European Journal of Internal Medicine 101 (2022) 93–97

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original article

Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination

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ARTICLE INFO

Keywords:
Micro-elimination
Linkage to care
Viral hepatitis
People who inject drugs

ABSTRACT

Background & Aims: The number of chronic hepatitis C virus (HCV)-infected patients who have been lost to follow-up (LTFU) is high and threatens HCV elimination. Micro-elimination focusing on the LTFU population is a promising strategy for low-endemic countries like the Netherlands (HCV prevalence 0.16%). We therefore initiated a nationwide retrieval project in the Netherlands targeting LTFU HCV patients.

Methods: LTFU HCV-infected patients were identified using laboratory and patient records. Subsequently, the Municipal Personal Records database was queried to identify individuals eligible for retrieval, defined as being alive and with a known address in the Netherlands. These individuals were invited for re-evaluation. The primary endpoint was the number of patients successfully re-linked to care.

Results: Retrieval was implemented in 45 sites in the Netherlands. Of 20,183 ever-diagnosed patients, 13,198 (65%) were known to be cured or still in care and 1,537 (8%) were LTFU and eligible for retrieval. Contact was established with 888/1,537 (58%) invited individuals; 369 (24%) had received prior successful treatment elsewhere, 131 (9%) refused re-evaluation and 251 (16%) were referred for re-evaluation. Finally, 219 (14%) were re-evaluated, of whom 172 (79%) approved additional data collection. HCV-RNA was positive in 143/172 (83%), of whom 38/143 (27%) had advanced fibrosis or cirrhosis and 123/143 (86%) commenced antiviral treatment.

Conclusion: Our nationwide micro-elimination strategy accurately mapped the ever-diagnosed HCV population in the Netherlands and indicates that 27% of LTFU HCV-infected patients re-linked to care have advanced fibrosis or cirrhosis. This emphasizes the potential value of systematic retrieval for HCV elimination.

Abbreviations

HCV	hepatitis C virus
LTFU	lost to follow-up
DAAs	direct-acting antivirals
CELINE	Hepatitis C Elimination in the Netherlands
WHO	World Health Organisation
SD	standard deviation
IQR	interquartile range
HCC	hepatocellular carcinoma
HBsAg	hepatitis B surface antigen
SVR	sustained virological response

1. Introduction

Achieving hepatitis C virus (HCV) elimination as a global health

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https://doi.org/10.1016/j.ejim.2022.04.024
Received 25 February 2022; Received in revised form 24 April 2022; Accepted 28 April 2022
Available online 5 May 2022

threat has been a priority of many countries since the World Health Organisation published their elimination targets [1]. In low-endemic countries, like the Netherlands (prevalence 0.16%) [2], micro-elimination may be a favourable approach [3].

In the Netherlands, HCV is restricted to key populations such as people who inject(ed) drugs, migrants from HCV endemic countries, men who have sex with men and people with inherited bleeding disorders [2]. These key populations are commonly identified as targets for HCV micro-elimination initiatives. A population worthy of attention are people with HCV who have been lost to follow-up (LTFU). Despite earlier diagnosis they dropped out of the continuum of care before adequate management had been delivered or after antiviral treatment without formal proof of HCV eradication.

Several Dutch regional projects demonstrated that the LTFU rate in people with HCV runs up to 30% [4–6]. These pilot studies drove the development of the current micro-elimination project "Hepatitis C Elimination in the Netherlands (CELINE)", that aimed to retrieve and re-evaluate LTFU HCV patients in a nationwide manner. Successful implementation would support the concept of micro-elimination in the LTFU HCV population as a tool towards achieving the World Health Organisation (WHO) hepatitis C elimination targets in low endemic countries [1].

2. Methods

2.1. Study setting and ethics

Care for patients with viral hepatitis in the Netherlands is covered by mandatory health insurance and centred in certified hepatitis treatment centres. Between 2018 and 2020 all 46 certified centres in the Netherlands were invited to participate. If a treatment centre had executed an independent, regional retrieval project, the outcomes were included in this study once a data sharing agreement was reached. Other non-certified centres were invited to participate if there was a close collaboration with a certified hepatitis treatment centre.

Local approval was provided by all participating centres. Retrieval and re-evaluation activities in the CELINE project were part of standard care. Collected clinical data of successfully retrieved patients were analysed for research purposes after patients provided informed consent. Participation in the research was voluntary and did not influence clinical care.

2.2. Study population and retrieval strategy

The study protocol has been described in detail previously [7]. An overview can be seen in Supplementary Fig. 1. In short, patients with a previously diagnosed HCV infection who had become LTFU were identified based on laboratory results and medical chart review. Patients with severe comorbidity or short life expectancy resulting in an expected lack of benefit from antiviral treatment were excluded. The Municipal Personal Records Database was queried to identify patients eligible for retrieval, defined as being alive and with a registered address in the Netherlands. Subsequently, patients eligible for retrieval were invited by letter for a re-evaluation visit at a hepatitis treatment centre of their choice. Patients younger than 18 were invited for re-evaluation but were not included in data collection.

2.3. Study endpoints and statistical analysis

The primary outcome was the number of LTFU patients successfully re-linked to care, defined as at least one visit at the outpatient clinic of a certified hepatitis treatment centre. Secondary outcomes included the total number of diagnosed and number of LTFU individuals, case ascertainment rate (i.e. established contact with invited patients), proportion of HCV-viraemic patients among re-evaluated patients, reasons for becoming LTFU, mode of HCV transmission, proportion of individuals with at least advanced liver fibrosis (liver stiffness measurement value ≥9.5 kPa or radiological, histological or clinical signs of cirrhosis [8,9]) among HCV-viraemic patients, and DAA treatment outcome.

Descriptive data are reported as percentage, mean (+/- standard deviation; SD) or median (with interquartile range; IQR). Analyses were performed using IBM SPSS Statistics® version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

3. Results

In total, CELINE was implemented in 45 sites, including 39/46 (85%) of certified hepatitis treatment centres in the Netherlands, five non-certified centres and one laboratory mainly serving primary care. Six centres with previously executed regional projects were included [4–6]. Among the remaining seven hepatitis treatment centres not included in the analyses, five centres had initiated own retrieval initiatives prior to CELINE roll-out and were not able to share data while two centres refused participation.

A total of 20,183 previously diagnosed patients were identified using laboratory records spanning median 14 years (IQR 11 – 17 years). The majority (n = 10,929, 54%) had already been successfully treated or spontaneously cleared infection (Fig. 1). In total 1,537 patients (8%) were identified as LTFU and eligible for retrieval.

Contact could not be established in 649 cases (Fig. 2), resulting in a case ascertainment rate of 58% (888/1,537). Of the 1537 invited patients, 369 (24%) were already cured or in care elsewhere and 131 (9%) refused to be re-linked to care. In total, 251 (16%) patients were referred, of whom 219 (87%) attended their visit. Three of the remaining 32 patients have their screening visit planned and 29 disregarded their scheduled visit.

Of the 219 screened individuals, 172 (79%) provided informed consent for data collection (Table 1). One hundred and ten patients ever had a liver stiffness measurement (n = 51) and/or abdominal ultrasound (n = 105), of whom 14 patients (13%) had evidence of advanced liver fibrosis or cirrhosis. One LTFU patient had a prior focal hepatocellular carcinoma (HCC). Among the re-evaluated patients, 27 patients (16%) never had a prior HCV-related appointment at an outpatient clinic and 18 patients (11%) reported being unaware of their possible HCV infection. HCV RNA was positive in 12 of these 18 patients (67%), of whom three (25%) had advanced fibrosis or cirrhosis at the re-evaluation visit.

In total, 143/172 patients (83%) tested HCV-RNA positive at re-evaluation (Table 2). HCV-RNA was negative in 24 patients (14%) and not (yet) tested in five (3%). Among the 167 patients with a known HCV-RNA status at re-evaluation, HCV-RNA was positive in 127/145 (88%) of those with a positive HCV-RNA status before becoming LTFU and 16/27 (59%) of those with positive HCV antibodies with unknown HCV-RNA status. At re-evaluation, none of the patients tested HIV positive, but two patients (1%) had a newly diagnosed hepatitis B virus infection. Among HCV-RNA positive patients, 38 (27%) had advanced fibrosis or cirrhosis, of whom two were classified as Child-Pugh B and one as Child-Pugh C. Additionally, two patients were diagnosed with an HCC at the time of the re-evaluation visit and another three patients developed an HCC during the period after their re-evaluation visit.

In 86% of HCV-RNA positive patients (123/143) DAA therapy was initiated. Sustained virological response (SVR) was achieved in all of the 91 individuals with a known HCV-RNA result twelve weeks after cessation of treatment. Four patients discontinued DAA, ten finished the treatment course but became LTFU again without formal proof of SVR, and 27 patients are awaiting their SVR-12 result. Among the 20 patients who did not initiate DAA, six refused treatment, four became LTFU again, five had severe comorbidity or short life expectancy, two died, two had addiction problems, while one will start DAA treatment shortly.

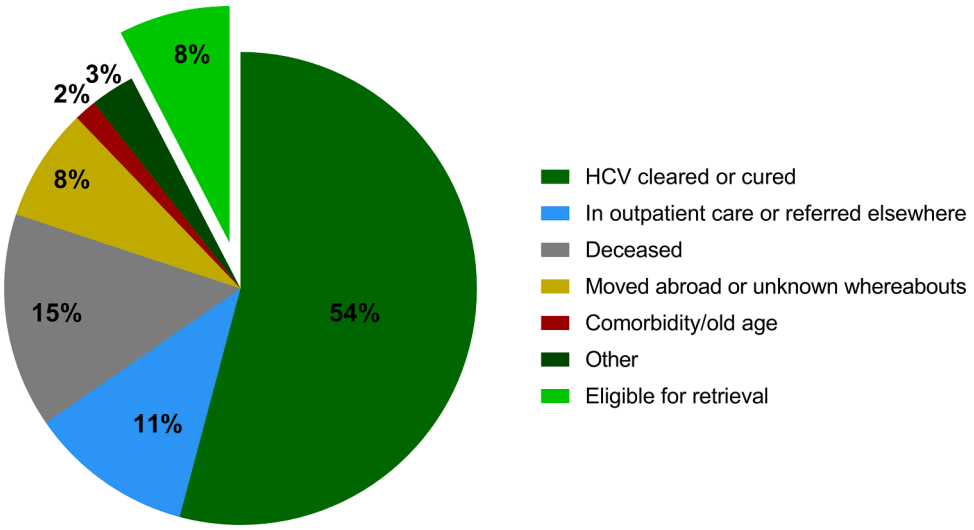

Fig. 1. Outcome of 20,183 anti-HCV positive patients, identified in 45 centres. Abbreviations: HCV, hepatitis C virus.

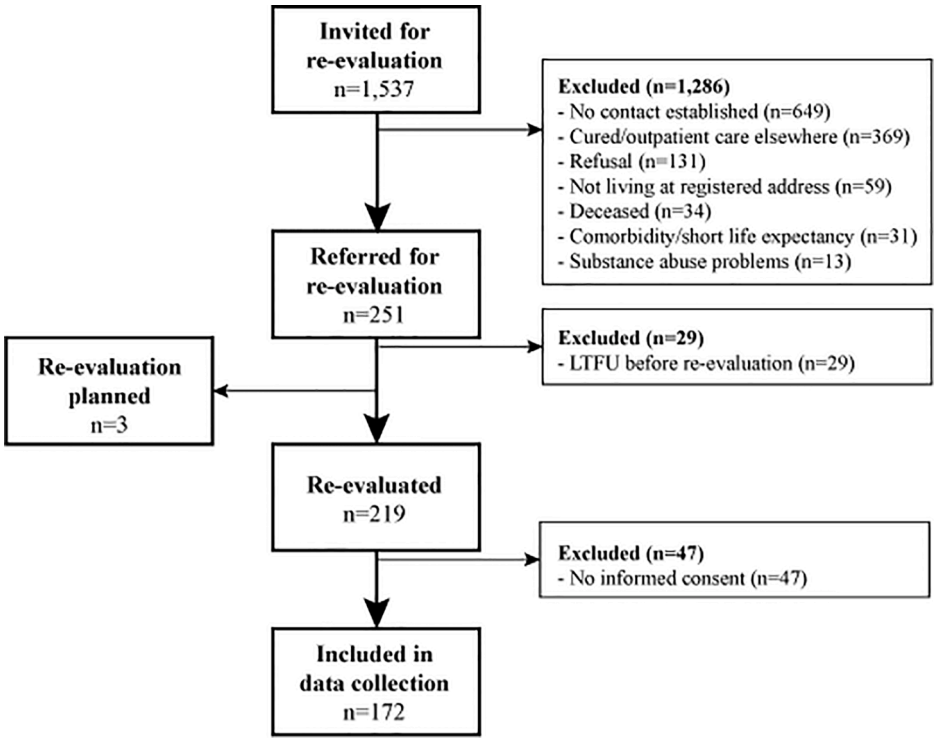

Fig. 2. Flow-chart of patients eligible for retrieval, who were invited for re-evaluation. Abbreviations: LTFU: lost to follow-up.

4. Discussion

CELINE was a nationwide retrieval project aiming to re-engage LTFU HCV patients with care. It was designed as a micro-elimination initiative to advance progress towards the WHO HCV elimination targets in the Netherlands. We demonstrated that the majority of individuals diagnosed in the past with HCV in the Netherlands had been cured prior to rollout of CELINE. We found that 8% was LTFU and eligible for retrieval. Advanced fibrosis or cirrhosis was diagnosed in 27% of HCV-RNA positive retrieved individuals.

Our retrieval efforts resulted in 219 patients that we could re-link to care, corresponding to 14% of individuals invited for re-evaluation. Thus, the retrieval rate of our nationwide approach was within the bandwidth observed in several previously conducted regional Dutch projects [4–6]. Our study included the vast majority of hepatitis treatment centres in the Netherlands, thereby maximising its impact and providing valuable insight into the epidemiology of patients ever diagnosed with HCV infection in the Netherlands. A higher number of re-linked patients might have been achieved if a national registry had been in place as this would improve adequate coordination of retrieval. Nevertheless, our retrieval was successful as a significant number of patients with advanced fibrosis or cirrhosis were re-linked to care. Furthermore, our study provided valuable insight into the HCV epidemiology of the Netherlands and demonstrated the feasibility of retrieval as a micro-elimination strategy. The robust and extensive framework that was laid out can serve as a blueprint for retrieval of patients with other diseases and in other countries.

The most common reasons for LTFU in our study were frequent no

Table 1
Characteristics of re-linked patients who provided consent for data collection.

	Re-linked patients (n = 172)
Male sex	121 (70%)
Age in years at re-linkage to care (median, IQR)	58 (52 - 63)
Reason for becoming LTFU[1]	
Patient-related	76 (44%)
Therapy-related	44 (26%)
Care-related	41 (24%)
Other/unknown	11 (6%)
Years since last HCV-related hospital visit (median, IQR)	7 (4 - 11)
First-generation migrant	59 (34%)
Route of HCV transmission	
Injecting drug use	119 (69%)
Transfusion	18 (11%)
Other[2]	19 (11%)
Unknown	16 (9%)
(History of) substance abuse	
Injecting drug use	125 (73%)
Alcohol[3]	57 (33%)
Currently on opioid substitution therapy	50 (29%)
HCV treatment experience	44 (26%)[4]
(PEG-)Interferon	40 (23%)
Direct-acting antivirals	7 (4%)
HCV-RNA positive	143 (83%)

[1] Patient-related reasons for LTFU included: multiple no shows, therapy refusal, addiction, or imprisoned. Therapy-related reasons for LTFU included: no indication for therapy, lack of therapy options. Care-related reasons for LTFU included: no consequence given to HCV test, absent SVR check, HCV follow-up postponed due to other comorbidities or pregnancy, absent follow-up appointment, treatment deferred, waiting for a new appointment.

[2] Nosocomial (5), needle prick injury (4), sexual (3), vertical (2), tattoo (1), injecting drug use or transfusion (1), injecting drug use or sexual (2), nosocomial or sexual (1).

[3] Defined as >14 units/week for females and >21 units/week for males.

[4] Several patients received both (PEG-)interferon and direct-acting antivirals. Abbreviations: IQR: interquartile range; LTFU, lost to follow-up; HCV, hepatitis C virus; PEG: pegylated.

Table 2
Characteristics of HCV-RNA positive patients.

	HCV-RNA positive patients (n = 143)
Advanced fibrosis or cirrhosis at re-evaluation[1]	38 (27%)
HCV genotype	
1a	61 (43%)
1b	29 (20%)
1, other/unknown subtype	4 (3%)
2	9 (6%)
3	27 (19%)
4	10 (7%)
unknown	3 (2%)
Co-infection	
Prior HBV (HBsAg-, anti-HBc+)	50 (35%)
Chronic HBV (HBsAg+)	2 (1%)
HIV	0 (0%)
DAA treatment initiated after retrieval	123 (86%)
SOF/LDV	10 (8%)
SOF/VEL	28 (23%)
GLE/PIB	67 (54%)
ELB/GRZ	13 (11%)
SOF/VEL/VOX	1 (1%)
Unknown	4 (3%)
Treatment outcome	
SVR	91 (75%)
Awaiting SVR-12 measurement	27 (22%)
Discontinued DAA therapy	4 (3%)

[1] Defined as a liver stiffness value ≥9.5 kPa or radiological, histological or clinical signs of cirrhosis. Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, antibodies against hepatitis B core antigen; HIV, human immunodeficiency virus; DAA, direct-acting antiviral; SOF, sofosbuvir; LDV, ledipasvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; ELB, elbasvir; GRZ, grazoprevir; VOX, voxilaprevir; SVR, sustained virological response. .

shows and refusal of HCV therapy. The most common reasons for unsuccessful retrieval were the inability to make contact with the patient, refusal of re-evaluation or substance abuse problems which complicated re-linkage to care. For these individuals it could be beneficial to perform retrieval as a standard annual or bi-annual procedure, instead of a one-time effort. Since current HCV treatment is highly effective, it could be argued that loss to follow-up is an unacceptable outcome and should be prevented or dealt with by all HCV care providers.

An important limitation of retrieval is that retrieval efforts are labour intensive. The current nationwide project was led by three full-time PhD candidates and required a commitment that is most likely impossible to meet by physicians and/or nurse consultants on top of the regular healthcare they provide. There are, however, some measures that can reduce the investments needed for future retrieval projects. First, make retrieval part of routine care and eliminate the collection of data for research purposes. This will bypass the laborious institutional review board process and will thereby reduce workload. Second, implementing digital innovations such as a case-finding algorithm that successfully identifies diagnosed but untreated HCV patients further reduces workload [10]. Last but not least, the framework now laid out by CELINE will increase efficacy and reduce costs of future retrieval efforts.

CELINE results must be placed in the greater context of HCV elimination. A recent modelling study predicting the Netherlands' progress towards the WHO HCV elimination targets concluded that the Netherlands is currently on track to meet these targets by 2030 [11]. However, this was only met under the assumption that annual HCV diagnosis and treatment rates were maintained at the 2019 levels. HCV micro-elimination in LTFU patients will mainly contribute to maintaining high treatment rates, especially if done repeatedly. In the Netherlands however, this contribution will be minor. Micro-elimination in other subpopulations in the Netherlands has already been highly successful, such as people living with HIV and people with inherited bleeding disorders [12,13]. Increased efforts to find and cure HCV-viraemic individuals in other subpopulations, like migrants from high-endemic countries, PWID and incarcerated individuals, are needed.

To conclude, the majority of patients in the Netherlands who received the diagnosis of chronic HCV infection since the early 2000s has been cured. Our nationwide micro-elimination effort retrieved another 14% of the population who were LTFU and eligible for retrieval. LTFU patients have a high risk of advanced liver disease, illustrated by the 27% of HCV-RNA positive retrieved individuals with evidence of advanced liver fibrosis or cirrhosis. With CELINE we demonstrated that systematic retrieval provides great value for a better understanding of the HCV epidemiology. Additionally, we established a robust diagnostic pipeline targeting the LTFU population that is worthy of replication in other health care environments. As such, our study supports the view that micro-elimination through retrieval is feasible and contributes to HCV elimination.

Funding statement

CELINE was supported with an unrestricted grant from Gilead Sciences. The funder did not have any role in study design, data collection, management, analysis and/or interpretation. Wherever possible, CELINE included and expanded on data from regional retrieval projects. The REtrieval And cure of Chronic Hepatitis C (REACH) project was supported with unrestricted grants from Gilead Sciences, Merck Sharpe & Dohme (MSD), AbbVie and Bristol-Myers Squibb (BMS). The Zuyderland project was financially supported by grants from Gilead Sciences and MSD. The Track Trace & Treat project was financially supported by a grant from MSD. Projects from the Leiden University Medical Centre,

Haga Teaching Hospital and Medical Centre Leeuwarden were financially unsupported.

Declaration of Competing Interest

C.J.I. has received research funding from Gilead, outside the submitted work. M.v.D. declares that the Radboudumc, on behalf of M.v.D., received honoraria due to participation in advisory boards of Abbvie and Gilead. R.d.K. declares that the Erasmus University Medical Centre, on behalf of R.d.K., received honoraria for consulting/speaking from Gilead, Janssen, Bristol-Myers Squibb (BMS), Abbvie, Merck Sharp & Dohme (MSD) and Roche and received research grants from Abbvie, Gilead, GlaxoSmithKline and Janssen. J.E.A. reports fees paid to the institution from Gilead, Janssen-Cilag, Abbvie, BMS, and MSD for advisory membership, all outside the submitted work. M.v.d.V. declares that Amsterdam UMC on behalf of M.v.d.V. received honoraria or research grants from Abbvie, Gilead, MSD, and ViiV Healthcare, all outside the submitted work. J.P.H.D. declares that the Radboudumc, on behalf of J.P.H.D., received honoraria or research grants from Novartis, Ipsen, Otsuka, Abbvie, and Gilead. J.P.H.D. served as consultant for Gilead and Abbvie, and in the last two years has been member of advisory boards of Otsuka, Norgine Gilead, BMS, Janssen, and Abbvie. All other authors report no conflict of interest.

Acknowledgments

All members of the CELINE study group have significantly contributed to this nationwide retrieval effort. All members of the CELINE study group have reviewed and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.04.024.

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