Received: 15 October 2021 | Revised: 9 December 2021 | Accepted: 26 January 2022

DOI: 10.1111/liv.15216

Liver INTERNATIONAL WILEY

BRIEF REPORT

Implementation of HCV screening in the 1969–1989 birth-cohort undergoing COVID-19 vaccination

Abstract

Background and Aim: The World Health Organization (WHO) goal of hepatitis C virus (HCV) elimination by 2030 relies on the scaling-up of both identification and linkage to care of the infected population, worldwide. In Italy, the estimated burden of HCV carriers who are unaware of their infection amounts to 200 000 persons, a projection that reinforces the need for broadening population access to effective screening programmes.

Methods: A pivotal screening programme targeting subjects born between 1969 and 1989 has been conducted in Lombardy, Northern Italy, where point-of-care (POC) testing was offered for free concomitantly to COVID-19 vaccination.

Results: Amongst 7219 subjects born between 1969 and 1989 who underwent HCV screening through POC, 7 (0.10%) subjects tested anti-HCV positive: 5 (0.07%) had confirmed anti-HCV positivity (Table 1) and 4 of them (0.05%) were HCV-RNA positive by standard confirmation tests.

Conclusions: This pivotal study demonstrated the feasibility of a POC-based anti-HCV screening programme in young adults undergoing COVID-19 vaccination. The prevalence of HCV infection in subjects born in the 1969–1989 cohort in Italy seems to be lower than previously estimated. Whether the extension of this programme to subjects born before 1969 could lead to improved screening effectiveness should be a matter of debate.

DAA, direct-acting antivirals; HCV, hepatitis C virus; PWID, people who inject drugs; POC, point-of-care; WHO, World Health Organization

1 | INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is still a major cause of morbidity and mortality, with an estimated burden of 58 million people affected worldwide.[1] Following the approval of the potent direct-acting antivirals (DAAs) against HCV, the World Health Organization (WHO) launched the Global Viral Hepatitis Strategy, an articulated set of interventions that aim at achieving HCV elimination by 2030. This led all Member States to develop specific Nation Hepatitis Plans to achieve the WHO elimination goal, based on expanding diagnosis, linkage to care and treatment strategies, coupled with a number of interventions for hepatitis prevention.[2]

Italy has historically been considered amongst the European Countries with the largest burden of HCV, with an estimated prevalence of 1% rising to 7% in the aged population.[3] At the end of July 2021, over 225 000 people had been already treated with DAAs,[4] whereas at least 280 000 people are unaware of their HCV status and have remained unlinked to care according to estimates from the Italian National Institute of Health.[5] Following the COVID-19 pandemic that slowed down the rates of newly diagnosed cases and treatments,[6] as in 2019 Italy was no longer on the track to achieve the WHO elimination goal. More recently, Centers reorganization following the COVID-19 pandemic has further contributed to slower both diagnostic and treatment programmes in most Italian regions.[7] In 2021, the Italian Government promulgated a decree specifically aimed at implementing HCV screening strategies, through the introduction of a free-of-charge screening programme focused on key populations like people who inject drugs (PWID), inmates and cohorts of the general population born between 1969 and 1989.[8] In fact, such a graduated screening model was previously suggested to be most cost-effective, also when compared to models only directed at at-risk populations or other birth-cohorts.[9]

To comply with the national screening plan and reduce the costs of mobilization of the general population to screen, we leveraged the ongoing COVID-19 vaccination programme starting a pivotal study of screening with point-of-care (POC) assays, aimed at identifying the prevalence of undiagnosed HCV infections amongst individuals aged 32–52 years (1969–1989 cohort) who attend the COVID-19 hubs.

2 | METHODS

Between the end of July and early September 2021, four tertiary Hepatology Centers (Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, ASST Grande Ospedale Metropolitano Niguarda in Milan, ASST Fatebenefratelli-Sacco in Milan; Azienda Ospedaliera Papa Giovanni XXIII in Bergamo) were selected by the Welfare Department of the Lombardy Regional Government to develop a pivotal study to explore the feasibility of large-scale population HCV screening in adults undergoing COVID-19 vaccination. Those Centers were selected based on their ability to fulfil the following criteria: (1) being a hub Center for COVID-19 vaccination, (2) being an expert Center for HCV management and treatment and (3) having regional authorization to DAA prescription. Enrolled in this programme were only subjects born between 1969 and 1989 who underwent COVID-19 vaccination in the predefined four hub Centers, in the established time period. The pre-defined target was 7500 tests to be performed according to hubs' capacities and volumes. Patients who had successfully been treated with anti-HCV therapies, either by Interferon or DAAs, were excluded from the screening programme.

Two different POC tests were used: In Tec Advanced Quality® Rapid HCV Antibody Test and Anti-HCV WB/S/P by Project: both tests are single-use qualitative immunoassays to detect antibodies against HCV in capillary blood from finger-stick. POC-positive subjects were referred to outpatient clinics for confirmatory tests, including peripheral vein blood anti-HCV antibodies and HCV-RNA by standard assays. As a predefined recall policy, patients who did not attend the re-test appointments were contacted directly by phone to solicit and reschedule the confirmatory test. HCV-RNA-positive patients were proposed DAAs. All patients signed a consent information form.

3 | RESULTS

Overall, over 50000 individuals underwent COVID-19 vaccination in the four hubs, and 22584 (2710-10484) of them were born between 1969 and 1989; the anti-HCV screening could be proposed to at least 7925 of them (data missing from one vaccination hub), and 7219 subjects agreed to be tested, with an acceptance rate ranging between 63% and 85%. Modalities of screening campaigns in each vaccination Center are reported in Table 1 and varied according to hubs' volumes and facilities in terms of time spent to reach the screening target, ranging from a few days to several weeks. The most relevant demographic features of the 7219 screened subjects are reported in Table 1.

Overall, 7 (0.10%) patients tested positive for anti-HCV by POC. They were mostly males (5; 71%), with a median age of 46 (41–52) years, of Caucasian ethnicity in 4 (57%), Arab in 2 (29%) and Asian in 1 (14%). Five of them were identified in the vaccination hub with the largest catchment area.

TABLE 1 Pivotal screening strategies according to each participating center

	Milan Policlinico (*N* = 4000)	Milan FBF-Sacco (*N* = 1222)	Milan Niguarda (*N* = 1000)	Bergamo (*N* = 997)
Time spent for screening programme, hours	53	25	128	16
Daily vaccinations[a]				
Any birth-cohort	7081 (5833–9440)	1803 (427–1978)	694 (260–894)	2365 (2080-2650)
1969–1989 birth-cohort	2726 (2077–3447)	766 (183–923)	336 (80–605)	1355 (1325–1385)
Proposed anti-HCV POC	4721	1629	NA	1575
Accepted anti-HCV POC	4000 (85%)	1222 (75%)	1000 (NA%)	997 (63%)
Age, years	42 (32–52)	44 (32–52)	44 (32–52)	43 (32–52)
Males	1840 (46%)	745 (61%)	432 (43%)	NA
Screening team (per day)	9–12	5–6	2–3	9–11
Physicians	3–4	2	1	2
Nurses	3–4	2–3	0–1	3–4
Others	3–4 Research Assistants	1 Auxiliary Nurse	0–1 Research Assistant	4–5 Volunteers[b]
Anti-HCV positive by POC test	6 (0.15%)	0	0	1 (0.10%)
Lost to follow-up after POC test	1 (0.01%)	–	–	0
Anti-HCV positive by confirmatory test	4 (0.10%)	–	–	1 (0.10%)
HCV-RNA positive	3 (0.08%)	–	–	1 (0.10%)

Note: Results are reported as number (*n*) and percentages (%) or median (range).

Abbreviations: HCV, hepatitis C virus; NA, not available; POC, point-of-care.

[a]Refers only to screening days, in each vaccination hub.

[b]All from patients' alliance.

Of these positive subjects, 4 (57%) were confirmed to be chronically infected with HCV (0.05%); one patient refused to complete the clinical workup after HCV infection confirmation. They were all male, aged 41 (41–46). Only one patient was Italian, whilst the remnants came from Bulgaria, Egypt and Bangladesh, respectively. Of the three patients with data available genotypes were 1b, 3 and 4, and HCV viral load ranged between 659 000 and 4 560 000 IU/ml. All patients had altered ALT values (44–61 U/L), whilst liver stiffness measurement was above the upper limit of normal in one patient, only (10.3, 4.5 and 4.6 kPa). None of the patients was co-infected by either HBV or HIV whereas in terms of co-morbidities one patient had arterial hypertension, only. In no case, recent risk factors suggestive for acute infection were reported.

Of the remnants of three POC-positive patients, 1 (14%) tested anti-HCV positive but HCV-RNA undetectable, 1 (14%) tested negative for both anti-HCV and HCV-RNA and 1 (14%) dropped re-test appointment, despite re-call policy.

In terms of use of resources, a high inter hubs variability of time allocated per type of professional per test was observed. Physician workload per test varied from 1.9 to 7.7 min, whilst nurses' workload per test varied from 3.2 to 7.7 min. Overall, a mean value of 3.5 min per test was dedicated to the activity by clinicians and of 4.0 min per test by nurses.

The mean cost per test (considering direct medical costs related to human resources and tests, and the cost of brochures), varied between 6.8 € and 16.1 €, as in one hub volunteers were also recruited. The overall mean cost per test (including confirmation tests) was equal to 9.8 €, of which 68.3% related to human resources (36.0% for clinicians, 21.8% for nurses, 10.5% for research assistants), 0.4% related to brochures illustrating the screening programme, and 31.3% related to tests. The cost per diagnosis was equal to 17.7 €.

4 | DISCUSSION

This pivotal study demonstrated not only the feasibility of a universal HCV screening through POC anti-HCV testing in subjects undergoing COVID-19 vaccination but also showed a lower than previously estimated prevalence of HCV infection in Italian subjects born between 1989 and 1969. To the best of our knowledge, this is the first study specifically aimed at prospectively assessing the prevalence of anti-HCV in an unbiased population, at least in Italy.

An unexpected finding of the study was the lower than the previously estimated prevalence of HCV markers in the 1989–1969 birth-cohort (0.10% for anti-HCV and 0.05% for HCV-RNA). Italy, in fact, has been historically considered to rank amongst Countries with the highest anti-HCV prevalence, ranging from 1.1% to 22.4% according to the 2010 ECDC report,[10] with higher seroprevalence rates in Southern regions (8% vs. 2%) and in elder populations.[11,12] Though decreasing rates of HCV prevalence have recently been reported in several studies throughout the Country,[13,14] mathematical models support the presence of a significant proportion of Italian people who are unaware of their infection and are still in need to be treated.[5,8,15] In 2017, the Polaris Observatory estimated a 1.1% prevalence of viraemic subjects in Italy compared to 0.5% of Western Europe,[16] which has more recently been resized to 0.68% by mathematical models.[15] Based on the same models, it was suggested that subjects born between 1969 and 1989 would be those with a higher risk of transmitting HCV infection, in addition to PWID and other risk groups,[5] thus supporting the cost-effectiveness of HCV screening amongst the 1969–1989 birth-cohort.[9] Along this line, it has been recently estimated that nearly 45 000 members of those cohorts living in Lombardy are anti-HCV positive, corresponding to a seroprevalence of approximately 0.20%, and 22 000 are HCV-RNA positive, the corresponding prevalence being approximately 0.10%, higher than what we have found in our pivotal study.[15,17]

There are several explanations for the lower-than-expected prevalence of HCV infection that we detected in the 1989–1968 birth-cohorts in our Region. First, the anti-HCV screening was offered contextually to COVID-19 vaccination, leaving untested subjects with poor linkage to care or refusing vaccination, potentially at high risk of carrying HCV infection. Second, the adherence rate of patients in the targeted age range who were offered COVID-19 vaccination was not absolute. Third, the study has been conducted in hubs serving two of the largest metropolitan areas in Lombardy, not involving more peripheral areas of the region where the HCV prevalence could be higher. Fourth, the proportion of patients tested in this screening programme represents only 0.23% of the overall resident population aged from 32 to 52 years, which accounts for approximately 3 million people. Finally, current epidemiological estimates of HCV prevalence have been generated from dated, retrospective studies, whose biases are well recognized. Particularly, a significant proportion of HCV-infected people from the 1969–1989 birth-cohort would probably belong to the 'high-risk' population, such as PWID and inmates, who may have lower access to screening programmes. This notwithstanding, we think that the study has several strengths: this is the first HCV screening study to be performed in the context of a vaccination hub, the sample size of the study is significant, the tested population is unselected, and adherence to HCV screening programme was excellent.

Study conduct at vaccination hubs was significantly influenced by logistic issues, as each vaccination Center dealt with several hundred or even thousand vaccinees every day (up to 10 000), depending on each hub capability. The anti-HCV screening had to be carried on without any interference with the vaccination programme, which had to be prioritized and remain free from delays due to concomitant testing, either before or after vaccine inoculation. These logistics issues were overcome by distributing a dedicated leaflet at the entry and/or in the hub, engaging targeted subjects just after vaccine inoculation, performing the POC anti-HCV test during the post-vaccination observation period, 15 min in most cases, and providing the results within the same time-frame. This was made possible in each vaccination hub thanks to an ad hoc 'anti-HCV Team' that joined the hub, fully and successfully integrating HCV screening with COVID-19 vaccination activities.

In light of these findings, a question arises as to whether opportunistic screening programmes could be really the best strategy. In fact, limitations of this kind of screening are well recognized, and mainly include logistic and organizational issues finally leading to low

adherence and/or suboptimal cost-effectiveness,[18] especially when compared to organized screening. Whether the inclusion of people born before 1969 or testing of any subject accessing Hospitals or NHS services would improve opportunistic screening results is unknown. Indeed, this screening campaign required important investments in terms of both money and human resources, and this point needs to be discussed by National and Regional authorities, when trying to set plans to reach the ambitious WHO goal.

To assess whether resources were efficiently allocated in the programme, a long-term perspective cost-effectiveness model should be implemented. It should be aimed at evaluating whether the clinical events avoided thanks to the identification and linkage to care of HCV carriers would lead to an increase in quality-adjusted life years (QALY) compared to lack of diagnosis (and treatment), and whether the incremental cost per QALY gained would fall under specific thresholds. In literature, examples of health economic analyses of HCV screening programmes in Europe were performed on high-risk populations or specific target populations only (i.e. pregnant women, inmates).[19–22] Results from these studies are discordant, and peculiar aspects of the national health systems, the target population and the cost per treatment in each context should be considered in terms of low generalizability of the results. Furthermore, the cost per QALY gained in such analyses heavily depends on the prevalence of HCV infection (up to 16% in Irish inmates) and the cost of the screening programme.

In Italy, a cost-consequence analysis based on a Markov model was implemented by Marcellusi and colleagues.[23] The authors found that the investment necessary to deliver antiviral therapy to newly diagnosed subjects (through active screening) would be recouped in 4.3 years in terms of costs avoided due to the prevention of disease complications, although the cost of the screening activity was not considered in the model.[23]

In conclusion, we run a pivotal study leading to the rapid screen of thousands of unselected subjects born between 1969 and 1989 who underwent COVID-19 vaccination, in the context of a national programme aimed to tackle undiagnosed HCV positive patients. The HCV screening programme activity lasted only a few days and did not interfere with the vaccination campaign. The overall results suggest a lower than previously estimated HCV prevalence in the 1969–1989 birth-cohort in our Region, which needs to be confirmed through additional population studies. Whether the extension of this screening to subjects born before 1969 could be useful to improve its effectiveness, is a matter of debate. Updated epidemiological data could be instrumental to get back Italy on track to reach the 2030 WHO elimination goal.

KEYWORDS

birth-cohorts, hepatitis C virus, POC, screening, WHO

ACKNOWLEDGEMENTS

The authors thank the Welfare Department of Lombardy Regional Government for supporting this activity.

CONFLICT OF INTEREST

Roberta D'Ambrosio: speaking, teaching and advisory board for AbbVie, Gilead, MSD; consultant for AbbVie and Takeda; research grant from AbbVie and Gilead. Giuliano Rizzardini: speaking, teaching and advisory board for AbbVie, Gilead, MSD, Viiv, GSK, Angelini, Janssen. Massimo Puoti: Advisory Board/Speaker Bureau for AbbVie, Bristo-Myers, Squibb, Boehringer Ingelheim, Janssen, Gilead, MSD and Roche; research grant from Gilead and MSD. Stefano Fagiuoli: Advisory Board/Speaker Bureau for AbbVie, Gilead, MSD, Bayer, Novartis, Kedrion, Intercept, Astellas. Luisa Pasulo: Advisory Board for AbbVie. Umberto Restelli: Speaker for Abbott. Massimo Colombo: Advisory Board/Speaker Bureau for Gilead Sciences, Intercept, Exelixis, Galapagos, Target HCC. Pietro Lampertico: Advisory Board/Speaker Bureau for BMS, Roche, Gilead Sciences, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, Spring Bank, MYR, Eiger, Aligos, Antios. The other authors have nothing to disclose.

Roberta D'Ambrosio[1]
Giuliano Rizzardini[2]
Massimo Puoti[3]
Stefano Fagiuoli[4]
Maria Paola Anolli[1]
Claudia Gabiati[5]
Federico D'Amico[3]
Luisa Pasulo[4]
Umberto Restelli[6,7]
Massimo Colombo[8]
Pietro Lampertico[1,9]

[1]*Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[2]*ASST Fatebenefratelli-Sacco, First Division of Infectious Diseases, Milan, Italy*
[3]*ASST Grande Ospedale Metropolitano Niguarda, Division of Infectious Diseases, Milan, Italy*
[4]*AAST Papa Giovanni XXIII, Gastroenterology, Hepatology and Transplantation, Bergamo, Italy*
[5]*ASST Fatebenefratelli-Sacco, Division of Internal Medicine, Milan, Italy*
[6]*LIUC Cattaneo University, Castellanza (VA), Italy*
[7]*Faculty of Health Sciences, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa*
[8]*Liver Center, Ospedale San Raffaele, Milan, Italy*
[9]*CRC "A. M. and A. Migliavacca" Center for Liver Diseases, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*

Handling editor: Alessio Aghemo

Correspondence
Roberta D'Ambrosio, Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: roberta.dambrosio@policlinico.mi.it

ORCID

Roberta D'Ambrosio https://orcid.org/0000-0003-0019-1153

Pietro Lampertico https://orcid.org/0000-0002-1026-7476

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed March 4, 2022.
2. World health organization global health sector strategy on viral hepatitis 2016-2021. WHO 2016. https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1. Accessed March 4, 2022.
3. Andriulli A, Stroffolini T, Mariano A, et al. Declining prevalence and increasing awareness of hepatitis C virus infection in Italy: a population-based survey. *Eur J Intern Med*. 2018;53:79-84.
4. Monitoraggio, U.R.D. Aggiornamento dati Registri AIFA DAAs, epatite C cronica. Agenzia Italiana del Farmaco. http://www.agenziafarmaco.gov.it/content/registri-farmaci-sottoposti-monitoraggio. Accessed July 30, 2021.
5. Kondili LA, Andreoni M, Alberti A, et al. Estimated prevalence of undiagnosed HCV infected individuals in Italy: a mathematical model by route of transmission and fibrosis progression. *Epidemics*. 2021;34:100442.
6. Blach S, Kondili LA, Aghemo A, et al. Impact of COVID-19 on global HCV elimination efforts. *J Hepatol*. 2021;74:31-36.
7. Ponziani FR, Aghemo A, Cabibbo G, et al. Management of liver disease in Italy after one year of the SARS-CoV-2 pandemic: a web-based survey. *Liver Int*. 2021;41:2228-2232.
8. Kondili LA, Aghemo A, Andreoni M, et al. Milestones to reach hepatitis C virus (HCV) elimination in Italy: from free-of-charge screening to regional roadmaps for an HCV-free nation. *Dig Liv Dis*. 2022;54:237-242.
9. Kondili LA, Gamkrelidze I, Blach S, et al. Optimization of hepatitis C virus screening strategies by birth cohort in Italy. *Liver Int*. 2020;40:1545-1555.
10. https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/TER_100914_Hep_B_C%20_EU_neighbourhood.pdf. Accessed March 4, 2022.
11. https://www.webaisf.org/wp-content/uploads/2019/01/libro-bianco-aisf-2011.pdf. Accessed March 4, 2022.
12. Guadagnino V, Stroffolini T, Rapicetta M, et al. Prevalence, risk factors, and genotype distribution of hepatitis C virus infection in the general population: a community-based survey in southern Italy. *Hepatology*. 1997;26:1006-1011.
13. Andriulli A, Stroffolini T, Mariano A, et al. Declining prevalence and increasing awareness of HCV infection in Italy; a population-based survey in five metropolitan areas. *Eur J Intern Med*. 2018;53:79-84.
14. Guadagnino V, Stroffolini T, Caroleo B, et al. Hepatitis C virus infection in an endemic area of southern Italy14 years later: evidence for a vanishing infection. *Dig Liver Dis*. 2013;45:403-407.
15. Kondili L, Andreoni M, Alberti A, et al. Prevalence of undiagnosed hepatitis C virus infected individuals estimates by regional mathematical-modelling in Italy. *Hepatology*. 2020;72:A982.
16. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2:161-176.
17. Kondili L. L'infezione cronica da virus dell' epatite C (HCV) in Lombardia. *Infez Med*. 2021;S2.
18. Carvalho-Gomes A, Cubells A, Pallares C, et al. A population-based screening for hepatitis C antibodies and active infection using a point-of-care test in a low prevalence area. *PLoS ONE*. 2020;15:e0228351.
19. Eijsink JFH, Al Khayat MNMT, Boersma C, et al. Cost-effectiveness of hepatitis C virus screening, and subsequent monitoring or treatment among pregnant women in The Netherlands. *Eur J Health Econ*. 2021;22:75-88.
20. McCormick CA, Domegan L, Carty P, et al. Routine screening for hepatitis C in pregnancy is cost effective in a large urban population in Ireland: a retrospective study. *BJOG*. 2021;129:322-327.
21. Ward Z, Mafirakureva N, Stone J, et al. Cost-effectiveness of mass screening for hepatitis C virus among all inmates in an Irish prison. *Int J Drug Policy*. 2021;96:103394.
22. Mohamed Z, Scott N, Al-Kurdi D, et al. Cost-effectiveness of strategies to improve HCV screening, linkage-to-care and treatment in remand prison settings in England. *Liver Int*. 2020;40:2950-2960.
23. Marcellusi A, Simonelli C, Mennini FS, Kondili LA; PITER Collaborating Group. Economic Consequences of Anti-HCV Treatment of Patients Diagnosed Through Screening in Italy: A Prospective Modelling Analysis. Appl Health Econ Health Policy. http://www.progettopiter.it. Accessed October 12, 2021.