OPTIMIZING DIAGNOSTIC ALGORITHMS TO ADVANCE HEPATITIS C ELIMINATION IN ITALY: A COST EFFECTIVENESS EVALUATION

A. MARCELLUSI[1,2], F.S. MENNINI[1,2], M. RUF[3], C. GALLI[4], A. AGHEMO[5], M.R. BRUNETTO[6], S. BABUDIERI[7], A. CRAXI[8], M. ANDREONI[9] and L.A. KONDILI[10]

[1]Economic Evaluation and HTA (EEHTA), CEIS, Faculty of Economics, University of Rome "Tor Vergata"; [2]Institute of Leadership and Management in Health, Kingston Business School, Kingston University, London, UK; [3]Medical Affairs, Gilead Europe, London, UK; [4]Medical, Clinical & Scientific Affairs, Abbott Core Laboratory, Roma, Italy; [5]Humanitas University and Humanitas clinical and Research Center IRCCS Rozzano Italy; [6]Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, University Hospital of Pisa, Pisa, Italy; [7]Infectious and Tropical Disease Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Italy; [8]Gastroenterology and Hepatology Unit, Department of Internal Medicine and Medical Specialties "PROMISE", University of Palermo, Palermo, Italy; [9]Department of Systems Medicine, University of Rome "Tor Vergata"; Infectious Diseases Clinic, University Hospital "Tor Vergata", Rome, Italy; [10]Center for Global Health,Istituto Superiore di Sanità, Rome Italy

INTRODUCTION

Italy is one of the countries with the greatest burden of HCV in Western Europe. In order to achieve HCV elimination by 2030 Italy, like many other countries, will need to succeed in tackling the undiagnosed proportion. The Italian Governative "Milleproroghe Decree", through an amendment approved in March 2020, has allocated €71.5 million for the period 2020-2021 to introduce free-of-charge screening for the general population born between 1969 and 1989. Although the screening budget has been established, optimization along the entire patient pathway is necessary to achieve elimination by 2030. Crucially, high enough coverage level for treatment in the first instance also depends on optimized diagnostic pathways to confirm active infection (1,2).

AIM

The aim of this study was to evaluate the cost-effectiveness of different diagnostic algorithms for active HCV infection including conventional two steps algorithms and same sample reflex testing (single step) combined with modelling treatment impacts and disease progression in order to provide for a complete overview of diagnostic costs and benefits.

METHOD

The primary outcome measure of screening effectiveness was the number of active infections diagnosed. An adapted multicohort Markov model capturing multiple states of morbidity and mortality was used to evaluate HCV disease progression and related costs for linked-to-care patients versus those not linked over a 10-year time horizon (years 2020-2030). We compared different screening strategies (**Fig.1**) in terms of the total costs of screening according to each diagnostic algorithm and treatment costs of active HCV infection versus the disease costs of those not diagnosed over time. We considered the Italian general population birth cohort (1969-1989) screening. The model inputs are shown in **Tab.1.**

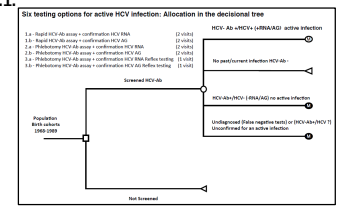


Figure 1. Decision tree model scheme

We have considered the following definitions:

1. Active infection is defined as the presence of markers of viral replication in chronic infection state.
2. 'Reflex testing' means that HCV-RNA of HCV-Ag are performed on the same serological specimen with a positive anti-HCV finding. "Undiagnosed" cases were defined as having active HCV infection but with HCV-Ab false negative results, or false negative confirmation test following an anti-HCV positive test result.
3. "Unconfirmed" active infection was defined as HCV-Ab+ without confirmation of active infection.

In both undiagnosed and unconfirmed groups, individuals with active infection will not be linked to care following the first HCV-Ab test.

Sensitivity Analysis. We performed deterministic sensitivity analyses (DSA) to identify parameters with the greatest impact on cost-effectiveness. During the Probabilistic Sensitivity Analysis (PSA) values were varied widely within the ranges stated in **Tab.1**, and were randomly sampled from the respective distributions with 5,000 Monte Carlo simulations. The cost-effectiveness acceptability curve (CEAC) for the best cost-effective scenario vs lower efficacy screening option and second most effective screening alternative were presented. We used the commonly cited Italian willingness-to-pay (WTP) threshold of €25,000/QALY.

Table 1. Decision Tree epidemiological parameters

	Base-case	Min	Max	Sources
Population born 1968 - 1989 (30-50 years)*	16,978,388	12,733,791	21,222,985	ISTAT. Resident Population, By Age. 2020. dati.istat.it. Accessed 17/10/2020.
Screening coverage rate	70%	53%	88%	Assumption
Number of prevalent undiagnosed HCV patient	115,000	86,250	143,750	Estimations from (3)
% of prevalent undiagnosed HCV patient	0.7%	0.5%	0.8%	Calculation
1.a) Rapid Ab assay + confirmation (RNA)				
Ab HCV+/HCV HCV RNA-	0.30%	0.24%	0.36%	(4)
Unconfirmed	45.00%	36.00%	54.00%	(5)
Undiagnosed	7.50%	6.00%	9.00%	False Negative 1st and 2nd line test (7% for anti-HCV (6,7); 0.5% for HCV-RNA – assumption)
1.b) Rapid Ab assay + confirmation (Ag)				
Ab HCV+/HCV AG	0.30%	0.24%	0.36%	(4)
Unconfirmed	45.00%	36.00%	54.00%	(5)
Undiagnosed	10.50%	8.40%	12.60%	False Negative 1st and 2nd line test (7% for anti-HCV (6,7); 3.5% for HCV-Ag (8)
2.a) Lab-based Ab assay + confirmation (RNA) with second sample taken				
Ab HCV+/HCV RNA-	0.30%	0.24%	0.36%	(4)
Unconfirmed	45.00%	36.00%	54.00%	(5)
Undiagnosed	2.50%	2.00%	3.00%	False Negative 1st and 2nd line test (2% for anti-HCV (9); 0.5% for HCV-RNA – assumption)
2.b) Lab-based Ab assay + confirmation (Ag) with second sample taken				
Ab HCV+/HCV Ag	0.30%	0.24%	0.36%	(4)
Unconfirmed	45.00%	36.00%	54.00%	(5)
Undiagnosed	5.50%	4.40%	6.60%	False Negative 1st and 2nd line test (2% for anti-HCV (9); 3.5% for HCV-Ag (10)
3.a) Lab-based Ab assay + confirmation (RNA) reflex testing				
Ab HCV+/HCV HCV RNA-	0.30%	0.24%	0.36%	(4)
Unconfirmed	17.00%	13.60%	20.40%	(5)
Undiagnosed	2.50%	2.00%	3.00%	False Negative 1st and 2nd line test (2% for anti-HCV (9); 0.5% for HCV-RNA – assumption)
3.b) Lab-based Ab assay + confirmation (AG) reflex testing				
Ab HCV+/HCV HCV RNA-	0.30%	0.24%	0.36%	(4)
Unconfirmed	17.00%	13.60%	20.40%	(5)
Undiagnosed	5.50%	4.40%	6.60%	False Negative 1st and 2nd line test (2% for anti-HCV (9); 3.5% for HCV-Ag (10)
Fibrosis distribution of patients that are undiagnosed				
F0-F2	75%	56%	94%	(3, 11)
F3	20%	15%	25%	(3, 11)
F4	5%	4%	6%	(3, 11)
DC+HCC	0%	0%	0%	(3, 11)
Fibrosis distribution of patients that are Unconfirmed/Unlinked to care				
F0-F2	75%	56%	94%	(3, 11), Assumption
F3	20%	15%	25%	(3, 11)
F4	5%	4%	6%	(3, 11)
DC+HCC	0%	0%	0%	(3, 11), Assumption
Fibrosis distribution of patients that will be diagnosed by screening				
F0-F2	70%	53%	88%	(3, 11)
F3	10%	8%	13%	(3, 11)
F4	15%	11%	19%	(3, 11)
DC+HCC	5%	4%	6%	(3, 11)
Years without diagnosis for Undiagnosed/ Unconfirmed patients				
F0-F2	10	7.5	12.5	Assumption
F3	4	3	5	Assumption
F4	1	0.75	1.25	Assumption
DC+HCC	1	0.75	1.25	Assumption

*HCV screening is offered free of charge in individuals from general population born between 1969 and 1989.

RESULTS

The comparison of cost effectiveness results is based considering as reference the option which produce the lower QALYs. As shown in **Tab. 2**, the reference is option 1b (Rapid Ab assays + confirmation HCV-Ag). All ICER estimated are far below the WTP threshhold. The best option is given by the HCV-RNA reflex testing in that it produces the highest QALYs (974,458). Comparing reflex versus two steps diagnostic algorithms a persistent increase in QALYs with a very low ICER varying from €566-635 per QALYs is estimated (**Tab. 3**).

Table 2 – Base-case cost results (Italy – assuming a 70% coverage rate); SCR= screening

	Screening Cost	Screening Administration Cost	Treatment Cost	Disease Cost
1.b - Rapid Ab assay + confirmation (Ag)	€ 60,553,442	€ 35,654,615	€ 414,125,553	€ 319,719,702
1.a - Rapid Ab assay + confirmation (RNA)	€ 64,458,378	€ 35,654,615	€ 418,340,716	€ 321,028,714
2.b - Lab-based Ab assay + confirmation (Ag) with second sample taken	€ 60,617,229	€ 59,424,358	€ 421,150,824	€ 321,905,388
2.a - Lab-based Ab assay + confirmation (RNA) with second sample taken	€ 64,733,486	€ 59,424,358	€ 425,365,486	€ 323,220,400
3.b - Lab-based Ab assay + confirmation (Ag) reflex testing	€ 60,974,490	€ 59,424,358	€ 460,489,341	€ 334,178,830
3.a - Lab-based Ab assay + confirmation (RNA) reflex testing	€ 66,274,096	€ 59,424,358	€ 464,704,203	€ 335,493,841

Table 3 – Base-case Cost-effectiveness

			ICER vs. less effective option			ICER Reflex vs SoC		
	Overall Cost	QALYs	Inc QALYs	Inc Cost	ICER	Inc QALYs	Inc Cost	ICER
1.b - Rapid Ab assay + confirmation (Ag)	€ 830,047,612	866,835	..	..	..	..	..	..
1.a - Rapid Ab assay + confirmation (RNA)	€ 839,482,421	875,803	8,969	€ 9,434,809	€ 1,052	..	..	..
2.b - Lab-based Ab assay + confirmation (Ag) with second sample taken	€ 863,097,608	881,782	14,948	€ 33,049,996	€ 2,211	..	..	..
2.a - Lab-based Ab assay + confirmation (RNA) with second sample taken (SoC)	€ 872,743,730	890,751	23,916	€ 42,696,118	€ 1,785	..	..	..
3.b - Lab-based Ab assay + confirmation (Ag) reflex testing	€ 915,067,026	966,489	98,654	€ 85,019,414	€ 862	74,738	€ 42,323,296	€ 566
3.a - Lab-based Ab assay + confirmation (RNA) reflex testing	€ 925,896,490	974,458	107,623	€ 95,348,896	€ 891	83,707	€ 53,152,768	€ 635

The deterministic sensitivity analysis (**Fig.2**) shows that the most sensitive parameters of the model are represented by the variation of the utilities associated with the disease states. Probabilistic sensitivity analysis confirmed that the reflex approach compared to the SoC would be cost-effective for >90% of simulations at a minimum WTP threshold of €1,000/QALY gained and for >99.9% of simulation at a maximum WTP threshold of €25,000/QALY gained (**Fig.3**).

Fig. 2. Tornado diagram: A)Lab-based HCV-Ab assay + confirmation (HCV-RNA) reflex testing; B)Lab-based HCV-Ab assay+confirmation (HCV-Ag) reflex testing

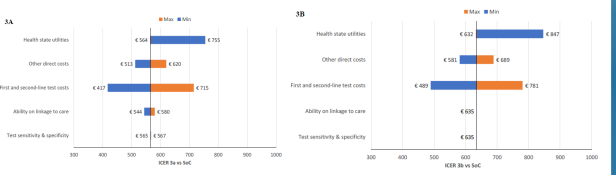
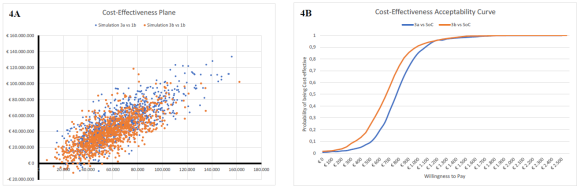


Fig. 3. A) Cost-Effectiveness Acceptability Curve of Lab-based Ab assay+confirmation (HCV-RNA or HCV-Ag) reflextest testing; B) Cost-Effectiveness Plane of Lab-based HCV-Ab assay+confirmation (HCV-RNA or HCV-Ag) reflex testing vs rapid HCV-Ab assay + confirmation (HCV-Ag)



CONCLUSIONS

In conclusion our findings suggest same sample reflex testing using either HCV-RNA or HCV-Ag is the most cost effective diagnostic algorithm for countries wanting to embark on high volume HCV testing. Our data confirm the European Association for the Study of the Liver (EASL) (12) and WHO guidelines recommending reflex testing as best practice in identifying HCV active infection in general population as compared to the other screening approaches.

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CONTACT INFORMATION

Loreta Kondili. Center for Global Health, Istituto Superiore di Sanità. Viale Regina Elena, 299 - 00161 Rome, Italy. Tel: +39 0649903813 loreta.kondili@iss.it