICE).<sup>20</sup> Thompson Coon *et al.*<sup>37</sup> reported the cost-effectiveness results of a decision-analytic model performed within an HTA report conducted by the NHS R&D HTA Program.<sup>36</sup> Only the original data from the HTA reports were considered, leaving seven studies in the review.

### Long-term effectiveness

In the absence of clinical trials, meta-analyses and health technology assessment reports evaluating the long-term effectiveness of HCV screening, we based our results on decision-analytic modelling studies that included an analysis of long-term effectiveness of screening for Hepatitis C virus infection and early HCV-treatment in terms of undiscounted life years and/or quality-adjusted life years gained compared to no screening and standard care.

Five out of seven cost-effectiveness studies reported undiscounted life years and/or quality-adjusted life years gained for screening and early HCV-treatment compared to no screening and standard care (table 1).<sup>20,29,30,35,36</sup>

The values for life years gained due to screening and early treatment varied from 0.0004 LYG (0.15 life days) for screening blood recipients to 0.066 LYG (24.1 life days) for screening all patients assessed for HBV vaccination attending drug and alcohol services. QALYs varied from no gain for screening in pregnant women to 0.072 QALYs (i.e. 26 quality-adjusted life days) for screening in patients assessed for HBV vaccination attending drug and alcohol services. Screening in populations with elevated HCV prevalence (e.g. IDU) was more effective in terms of life-years or QALYs gained. Studies reported 0.036–0.066 LYG (13.1–24.1 life days) for populations with 42–68% HCV prevalence (0.010–0.072 QALYs/3.7–26.3 quality-adjusted life days; 32–68% HCV prevalence) vs. 0.0004–0.013 LYG (0.1–4.7 life days) for populations with 3–16% HCV prevalence (0–0.022 QALYs/0–8.0 quality-adjusted life days; 1–16% HCV prevalence).

### Long-term cost-effectiveness

#### Health technology assessment reports

Two HTA reports were included. One summarized results from economic studies evaluating HCV-screening programmes, and both HTA reports conducted a cost-effectiveness analysis.

Stein *et al.*<sup>20</sup> systematically reviewed the evidence from health economic studies evaluating HCV-screening programmes. All reviewed studies had methodological limitations and the results were of limited transferability to the UK context. Based on their decision-analytic results, the authors concluded that screening for Hepatitis C in intravenous drug users in contact with medical services may be moderately cost-effective. However, the authors recommend interpreting their results with caution because of substantial uncertainty around the acceptability of screening, the adherence to treatment and the simple nature of the model. General screening in genitourinary medicine (GUM) clinics is less cost-effective and associated with greater uncertainty than screening IDUs in contact with medical services.

**Table 1** Long-term effectiveness of screening for hepatitis C: undiscounted life years and/or QALY

Study, Country	Population	HCV prevalence (%)	Screening/Treatment	Incremental life years (LYG)	Incremental quality-adjusted life years (QALY)
Castelnuovo <i>et al.</i> <sup>36</sup> (Thompson Coon <i>et al.</i> <sup>37</sup> ) NHS R&D HTA Programme UK	Former IDUs, mean age 37 years	49	Systematic screening vs. no systematic screening (spontaneous presentation to screening possible); HCV-positives receive treatment: PegIFN+RBV	0.058	0.071
	General practice, mean age 37 years	12.5		0.010	0.017
	Former and current IDUs in general practice, mean age 37 years	49		0.036	0.071
Jusot and Colin <sup>30</sup> France	All patients assessed for HBV vaccination attending drug and alcohol services, mean age 37 years	68	Screening with EIA3 after transfusion, treatment for HCV-positives with Knodell score 5: IFN vs. no screening + no medical therapy	0.066	0.072
	Prisoners at reception, mean age 37 years (general counseling)	16		0.013	0.022
	Prisoners at reception, mean age 37 years (counseling with IDU focus)	42		0.036	0.058
	Blood recipients < 40 years	3		0.0085	n.a.
Leal <i>et al.</i> <sup>29</sup> UK	Blood recipients 40–65 years or receiving low-volume transfusions or hospitalized in a surgery department	3	Screening with EIA3 after transfusion, treatment for HCV-positives with Knodell score 5: IFN vs. no screening + no medical therapy	0.0004	n.a.
	Blood recipients receiving high-volume transfusions	3		0.0030–0.0047 <sup>a</sup>	n.a.
	IDUs in contact with drug services, mean age: n.a.	60		n.a.	0.015 <sup>b</sup>
Plunkett <i>et al.</i> <sup>35</sup> USA	Pregnant women, mean age 30 years	1	Screening vs. no screening; HCV-positives with moderate to severe CHC receive treatment: IFN	n.a.	–0.00011
	IDUs in contact with drug services, mean age 32 years	32	Screening vs. no screening; 70%(screened) or 20% (unscreened) of HCV-positives with moderate CHC receive treatment: PegIFN + RBV	n.a.	0.0001
Stein <i>et al.</i> <sup>20</sup> (Stein <i>et al.</i> 2003 <sup>33,34</sup> ) NHS R&D HTA Programme UK	Genito-urinary medicine clinic attendees, mean age 36 years	1.5	Screening and treatment as above plus Caesarian delivery	n.a.	0.01003 <sup>b</sup>
			Screening vs. no screening; 50% of HCV-positives with moderate CHC receive treatment: IFN + RBV	n.a.	0.00047 <sup>b</sup>

a: Range reported in the original study for the first, second and third year

b: Calculated with data in the original publication

n.a. = not available; IFN = interferon; RBV = ribavirin; EIA3 = enzyme linked assay third generation; PCR = polymerase chain reaction.

Castelnuovo *et al.*<sup>36</sup> performed a decision-analytic cost-effectiveness study to evaluate screening (named 'case-finding') in patients attending general medical practice or special drug and alcohol services, and in prisoners at reception with a focus on former IDUs. Based on their analyses, the authors concluded that screening in these target populations is likely to be cost-effective despite some uncertainty around the acceptance of testing and treatment.

### Cost-effectiveness studies

Seven cost-effectiveness studies evaluating HCV screening in different population settings were included in our review (table 2). Three studies were conducted in the UK,<sup>20,29,36</sup> two in France,<sup>30,32</sup> and two in the USA.<sup>31,35</sup>

Studies varied in terms of target population, study perspective, time horizon, discount rate and compared strategies including screening and antiviral treatment mode.

Five studies<sup>20,30–32,35</sup> evaluated populations at average risk for Hepatitis C (HCV prevalence 1–3.8%). Of those one study evaluated HCV screening in asymptomatic, average-risk adults in the USA,<sup>31</sup> one study examined screening in the general French population,<sup>32</sup> and another study analysed screening in pregnant women in the USA,<sup>35</sup> two studies considered screening in blood recipients,<sup>30,32</sup> and one in general Genito-urinary medicine clinic attendees.<sup>20</sup>

Four studies<sup>20,29,32,36</sup> evaluated the cost-effectiveness of screening in different populations at higher risk for HCV (HCV prevalence 7–80%). Four studies evaluated HCV screening in populations with a history of IDU in different settings,<sup>20,29,32,36</sup> two studies analysed the cost-effectiveness of general screening in attendees of special medical services,<sup>20,36</sup> and one study evaluated HCV screening in prisoners at reception.<sup>36</sup>

Most studies compared systematic screening (and antiviral treatment for detected HCV-positives) to non-systematic screening, allowing for the possibility of spontaneous case detection with subsequent antiviral treatment.<sup>20,31,35,36</sup> The percentage of HCV positives eligible for treatment varied. Some studies compared screening and antiviral treatment for detected HCV positives to no screening and no treatment.<sup>29,30,32</sup> The antiviral treatment regimens (interferon/interferon plus ribavirin/peginterferon plus ribavirin) and algorithms (e.g. treat all HCV-positives or only those with severe liver histology) varied. Only three studies<sup>20,35,36</sup> evaluated screening followed by peginterferon plus ribavirin, the current recommended standard antiviral therapy.<sup>38–40</sup>

The incremental cost-effectiveness ratios (ICER) of HCV screening vs. no screening varied over a wide range (18 300–1 151 000 €/QALY, if not dominated) depending on target population, study perspective, time horizon, discount rate and compared strategies including screening mode and antiviral treatment strategies. In summary, HCV screening in populations with an average HCV prevalence and in pregnant women was dominated by no screening. Screening in blood recipients yielded an ICER over 140 600 €/LYG and was considered not to be cost-effective.<sup>30</sup> However, this study had a time horizon of 30 years instead of lifetime, and used interferon monotherapy as antiviral treatment option. In contrast, HCV screening in populations with a high HCV prevalence such as current or former intravenous drug users was considered cost-effective. HCV screening in current and/or former intravenous drug users yielded discounted incremental cost-effectiveness ratios below 46 700 €/QALY.<sup>20,36</sup> General HCV screening amongst members of special medical practices (140 500 €/QALY)<sup>20</sup> or in prisoners at reception (30 200 €/QALY)<sup>36</sup> were associated with higher

cost-effectiveness ratios compared to more targeted screening (e.g. screening only IDUs in these settings).

Figure 1 shows the incremental ICER and ICUR ratios of screening for different HCV prevalence and different antiviral treatment strategies. Most studies evaluated the ICERs/ICURs in populations with HCV prevalence above 10%. Only four studies reported results for populations with a lower HCV prevalence. Many studies evaluated screening followed by antiviral treatment with interferon or interferon plus ribavirin, which are not current standard treatment options anymore. Peginterferon plus ribavirin, the recommended standard antiviral treatment yields more LYs/QALYs gained and results in much lower ICERs/ICURs. Therefore, figure 1c and d shows ICERs/ICURs for screening followed by treatment with peginterferon plus ribavirin, only. The majority of these studies reported ICURs below 40 000 €/QALY gained (ICER: 50 000 €/LYG) in populations with HCV prevalence above 10%, and higher ICURs (77 000–1 150 000 €/QALY gained) in low HCV prevalence populations (results from two studies).

### Discussion

We performed a systematic review on the long-term effectiveness and cost-effectiveness of screening for HCV infection.

Depending on HCV prevalence and risk selection mode, the incremental long-term effectiveness of HCV screening and early treatment compared to no screening and standard care varied from 0.0004 LYG (0.15 life-days gained) to 0.066 LYG (24 life-days gained) and from 0.0001 QALY (0.04 quality-adjusted life-days gained) to 0.072 QALY (26 quality-adjusted life-days gained). To put these figures into perspective, they can be compared with other screening programs. For example, biennial cervical cancer screening compared to no screening is associated with a gain of 92 life days. Moving from a 2-year to a 1-year interval is associated with a gain of four life days.<sup>41</sup> Given 1% undetected HIV-prevalence, one-time HIV screening in US health care settings was reported to increase life-expectancy by 3.9 days (2.9 quality-adjusted life days). Screening every 5 years would gain additional 0.97 days (0.70 quality-adjusted life days).<sup>42</sup>

It must be noted, that these numbers reflect the average incremental life expectancy per person screened. This translates to many persons with no gain and some persons with several years or decades gain in life expectancy.

The incremental cost-effectiveness ratios varied over a wide range depending on target population (e.g. HCV prevalence, age, etc.), study perspective, time horizon, discount rate and compared strategies including screening settings and antiviral treatment strategies. Therefore, the comparability of the results is limited.

HCV screening vs. no screening resulted in ICURs ranging from 18 300 to 1 151 000 €/QALY, if screening was not dominated. In the reviewed studies, HCV screening was considered cost-effective (ICURs below 40 000 €/QALY for treatment with peginterferon plus ribavirin) in populations with an elevated HCV prevalence such as intravenous drug users. General HCV screening in average-risk adults was unlikely to be effective and cost-effective.

However, cost-effectiveness should not be the main criterion for the decision to implement HCV screening. Given the substantial number of prevalent iatrogenic HCV-infected cases other ethical concepts such as fairness and equity may be considered as well.

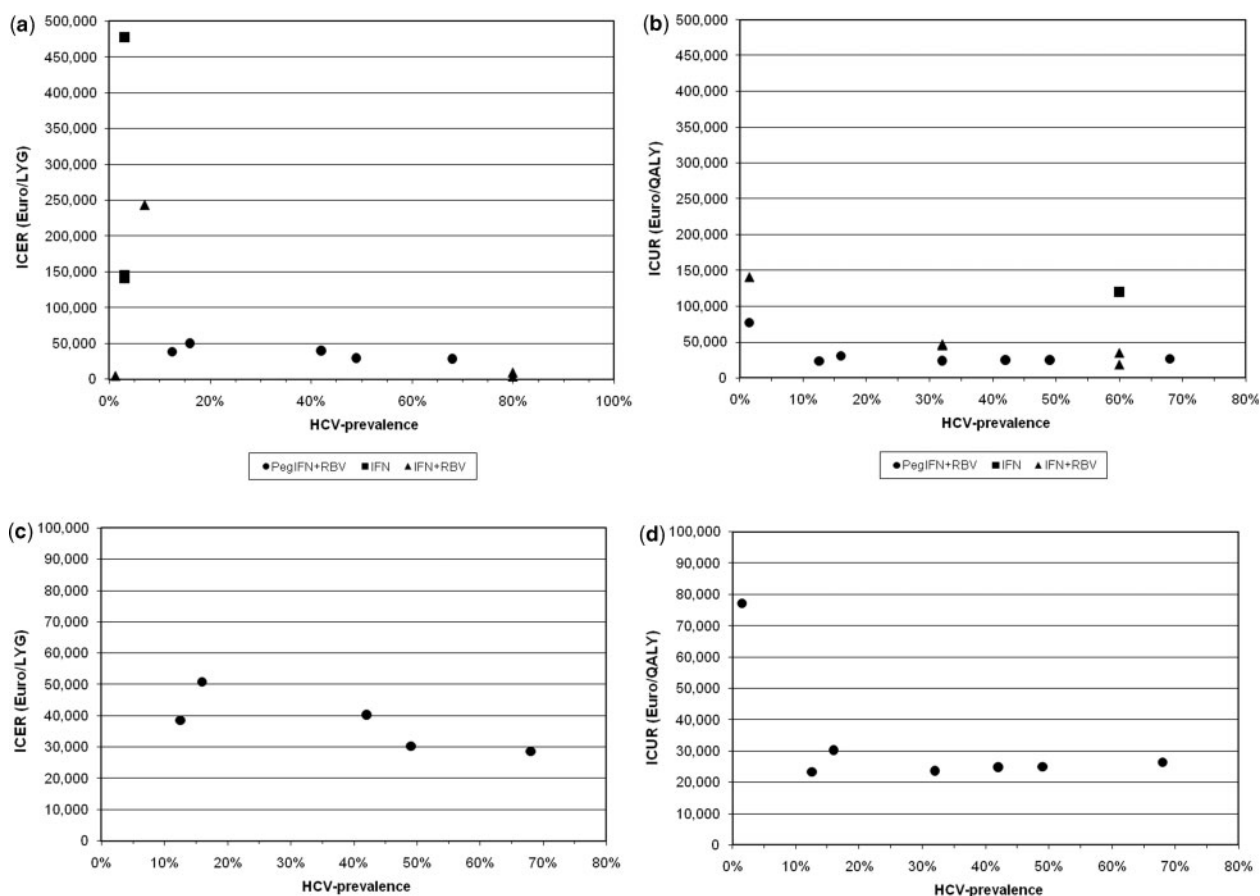
Cost-effectiveness is depending on the willingness-to-pay in a certain society, which depends on several economical, social and political factors. There is currently no general agreement across countries about the cost-effectiveness threshold. To give a measurement on the incremental cost-effectiveness ratios of

**Table 2** Discounted incremental cost-effectiveness-ratios (ICER) and discounted incremental cost-utility-ratios (ICUR) for screening for hepatitis C

Study, Country	Currency, Year, Perspective	Discount rate (%)	Comparator	Target Population	ICER (€/LYG)	ICUR (€/QALY)
Castelnuovo <i>et al.</i> <sup>26</sup> (Thompson Coon <i>et al.</i> <sup>27</sup> ) NHS R&D HTA Programme UK	UK£, 2004, National Health Services (NHS)	6 (costs), 1.5 (effects)	Systematic screening vs. no systematic screening (spontaneous presentation to screening possible); HCV-positives receive treatment: PegIFN + RBV	Former IDUs, general case, mean age 37 years, 49% HCV prevalence General practice, mean age 37 years, 12.5% HCV prevalence Former and current IDUs in general practice, mean age 37 years, 49% HCV prevalence All patients assessed for HBV vaccination attending drug and alcohol services, mean age 37 years, 68% HCV prevalence Prisoners at reception, mean age 37 years, 16% HCV prevalence Prisoners at reception, mean age 37 years, 42% HCV prevalence	30 232 38 633 30 194 28 689 50 833 40 301	24 858 23 321 24 827 26 365 30 231 24 813
Jusot and Colin <sup>30</sup> France	FF, 1996, Health care system, 30 years time horizon	No discount rate	Screening with EIA3 after transfusion, treatment for HCV-positives with Knodell score 5: IFN vs. no screening + no medical therapy Screening with EIA3 after transfusion, treatment for HCV-positives with Knodell score 5: IFN vs. no screening + no medical therapy Screening with EIA3 before and after transfusion, (treatment same as above)	Blood recipients <40 years, 3% HCV prevalence	140 674	—
Leal <i>et al.</i> <sup>29</sup> UK	UK£, 1997, n.a.	6	Screening vs. no screening; HCV-positives with moderate to severe CHC receive treatment: IFN (IFN + RBV)	IDUs in contact with drug services, 60% HCV prevalence	—	119 754 (18267-34 537 <sup>a</sup> )
Loubiere <i>et al.</i> <sup>32</sup> France	€, 1998, Health care system	3	Screening with EIA3 + EIA3 vs. no screening + no treatment; 50% of CHC cases and 40% of cirrhosis cases receive treatment: IFN + RBV Screening with EIA3 + PCR vs. no screening + no treatment; treatment as above Screening with EIA3 + EIA3 vs. no screening + treatment if cirrhosis; treatment as above Screening with EIA3 + PCR vs. no screening + treatment if cirrhosis; treatment as above Screening with EIA3 + EIA3 vs. no screening + treatment if cirrhosis; treatment as above Screening with EIA3 + PCR, vs. no screening + treatment if cirrhosis; treatment as above	Blood recipients 40–65 years or receiving low-volume transfusions or hospitalized in a surgery department, 3% HCV prevalence Blood recipients receiving high-volume transfusions, 3% HCV prevalence IDUs, 80% HCV prevalence	477 654 144 970 3881 9742	— — — —
Plunkett <i>et al.</i> <sup>35</sup> USA	US\$, 2003, Health care system	3	Screening vs. no screening; HCV-positives receive treatment: PegIFN + RBV	Pregnant women, 1% HCV prevalence	—	No screening dominant 1 150 976
Singer <i>et al.</i> <sup>31</sup> USA	US\$, 2001, Societal	3	As above plus Caesarian delivery Screening vs. no screening; 20% of HCV-positives receive treatment: IFN + RBV	Asymptomatic, average risk adults, mean age 35 years, 3.8% HCV prevalence	—	No screening dominant
Stein <i>et al.</i> <sup>20</sup> (Stein <i>et al.</i> <sup>33,34</sup> ) NHS R&D HTA Programme UK	UK£, 2001, National Health Services (NHS)	6 (costs), 1.5 (effects)	Screening vs. no screening; 50% of HCV-positives with moderate CHC receive treatment: IFN + RBV (PegIFN + RBV) All screened, 50% of HCV-positives with moderate CHC receive treatment: IFN + RBV (PegIFN + RBV) IDUs screened, 50% of HCV-positives with moderate CHC receive treatment: IFN + RBV	IDUs in contact with drug services, mean age 32 years, 32% HCV prevalence Genito-urinary medicine clinic attendees, mean age 36 years, 1.5% HCV prevalence 32% HCV prevalence	— — —	46 707 (23 598) 140 471 (77 052) 45 076

a: Depending on treatment duration (24 or 48 weeks) and ribavirin dosage (1000 or 1200 mg/d) n.a. = not available; IFN = interferon; RBV = ribavirin; EIA3 = enzyme linked assay third generation; PCR = polymerase chain reaction.





**Figure 1** Incremental cost-effectiveness ratio of screening compared to no screening in Euro per life year gained (Euro/LYG) or quality-adjusted life-year gained (Euro/QALY) for different HCV prevalence in the target population. (a) ICER (in Euro/LYG) of HCV screening and different antiviral treatment, (b) ICUR (in Euro/QALY) of HCV screening and different antiviral treatment, (c) ICER (in Euro/LYG) of HCV screening and antiviral treatment with peginterferon plus ribavirin, (d) ICUR (in Euro/QALY) of HCV screening and antiviral treatment with peginterferon plus ribavirin. (Each point represents the ICER/ICUR of a specific target population and screening/treatment strategy. Multiple points may come from the same modelling study.) IFN = interferon, RBV = ribavirin, PegIFN = peginterferon. One point out of range of figure 1(d): 1 150 976/QALY with 1% HCV prevalence, PegIFN+RBV.

well-accepted screening programs, cytological screening for cervical cancer every 3 years compared to no screening costs £1800 per life year gained in the UK,<sup>43</sup> 1400 €/LYG in Germany,<sup>44</sup> and 8400 US\$/LYG in the USA.<sup>45</sup> Screening blood donors for HIV costs 14 000 US\$/LYG.<sup>46</sup> Given 1% undetected HIV-prevalence, one-time HIV screening in US health care settings would result in 41 700 US\$/QALY, screening every 5 years 123 600 US\$/QALY.<sup>42</sup>

In the absence of long-term clinical trials, all results were retrieved from decision-analytic studies, which link diagnostic and clinical short-term outcomes (e.g. test sensitivity and specificity or viral response) to clinical long-term outcomes (e.g. mortality and long-term quality of life).<sup>47</sup> The included studies were heterogeneous in regard to health economic analysis techniques (e.g. time horizons, discounting, etc.), HCV population prevalence, acquisition risk factors and antiviral therapy. Therefore, the outcomes in terms of life years gained, quality adjusted life years and incremental cost effectiveness ratios varied over a wide range. However, several results were logical and predictable, for example, screening is more cost effective in higher prevalence or higher risk populations—a result that has been reported for other diseases, too.<sup>48,49</sup>

Like all decision-analytic models, screening models must simplify the real world for more transparency and the possibility to analyse specific research questions.<sup>47</sup> However,

some methodological and structural model assumptions may have an important impact on clinical and economic outcomes and could lead to bias in favour for or against HCV screening. Thus, it is important to discuss some aspects essential for a valuable screening model.

First, it is important to allow for the possibility of spontaneous case detection by symptoms with subsequent antiviral treatment in the non-screening strategy of any HCV-screening model. Without these estimates, the benefits of the screening strategy are overestimated and outcomes are biased in favour of the HCV-screening strategy. Second, the setting of antiviral treatment in both strategies is very important. No treatment in the non-screening strategy or 'wait and treat cirrhosis' vs. 'screen and treat all HCV-positive patients' may overestimate both the incremental benefits and costs of screening. Therefore, antiviral treatment should be considered for chronic HCV-patients (detected through screening, symptoms or spontaneous presentation) in both strategies according to recent treatment guidelines. Third, most studies considered antiviral therapy with interferon plus ribavirin,<sup>20,29,31,32</sup> and two studies used even interferon monotherapy.<sup>29,30,32</sup> Only three studies considered peginterferon plus ribavirin.<sup>20,35,36</sup> Having better treatment options and administering antiviral treatment according to genotype-specific guidelines with early treatment stop for patients not responding would allow tailoring treatment efficiently, which

would reduce adverse effects, harms, and antiviral treatment costs, and improve the cost-effectiveness of HCV screening due to better clinical and economic outcomes. Fourth, eligibility of patients for and adherence to antiviral treatment should be considered. In particular, any HCV-screening model should consider a 'wait and see' strategy in the screening arm, because not all patients necessarily should or want to be treated immediately after HCV detection.<sup>50</sup> HCV screening and watchful monitoring HCV-infected patients may be more effective and cost-effective than screening with immediate treatment of all HCV-infected patients, since a fraction of HCV-infected patients may not develop fibrosis or cirrhosis during their lifetime. This is particularly important for the elderly.

The age at which HCV-infected patients are identified and treated is a very important modelling factor as well. Most studies used an average age of 40 years for the evaluated population, which may be adequate for patients with CHC, which already developed symptoms. However, HCV screening may detect HCV-infected individuals earlier at significantly younger age. In addition certain HCV-infected populations at risk for advanced liver disease, such as intravenous drug user or ethnic minority groups, who have acquired HCV iatrogenically in early childhood, have a significantly younger average age. Thus, in these cases benefits from early detection and treatment may be underestimated.

Discounting costs and effects is important and affects ICERs, since the clinical and economic benefits of screening due to avoided cirrhosis and its sequelae occur in the distant future, whereas the costs of screening and antiviral treatment occur much earlier. One study<sup>30</sup> in France did not discount at all and two studies<sup>20,36</sup> conducted in the UK used different discount rates for costs and effects. The ICERs increased significantly in sensitivity analyses when cost and effects were equally discounted with 3.5% annually (e.g. from 16 514 £/QALY to 33 235 £/QALY<sup>36</sup>).

Most studies used a lifelong time horizon for their analyses which is the most adequate timeframe to use. As benefits that occur far in the future will not be considered within shorter time horizons, estimated cost-effectiveness ratios may be too high. One study used a 30 year time horizon.<sup>30</sup> As cirrhosis and its complications develop slowly within 10–30 years, even this time horizon may be too short and benefits may be underestimated.

All studies included in this review take into account the natural history of chronic Hepatitis C disease progression and mortality from CHC-related complications. Only one study used the natural history of chronic Hepatitis B disease progression, as at that time no information existed regarding Hepatitis C progression. However, it was not always clear whether slower progression rates were considered for screened populations tending to present histological milder Hepatitis C compared to non-screened populations mostly detected by symptoms. Several studies reported that patients with mild CHC and normal ALT levels may have a reduced risk of progression to cirrhosis compared to patients with more severe histology or elevated ALT levels.<sup>7,51–54</sup> Furthermore, analyses for CHC patients co-infected with HIV should assume higher progression rates to CHC-related liver diseases than analyses in non-co-infected CHC patients.<sup>55,56</sup>

In addition, most studies used age- and gender-specific mortality rates of the general population for the background mortality for CHC patients. However, background mortality is often higher due to co-morbidity from other diseases such as HIV- or HBV-coinfection, or in case of IDUs from continuation of or relapse to drug abuse. Even patients with moderate CHC or cirrhosis that respond to antiviral treatment continue

to have an increased risk of developing hepatocellular carcinoma, which is associated with significant mortality.

Overall, this review discovered many study limitations and the need for further systematic research in HCV screening. Particularly, health-economic studies in population with low or average HCV prevalence evaluating HCV screening combined with different strategies of monitoring and antiviral treatment of HCV-positives according to current treatment standard are required.

Finally, it must be mentioned, that due to different epidemiology, health care systems, disease management practice patterns and treatment costs in different European countries, results cannot be generalized and are difficult if not impossible to be directly transferred from one country to another. Further research should focus on the development of a Pan-European Hepatitis C screening model that fulfils the quality criteria discussed above and which can be adapted to the context of the different health care systems and countries within Europe.

## Conclusion

Although HCV screening fulfils general population screening criteria, specific well-formulated national programs for Hepatitis C screening are lacking in most European countries. Based on current evidence, HCV screening and early treatment has the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Further research is needed to investigate the long-term health-economic impact of HCV screening when combined with appropriate monitoring and treatment strategies in different European health care systems. Further assessments should focus on determining optimal target groups and settings that yield effective and cost-effective HCV screening strategies.

## Acknowledgements

We thank the members of the PanEuropean Hepatitis C Expert Panel for providing local information and reviewing the results of our study: Maria Buti, MD, Hospital General Universitario Vall de Hebron, Barcelona, Spain; Florin Caruntu, Matei Bals Infectious Disease Institute, Bucharest and Carol Davila Medicine and Pharmacy University, Bucharest, Romania; Charles Gore, The Hepatitis C Trust, London, UK; Scott D Holmberg, MD, MPH, Epidemiology and Surveillance Branch, Division of Viral Hepatitis Prevention, NCHHSTP, Centers for Disease Control and Prevention, Atlanta, GA, USA; Nadine Piorkowsky, The European Liver Patients Association (ELPA), Germany; Prof William Rosenberg, Institute of Hepatology, University College London, UK. However, the authors alone are responsible for the results reported and views expressed in the paper. The authors had complete and independent control over study design, analysis and interpretation of data, report writing and publication, regardless of results.

## Funding

This project was supported in part by an unrestricted educational grant from Hoffmann La-Roche Ltd., Basel, Switzerland.

*Conflicts of interest:* N.M. has received travel support from Hoffmann La-Roche Ltd. to present preliminary results of the study to different audiences. U.S. has received health technology assessment research grants from the German Federal Ministry of Health and the Austrian Academy of

Sciences and unrestricted research grants from Schering Plough and Roche.

### Key points

- Although HCV screening fulfils general population screening criteria, specific well-formulated national public health programs for hepatitis C screening are lacking in most European countries.
- According to this review, HCV screening with early treatment has the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Appropriate target groups could be selected based on risk factor profiles.
- Appropriate monitoring and treatment strategies for detected early disease may improve the cost-effectiveness of HCV screening.
- In view of the multitude of iatrogenic infections, however, cost-effectiveness may not be the only decision criterion for the implementation of HCV screening. Aspects like fairness might be considered as well.
- Further research should focus on the public-health impact of HCV screening when combined with appropriate monitoring and treatment strategies and on determining optimal target groups and settings.

### References

- 1 Weissing L, Roy K, Sapinho D, et al. Surveillance of hepatitis C infection among injecting drug users in the European Union. In: Jager J, Limburg W, Kretzschmar M, et al, editors. *Hepatitis C and injecting drug use*. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction, 2006, 91–135.
- 2 European Centre for Disease Prevention and Control (ECDC). *Annual epidemiologic report on communicable diseases in Europe 2007*. <http://www.ecdc.europa.eu> (date last accessed 28 June 2007).
- 3 Rantala M, van de Laar MJ. Surveillance and epidemiology of hepatitis B and C in Europe – a review. *Euro Surveill* 2008;13. Available online: <http://www.eurosurveillance.org> (date last accessed 13 December 2008).
- 4 Alter H, Seeff L. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;20:17–35.
- 5 Anonymous. EASL international consensus conference on hepatitis C. Paris, 26–27 February 1999. Consensus statement. *J Hepatol* 1999;31(Suppl 1):3–8.
- 6 Dore GJ, Freeman AJ, Law M, Kaldor JM. Is severe liver disease a common outcome for people with chronic hepatitis C? *J Gastroenterol Hepatol* 2002;17:423–30.
- 7 Freeman A, Dore G, Law M, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;34:809–16.
- 8 Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. *J Viral Hepat* 2003;10:285–93.
- 9 Hopf U, Moller B, Kuther D, et al. Long-term follow-up of posttransfusion and sporadic chronic hepatitis non-A, non-B and frequency of circulating antibodies to hepatitis C virus (HCV). *J Hepatol* 1990;10:69–76.
- 10 Koretz R, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis. Looking back in the second decade. *Ann Intern Med* 1993;119:110–5.
- 11 Mattsson L. Outcome of acute symptomatic non-A, non-B hepatitis: a 13-year follow-up study of hepatitis C virus markers. *Liver* 1993;13:274–8.
- 12 Tremolada F, Casarin C, Alberti A, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol* 1992;16:273–81.
- 13 World Health Organization (WHO). Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepatitis* 1999;6:35–47.
- 14 Wilson J, Jungner Y. Principles and practice of mass screening for disease. *Bol Oficina Sanit Panam* 1968;65:281–393.
- 15 Wilson J. The evaluation of the worth of early disease detection. *J R Coll Gen Pract* 1968;16(Suppl 2):48–57.
- 16 Brady B, Siebert U, Sroczynski G, et al. *Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology Report No. 82]*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2007.
- 17 Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;10:1–132.
- 18 Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. *Lancet* 2008;372:321–32.
- 19 Jullien-Depradeux AM, Bloch J, Le Quellec-Nathan M, Abenham A. National campaign against hepatitis C in France (1999–2002). *Acta Gastroenterol Belg* 2002;65:112–4.
- 20 Stein K, Dalziel K, Walker A, et al. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002;6:1–122.
- 21 Department of Health/General Health Protection. Hepatitis C Action Plan for England, July. 2004. Available at: [www.dh.gov.uk/publications](http://www.dh.gov.uk/publications) (date last accessed 12 November 2006).
- 22 European Liver Patient Association (ELPA). *European Parliament demands EU-wide action on Hepatitis C 2007*. <http://www.elpa.org> (date last accessed 15 May 2007).
- 23 European Liver Patient Association (ELPA). *Promoting Hepatitis C Screening in Europe*. 2007. <http://www.elpa.org> (date last accessed 8 May 2008).
- 24 Shepherd J, Brodin HFT, Cave CB, et al. Clinical- and cost-effectiveness of pegylated interferon alfa in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Int J Technol Assess Health Care* 2005;21:47–54.
- 25 Siebert U, Sroczynski G, on behalf of the German Hepatitis C Model (GEHMO) Group and the HTA Expert Panel on Hepatitis C. *Antiviral therapy for patients with chronic hepatitis C in Germany. Evaluation of effectiveness and cost-effectiveness of initial combination therapy with Interferon/Peginterferon plus Ribavirin*. Series of the German Institute for Medical Documentation and Information commissioned by the Federal Ministry of Health and Social Security. Cologne: DIMDI, 2003.
- 26 Organisation for Economic Co-operation and Development (OECD). *Gross domestic product purchasing power parities*. 2006. <http://www.oecd.org>.
- 27 German Federal Statistical Office. *German Consumer Price Index (CPI)*. 2006. <http://www.destatis.de>.
- 28 Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. *World population prospects: the 2006 revision and world urbanization prospects: the 2005 revision*. <http://esa.un.org/unpp>.
- 29 Leal P, Stein K, Rosenberg W. What is the cost utility of screening for hepatitis C virus (HCV) in intravenous drug users? *J Med Screen* 1999;6:124–31.
- 30 Jusot JF, Colin C. Cost-effectiveness analysis of strategies for hepatitis C screening in French blood recipients. *Eur J Public Health* 2001;11:373–9.
- 31 Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *Am J Med* 2001;111:614–21.
- 32 Loubiere S, Rotily M, Moatti JP. Prevention could be less cost-effective than cure: the case of hepatitis C screening policies in France. *Int J Technol Assess Health Care* 2003;19:632–45.
- 33 Stein K, Dalziel K, Walker A, et al. Screening for hepatitis C in genito-urinary medicine clinics: a cost utility analysis. *J Hepatol* 2003;39:814–25.
- 34 Stein K, Dalziel K, Walker A, et al. Screening for Hepatitis C in injecting drug users: a cost utility analysis. *J Public Health* 2004;26:61–71.

- 35 Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2005;192:1153–61.
- 36 Castelnuovo E, Thompson-Coon J, Pitt M, et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health Technol Assess* 2006;10: iii–iv, ix–xii, 1–93.
- 37 Thompson Coon J, Castelnuovo E, Pitt M, et al. Case finding for hepatitis C in primary care: a cost utility analysis. *Fam Pract* 2006;23:393–406.
- 38 Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis C: consensus guidelines. *Can J Gastroenterol* 2007;21(Suppl C):25C–34C.
- 39 NIH Consensus Statement. National institutes of health consensus development conference: management of Hepatitis C: 2002 - June 10–12, 2002. *Hepatology* 2002;36(5 Suppl 1):S3–20.
- 40 Zeuzem S. Standard treatment of acute and chronic hepatitis C. *Z Gastroenterol* 2004;42:714–9.
- 41 Siebert U, Sroczynski G, Hillemanns P, et al. The German cervical cancer screening model: development and validation of a decision-analytic model for cervical cancer screening in Germany. *Eur J Public Health* 2006;16:185–92.
- 42 Sanders G, Bayoumi A, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med* 2005;352:570–85.
- 43 Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess*. 2000;4:1–73.
- 44 Siebert U, Muth C, Sroczynski G, et al. *Liquid-based preparation and computer-assisted examination of cervical smears in cervical cancer screening. Clinical effectiveness, economic evaluation, and systematic decision analysis.* Series of the German Institute for Medical Documentation and Information commissioned by the Federal Ministry of Health and Social Security. St. Augustin: Asgard, 2004.
- 45 McCrory DC, Matchar DB. Evaluation of cervical cytology - systematic review. HTA Report: Agency for Health Care Research and Quality (AHRQ), Report No: 5, 1999.
- 46 Tengs T, Adams M, Pliskin J, et al. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;15:369–90.
- 47 Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? [Editorial]. *Eur J Health Econ* 2003;4:143–50.
- 48 Shamir R, Hernell O, Leshno M. Cost-effectiveness analysis of screening for celiac disease in adult population. *Med Decis Making* 2006;26:282–93.
- 49 Hayashino Y, Shimbo T, Tsujii S, et al. Cost-effectiveness of coronary artery disease screening in asymptomatic patients with type 2 diabetes and other atherogenic risk factors in Japan: factors influencing on international application of evidence-based guidelines. *Int J Cardiol* 2007;118:88–96.
- 50 Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;133:665–75.
- 51 Alberti A, Morsica G, Chemello L, et al. Hepatitis C viremia and liver disease in symptom-free individuals with anti-HCV. *Lancet* 1992;340:697–8.
- 52 Alter H, Conry-Cantilena C, Melpolder J, et al. Hepatitis C in asymptomatic blood donors. *Hepatology* 1997;26(3 Suppl 1):29S–33S.
- 53 Marcellin P, Levy S, Erlinger S. Therapy of hepatitis C: patients with normal aminotransferase levels. *Hepatology* 1997;26(3 Suppl 1):133S–6S.
- 54 Mathurin P, Moussalli J, Cadranel J, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology* 1998;27:868–72.
- 55 Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001;33:562–9.
- 56 Soto B, Sánchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;26:1–5.

Received 14 September 2008, accepted 22 December 2008