Cost-effectiveness of HCV screening: a systematic review of the literature from 2007 to 2012

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ABSTRACT

BACKGROUND: currently, 123-170 million people in the world are infected with Hepatitis C Virus (HCV) and 75% of them remain undiagnosed. HCV-positive individuals will develop Chronic Hepatitis C (CHC) or hepatocellular carcinoma (HCC) within 25 years in 20-30% of cases. Early detection of HCV has been demonstrated to increase quality-adjusted life years (QALY) and to improve the behaviour of the infected population. Current national policies usually recommend regular screenings only for at-risk populations. A systematic review of the recent evidence on long-term cost-effectiveness of HCV screening in different populations was performed.

METHODS: resources were searched on publicly available databases (PubMed, ScienceDirect, NHS EED, Cochrane Library) and Google®. Studies were considered eligible if published between 2007 and 2012 and if providing measures of incremental cost-effectiveness ratio (ICER) or incremental cost utility ratio (ICUR) of HCV screening in terms of cost/life years gained (LYG) and cost/QALY. All the costs were converted into Euro (€) for 2011. A weighted version of the Drummond checklist was used to further assess the quality of the included studies. Results: six articles were selected and analysed. Three U.S. and one Japanese studies suggested a positive cost-effectiveness profile of broad birth-cohort and population screening. Other studies conducted in Italy and the UK demonstrated high variability in the cost-effectiveness in different study populations. All the studies were judged of medium-high quality.

CONCLUSIONS: cost-effectiveness of HCV screening significantly varies among countries and study populations. Prevalence in the population should be one of the criteria for policy-makers for future decisions and recommendations. New Direct-Acting Antiviral agents might increase the cost-effectiveness of early HCV screening. Future studies should also focus on migrants and men who have sex with men (MSM) populations.

Key words: Chronic hepatitis C; Cost-effectiveness; HCV-screening

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INTRODUCTION

It is estimated that currently 123-170 million people worldwide are infected with HCV (2-3% of world population) and up to 75% of population infected remains undiagnosed [1, 2]. Infection is usually due to transmission of body fluids. Risk groups of HCV are injection drug users (IDU), recipients of blood transfusions or organ transplants before 1992

and of clotting factor concentrates before 1987, long-term dialysis patients, children born to HCV-positive women, and health care workers exposed to HCV [3]. Twenty-five years after the infection onset, around 30% of HCV-positive subjects develop Chronic Hepatitis C (CHC) infection, a slowly progressive disease that can lead to cirrhosis or hepatocellular carcinoma (HCC). These complications in parallel would increase the cost burden of Hepatitis C, which is further worsened by the fact that a liver transplant becomes necessary in some cases.

The current standard treatment based on the association of peg-interferon and ribavirin has progressively supplanted the less effective combination of interferon and ribavirin. Very recently a new class of protease inhibitors, namely boceprevir and telaprevir, has been demonstrated to be able to boost the virological response rate of the combination treatment [4]. In contrast to Hepatitis A virus (HAV) and Hepatitis B virus (HBV), no vaccine has been approved for the prevention of Chronic Hepatitis C so far.

The economic burden of HCV is associated with the fact that people usually are not screened until the appearance of the first symptoms of liver disease. Early screening has been demonstrated to be advantageous both in terms of clinical outcomes and cost-effectiveness, since it allows to detect patients who have not developed advanced liver disease (e.g. hepatic fibrosis) and to decrease the number of liver transplants and to prevent further contagion in the population favouring correct behaviours of positive patients. The costs of HCV are considered to be over US$ 5 bln/year in the U.S. [5] alone, where HCV testing is routinely recommended to subjects who ever injected illegal drugs, were recipients of clotting factors made before 1987 or blood/organs before July 1992 and individuals who were under chronic haemodialysis [6]. In Europe, although single countries have developed and implemented their own national policies and recommendations, some practices (e.g. screening of blood donors) are common in all regions [7].

Since a systematic review on the cost-effectiveness of screening for HCV was published in 2007 [8], we aimed to systematically review all the papers published after January 2007.

METHODS

The systematic review was performed following the PRISMA statement [9]. In order to retrieve the recent literature regarding the cost-effectiveness of HCV screening, a PubMed search was performed from January 2007 until March 2012. The key-words used were: “cost-effectiveness” AND “ HCV” AND “Screening”. Papers were considered eligible only if they included measures of long-term effectiveness or cost-effectiveness in terms of life-years gained (LYG), quality-adjusted life years (QALYs) gained, cost per life-year gained (Cost/LYG) or cost per quality-adjusted life-year gained (Cost/QALY). Articles retrieved through this search were integrated with results found with Google® and additional literature was sought on www.sciencedirect.com and Cochrane Library. Languages considered were Italian, English and Spanish. A further literature search was conducted on the NHS Economic Evaluation Database (NHS EED - http://www.crd.york.ac.uk/CRDWeb/SearchPage.asp). Resources retrieved were imported in a literature management software program (EndNote X5, Thomson Research Soft TM, Thomson Corporation, Stamford, CT, USA). Data were systematically extracted from the publications and cost-effectiveness outcomes together with details about single studies were summarised in a table (Table 1).

In order to compare the results of different studies, which were realised in different countries over a time-span of five years, all the costs were converted into Euro (€). Values reported in US Dollars and British Pound were first converted into Euros with a historical conversion rate obtained from www.oanda.com and then adjusted for 2011 inflation with the Italian Consumer Price Index (CPI) obtained from www.ycharts.com.

Quality assessment

A weighted version of the Drummond checklist [10, 11] was used to further evaluate the quality of the studies included in the systematic review. The checklist was developed to assess the quality of an economic evaluation considering the following sections: study design, data collection, analysis and interpretation of results. All of the 35 items were explored by

TABLE 1

QUALITY OF INCLUDED STUDIES - ASSESSMENT AND SCORE FOR EACH ITEM

	REFEREE'S CHECKLIST												
	ITEM	TRAMARIN ET AL., 2008 [15]		NAKAMURA ET AL,. 2007 [16]		REIN ET AL., 2011 [14]		COFFIN ET AL., 2010 [13]		MCGARRY LJ, ET AL., 2010 [12]		SUTTON ET AL., 2007 [17]	
		ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE
STUDY DESIGN	(1) The research question is stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(2) The economic importance of the research question is stated	Y	3	Y	3	Y	3	Y	3	Y	3	Y	3
	(3) The viewpoint(s) of the analysis are clearly stated and justified	Y	4	N	_	Y	4	NA		Y	4	Y	4
	(4) The rationale for choosing the alternative programmes or interventions compared is stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(5) The alternatives being compared are clearly described	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(6) The form of economic evaluation used is stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Y	3	Y	3	Y	3	Y	3	Y	3	Y	3
DATA COLLECTION	(8) The source(s) of effectiveness estimates used are stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(9) Details of the design and results of effectiveness study are given (if based on a single study)	Y	3	N		Y	3	Y	3	Y	3	Y	3
	(10) Details of the method of synthesis or meta-analysis of estimates are given (overview)	NA		NA		NA		NA		NA		NA	
	(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(12) Methods to value health states and other benefits are stated	Y	4	NA		Y	4	Y	4	NC		Y	4
	(13) Details of the subjects from whom valuations were obtained are given	N		NC		N		N		N		N	
	(14) Productivity changes (if included) are reported separately	NA		NA		Y	2	N		N		NA	
	(15) The relevance of productivity changes to the study question is discussed	NA		NA		N		N		N		NA	
	(16) Quantities of resources are reported separately from their unit costs	N		N		N		Y	3	Y	3	N	
	(17) Methods for the estimation of quantities and unit costs are described	Y	4	NC		Y	4	N		Y	4	Y	4
	(18) Currency and price data are recorded	Y	3	Y	3	N		NC		Y	3	N	
	(19) Details of currency of price adjustments for inflation or currency conversion are given	Y	3	Y	3	N		Y	3	Y	3	Y	3
	(20) Details of any model used are given	Y	3	Y	3	N		Y	3	Y	3	Y	3
	(21) The choice of model used and the key parameters on which it is based are justified	Y	4	Y	4	N		Y	4	Y	4	Y	4

TABLE 1 (CONTINUED)

QUALITY OF INCLUDED STUDIES - ASSESSMENT AND SCORE FOR EACH ITEM

	REFEREE'S CHECKLIST												
	ITEM	TRAMARIN ET AL., 2008 [15]		NAKAMURA ET AL,. 2007 [16]		REIN ET AL., 2011 [14]		COFFIN ET AL., 2010 [13]		MCGARRY LJ, ET AL., 2010 [12]		SUTTON ET AL., 2007 [17]	
		ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE	ASSES-SMENT	SCORE
ANALYSIS AND INTERPRETATION OF RESULTS	(22) Time horizon of costs and benefits is stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(23) The discount rate(s) is stated	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(24) The choice of rate(s) is justified	N		Y	3	N		NC		N		Y	3
	(25) An explanation is given if costs or benefits are not discounted	NA		NA		NA		NA		NA		NA	
	(26) Details of statistical tests and confidence intervals are given for stochastic data	NA		Y	3	N		N		N		Y	3
	(27) The approach to sensitivity analysis is given	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(28) The choice of variables for sensitivity analysis is justified	NA		Y	3	N		N		N		Y	3
	(29) The ranges over which the variables are varied a-re stated	Y	3	Y	3	Y	3	NC		Y	3	NC	
	(30) Relevant alternatives are compared	Y	3	N		Y	3	Y	3	Y	3	Y	3
	(31) Incremental analysis is reported	Y	3	Y	3	N		Y	3	Y	3	Y	3
	(32) Major outcomes are presented in a disaggregated as well as aggregated form	Y	3	Y	3	N		Y	3	Y	3	Y	3
	(33) The answer to the study question is given	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(34) Conclusions follow from the data reported	Y	4	Y	4	Y	4	Y	4	Y	4	Y	4
	(35) Conclusions are accompanied by the appropriate caveats	NC		N		Y	4	Y	4	Y	4	N	
	FINAL SCORE	90		81		77		83		89		93	

Y=Yes; N=No; NC= Not Clear; NA=Not Appropriate

Score 1: Less important item; Score 2: Important item; Score 3: Very important item; Score 4: Essential item

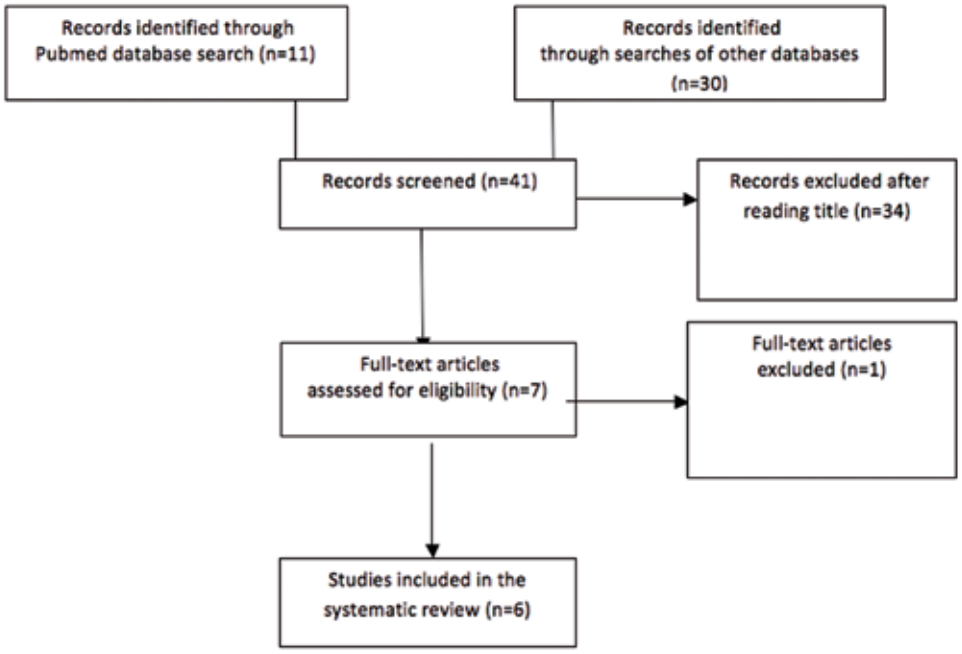
two independent reviewers per each one of the included studies. The weighted version assigned a maximum global score of 26 for study design, 45 for data collection, 48 for analysis and interpretation of the results section, while the global highest available score was 119.

RESULTS

The search engine provided a total of 140 results. After screening of the full text, six articles, all in English, were considered eligible for the systematic review. A flow diagram (Figure 1) shows the flowchart of the literature

FIGURE 1

FLOWCHART OF THE LITERATURE SEARCH



search, while the main characteristics of the studies are reported in the Table 2.

Three studies were conducted in the US [12-14], one in Italy (Veneto region) [15], one in Japan [16] and one in England/Wales [17].

Different study populations were investigated: in the three U.S. studies the target populations were entire birth cohorts: 1946-1970 [14]; population aged 20-65 with sub-analysis of birth cohort 1945-1965 [13]; 1945-1965 with 1 or more visits to a primary care provider annually [12]. Nakamura et al. compared the cost-effectiveness of both the entire Japanese population and high-risk population with no screening. The study was based on clinical data collected from the HCV national screening program initiated in 2003 and included data on HCV in the general population (99 001 subjects) and high-risk groups (42 538 subjects).

The Italian study focused on two high risk groups: IDU and Individuals with Surgery (IWS) in the Veneto region, while Sutton et al. performed a cost-effectiveness analysis on individuals who entered a prison over a three-month period [17] (see Table 2).

All the articles considered a life-long perspective and compared the cost-effectiveness of HCV screening in the target population with the status quo.

In order to simulate disease progression and to predict costs associated with the disease, all the authors developed or used existing decision-analytic modelling studies (Markov simulations). While two papers described in detail the characteristics of the model used [12, 14], other articles lacked some information regarding the assumptions and the parameters used in implementing the model [16].

Five publications used quality adjusted life years (QALYs) to measure the benefit of the intervention apart from Nakamura, who used life years gained (LYG) as outcome indicator.

Results on ICER and ICUR extracted from the article demonstrated a significant variability, in particular comparing broad population and risk-population screening (Table 2). The three US and the Japanese studies showed strong cost-effectiveness of broad birth-cohort based HCV-screening campaigns among their populations. The three US studies [12-14] reported ICURs ranging from 2 986 €/QALY to 55 238 €/QALY, while Nakamura et al. had 695.8 €/LYG (aged 40 to 49 years) to 3 959 €/LYG for 70-year-old patients. The study conducted in Italy [15] demonstrated dominance (negative ICUR) for screening for IDU and scarce cost-effectiveness for individuals with IWSs. Surprisingly, the results of the study performed on a cohort of prisoners in England and Wales [17] demonstrated an elevated ICUR (89 340 €/QALY), suggesting that interventions in contexts where the prevalence

TABLE 2

MAIN CHARACTERISTICS OF THE 6 STUDIES INCLUDED

AUTHORS	COU-NTRY	CURRENCY, YEAR, PERSPECTIVE	DISCOUNT RATE	COMPA-RATOR	TARGET POP	ICER	ICUR
MCGARRY ET AL [12]	U.S.	US$, 2010, Payer (only direct medical costs)	0-5%	Risk Based Screening	Adult born from 1945 through 1965 with 1 or more visits to a primary care provider annualy		26 804 €/QUALY (birth cohort vs risk based)
COFFIN ET AL [13]	U.S.	US$, 2010, Societal	3%	Risk Based Screening			General population: 5 617€/QUALY; Birth cohort (1945-1965): 2 986 €/QUALY
REIN ET AL [14]	U.S.	US$, 2010, Societal, Healthcare	3%	Risk Based Screening	U.S. residents born 1946-1970 with non previous HCV diagnosis		Standard treatment: 11 767 €/QUALY (compared with risk based treatment); DAA + standard treatment: 26 757 €/QUALY (if compared with risk-based screening) and 55 238 €/QUALY (if compared with birth cohort screening with standard treatment)
TRAMARIN ET AL [15]	Italy	€, 2008 (2007), Societal	3%/3%	No Screening	IDU and IWS		IDU: -3 393 €/QUALY (genotype 1, 4: -5 565 €/QUALY; genotype 2, 3: 10 460 €/QUALY); IWS: 994 353 €/QUALY (genotype 1, 4: 758 090 €/QUALY; genotype 2, 3: 2 517 402 €/QUALY);
NAKAMURA ET AL [16]	Japan	US$, 2007, not explicitely reported (likely to be healthcare perspective)	3%	No Screening	High-risk population (high level of amino-transferase, those who had undergone a major operation or had received a blood transfusion during childbirth); the general population (99 001 people)	ICER in the general population ranged from 695.8 €/LYG (aged 40 to 49 ys) to 3 959 €/LYG (70-year-olds). In the high-risk group, the screening was dominant for population subgroup aged 40 to 49 years and ICUR was 1 884.95 €/LYG for 70-year-olds	
SUTTON ET AL [17]	England and Wales	£, 2007, HC provider	3.5% (scenario analysis 6% and 1.5% for QALYs, cost/QUALY=€ 19 595	Spontaneous presentation of infected individuals (independent of disease progression) in a community setting	Individuals who entered a prison over a 3 months period		89 340 €/QUALY

of HCV is expected to be high (such as a prison) is not always clearly cost-effective (Table 2).

Sensitivity and scenario analyses were performed in almost all studies. It is interesting to note that in the study performed by Sutton et al., the use of a different discount rate (3.5% in both costs and benefits vs. 6% for costs and 1.5% for benefits) changed radically the results of the model, suggesting strong cost-effectiveness of HCV screening on individuals within 3 months of entering prison (21 829 €/QALY).

Quality of characteristics included in the study and quality of the included studies

Table 1 reports a qualitative evaluation assigned to each included study according to the 35 items explored. All the studies defined the research question (item 1) and its economic importance (item 2), stated the rationale for choosing alternative interventions (item 4) and described the alternative being compared (item 5), the form of economic evaluation (item 6), and justified it (item 7); all the studies stated the sources of estimated effectiveness used (item 8), the primary outcome measures for economic evaluation (item 11), time horizon of costs and benefits (item 22), gave an approach to sensitivity analysis (item 27), gave an answer to the study question (item 33) and reported conclusions drawn from the data (item 34). According to the Weighted Drummond's scale the median quality score of selected studies was 86.5, with a minimum score of 77 and a maximum of 93. The highest score was reached in study design section, with a median score of 26 (min. 22, max. 26); in Data collection the median score was 28.5 (min. 21, max. 32), while in Analysis and interpretation of results section the median score was 34.5 (min. 30, max. 38).

CONCLUSIONS

Following this systematic review, HCV screening appears to be more cost-effective in high-risk subgroups where the prevalence of the virus is higher. However, some recent articles have shown that it could be reasonable for policy-makers to extend or introduce HCV screening in a broader subset of the population. In particular, the three studies conducted in the U.S. and the one carried out in Japan showed a very positive cost-effectiveness profile for the extension of HCV screening to an entire birth-cohort of citizens.

Significant variability in terms of cost-effectiveness among studies might be explained by the different contexts in which studies were performed; in particular, the prevalence of the virus is a key factor in the overall effectiveness of broader HCV screening program. In addition, Markov models may differ very much and a lack of transparency impedes an extensive comparison.

In particular, the choice of the discount rate and the assumptions made on the effectiveness of the treatments used were found to be relevant factors for the final ICER and ICUR results.

While the clinical benefits of HCV screening are clear in terms of disease progression in the HCV-positive population, the cost-effectiveness of such intervention is very context-specific and thus it is difficult to make a generally universal recommendation to policy-makers.

Moreover, future studies on cost-effectiveness of HCV screening will need to focus on the migrant worker and homosexual (MSM) populations. In the first group, due to the high prevalence of HCV in many countries of origin, the early detection of HCV is likely to be highly cost-effective, as it is suggested by one of the studies that was excluded from this analysis [18]. This is also suggested by recent US and Dutch studies that found that early treatment of migrants for chronic HBV was cost-effective [19]. Furthermore, we can hypothesize that an analysis of the second might have high cost-effectiveness results due to the high prevalence of HCV in people who practice unsafe sex.

Further effectiveness and cost-effectiveness studies are needed to better understand the impact of the recently approved direct-acting antiviral (DAA) agents that have the potential to significantly improve the treatment of patients and to decrease the economic burden due to HCV.

Although the six studies included in the systematic review are of medium-high quality, some deficiencies have been documented in Data collection and Analysis and Interpretation of results sections. Future studies will need to take better account of the items related to data collection and results from a methodological point of view.

The literature analysed in this review should give important suggestions to policy-makers regarding possible extensions or changes of recommendation on HCV screening among their citizens.

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