

**Title:**

**Towards the elimination of hepatitis C: implementation of reflex testing in Andalusia**

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**Article title:** Towards the elimination of hepatitis C: Implementation of reflex testing in Andalusia

**Título del artículo:** Hacia la eliminación de la hepatitis C: Implementación del diagnóstico en un solo paso en Andalucía

**Short title:** Implementation of reflex testing in Andalusia

**Título abreviado:** Implementación del diagnóstico en un solo paso en Andalucía

**Key words:** Hepatitis C, micro-elimination, reflex testing, linkage to care, treatment cascade.

**Palabras clave:** Hepatitis C, micro-eliminación, prueba reflejo, vinculación al cuidado, cascada de tratamiento.

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**Declaración de intereses:** Ninguno de los autores tiene declaración de intereses

## **Abstract**

**Background and aim:** Undiagnosed HCV infection and/or inadequate linkage to care are barriers to HCV elimination. Reflex testing has proven to facilitate linkage to care, access to treatment and viral elimination. In our study, we implemented a reflex testing program in Andalusia and we evaluated its impact on access and linkage to care.

**Patients and methods:** An observational, retrospective and prospective study across diagnostic laboratories responsible for HCV diagnosis in southern Spain was conducted. After surveying the barriers to performing reflex testing, we retrospectively studied how many patients were not linked to care in 2016 (pre-reflex cohort). Then we proposed several measures to overcome the identified barriers. Finally, we implemented reflex testing and evaluated its impact.

**Results:** The pre-reflex cohort included information from 1053 patients. Slightly more than half of the patients (n=580; 55%) visited a specialist for treatment evaluation in a median period of 71 days (interquartile range=35-134) since the date of diagnosis. The post-reflex cohort (September 2017 to March 2018) included 623 patients; only 17% (n=106) of the patients had not been linked to care or evaluated for treatment in a median period of 52 days (interquartile range=28-86).

**Conclusions:** In 2016, nearly half of new HCV diagnoses in southern Spain were not linked to care. Barriers to the implementation of reflex testing have been overcome in our study. Moreover, this strategy was effectively implemented in 2017. Reflex testing contributed to improve linkage to care. This program will contribute to the micro-elimination of hepatitis C in Spain.

## Resumen

**Antecedentes:** La infección por VHC no diagnosticada y la falta de acceso a la atención sanitaria son barreras para la eliminación del VHC. En nuestro estudio, implementamos un programa de diagnóstico en un paso (réflex) en Andalucía y evaluamos su impacto en el acceso y la vinculación con la atención.

**Pacientes y métodos:** Estudio observacional, ambispectivo en laboratorios responsables del diagnóstico de VHC en el sur de España. Después de analizar las barreras para realizar el diagnóstico, estudiamos retrospectivamente cuántos pacientes no habían sido atendidos durante 2016 (cohorte pre-reflex). Tras proponer medidas para superar las barreras que se identificaron, implementamos el diagnóstico en un paso (cohorte réflex) y evaluamos su impacto.

**Resultados:** La cohorte pre-réflex incluyó 1053 pacientes. Poco más de la mitad (n=580;55%) visitaron a un especialista para la evaluación del tratamiento, tras una mediana de 71 días desde la fecha del diagnóstico (rango intercuartílico=35-134). La cohorte réflex (6 meses) incluyó 623 pacientes; solo el 17% (n=106) de los pacientes no fueron evaluados para tratamiento, en este caso tras una mediana de 52 días (rango intercuartílico=28-86).

**Conclusiones:** Durante 2016, casi la mitad de los nuevos diagnósticos de VHC en el sur de España no fueron derivados al especialista para tratamiento. La implementación del diagnóstico en un paso a contribuido a mejorar la vinculación con la atención especializada. Este programa contribuirá a la micro-eliminación de la hepatitis C en Andalucía.

## **INTRODUCTION**

Hepatitis C virus (HCV) infection becomes chronic in up to 80% of infected patients. If left untreated, HCV infection progresses to cirrhosis in a large percentage of patients (30%), and to hepatocellular carcinoma in 5% of patients (1). This infection affects more than 300 000 people in Spain. Recent studies estimate that the prevalence of patients with active infection (viraemia) in the Spanish population is between 0.3 and 0.5% (2,3).

In May 2015, the Spanish Ministry of Health established the Strategic Plan for Tackling Hepatitis C in the Spanish National Health Service (4). The national plan has enabled large numbers of patients to be treated, initially those with advanced fibrosis (F3, F4), and more recently all patients with no restriction in terms of the fibrosis stage, thus placing Spain among the countries with the highest treatment rates worldwide (5). Access to treatment for all patients with chronic HCV infection is a priority in any hepatitis C elimination plan. Moreover, treatment with direct-acting antiviral agents (DAAs) achieves cure in more than 95% of patients (6,7). In the light of this, the World Health Organization has set the goal of eliminating the disease by 2030 (8) and some countries are on track towards meeting this target (9,10), including Spain (11).

The diagnostic algorithm for hepatitis C begins with the detection of antibodies, but the techniques used do not distinguish between active and resolved HCV infections (12). The detection of HCV RNA indicates viral replication, therefore this marker is used to confirm active HCV infection, to select candidates for antiviral treatment and to monitor the treatment response.

Universal screening has been shown to be cost-effective in Spain (13,14), and should undoubtedly be implemented to achieve the elimination of HCV. However, in addition to screening strategies, appropriate strategies for the diagnosis of HCV infection are also needed to reach this goal. Several authors (15,16) have shown how the increase in the number of visits to the doctor before starting antiviral treatment has a direct effect on loss to follow-up and it is therefore an important barrier to HCV elimination. In our setting, two recent studies (one conducted at the national (17) level

and the other one conducted in the region of Andalusia (18)) have revealed barriers for prompt and efficient diagnosis of the active infection in the diagnostic laboratories, with a significant increase in the number of visits required by patients before they are eventually evaluated for antiviral treatment. In Spain, even though more than 80% of hospitals have the resources to diagnose viraemia directly using the same sample in which the antibodies were analysed (reflex testing), just 30% of the hospitals conduct the reflex testing; the remaining hospitals issue a report in which only the antibody results are presented, with no indication of viraemia.

A pilot study recently conducted in two healthcare centres in Spain (19) showed a notable increase in the number of patients referred to specialists for antiviral treatment when the active infection was diagnosed in a single step. In our study, we evaluated the impact of reflex testing and the inclusion of warning messages to the requesting physician to recommend the referral of patients in order to be evaluated for treatment initiation. To evaluate the impact of this measure, we analysed the baseline situation regarding referral of patients with HCV in 2016.

## **PATIENTS AND METHODS**

We conducted an observational, retrospective and prospective study in which all hospitals belonging to the Andalusia Health Service (Spain) were invited to participate. Prior to the beginning of the study, a survey was conducted at the hospitals to obtain data regarding the diagnosis of HCV. In addition to data on the type of hospital and number of beds, the respondents answered questions on aspects related to their workload and the possibility of implementing reflex testing.

The retrospective phase of the study began then at the hospitals that agreed to participate (pre-reflex cohort). In this phase, patients who had been diagnosed with HCV infection in 2016 using the traditional diagnostic system (HCV serology, with confirmation of positive results by immunoblot and a report issued to the requesting physician) were identified. After retrieving the electronic medical records and data from the laboratory information systems, the number of patients who were not evaluated for antiviral treatment within one year of the initial diagnosis was calculated.

A two-month period was allowed to all the participating centres to implement reflex testing. The prospective phase began in September 2017. Patient inclusion continued for 6 months, ending in March 2018 (reflex cohort). In this phase, the participating hospitals implemented reflex testing, automatically incorporating the detection of viraemia by using viral load detection (Cobas-AmpliPrep-Cobas-TaqMan HCV v2.0/Cobas 6800, Roche Diagnostics; Abbott RealTime HCV assay, Abbott Diagnostics; Cepheid, Xpert® HCV Viral Load) on the same sample on which the positive serology result had been obtained for all newly-diagnosed patients and for those in whom previous interferon-based therapies had failed and who for some reason had returned to primary care. Core antigen (Architect HCV core Ag assay®, Abbott Diagnostics) was used for the reflex testing instead of HCV RNA in 2 out of the 18 participating hospitals. Furthermore, a statement was included in all the reports recommending that patients with active infection should be referred to a specialist to be evaluated for treatment. Similarly to the prospective phase, we retrieved the electronic medical records and

data from laboratory computer systems. Then the number of patients who were not evaluated in hospital care for antiviral treatment was calculated.

To avoid bias, patients diagnosed at hepatology and/or infectious disease units were not included in the analyses.

## **RESULTS**

Most hospitals (93%; 26/28) in the Andalusian Public Health Service responded to the invitation to participate in the study. Half of the hospitals (50%; 13/26) were primary-level centres and HCV serology was performed at the microbiology department in a large number of participating hospitals (80%, 21/26). In 10 hospitals, the microbiology laboratories performed only antibody screening (38%), that is, serology tests (not detection of viraemia), and the microbiology laboratories of another 10 hospitals have no relationship with the hepatology and infectious diseases services. When asked to implement reflex testing, 90% (23/26) of hospitals responded positively. The respondents who did not conduct reflex testing specified the following barriers to its implementation: HCV viraemia determination was performed in another department; there was no agreed protocol with the hepatology and/or infectious diseases departments; lack of resources; and opposition of management to the introduction of new parameters. Hospitals that could not implement the reflex testing were not included in the study (neither in the retrospective nor in the prospective phases).

In the retrospective phase (pre-reflex cohort), we evaluated a total of 1053 patients who met the inclusion criteria, 69% (727/1053) men, with a mean age of 52 years (interquartile range [IQR] 45-59). The request for HCV serology for these patients had been received from primary care (PC) in 54% (569/1053) of patients, from the hospital itself in 17% (179/1053) of patients and from other centres (prisons, addiction centres, shelter homes, etc.) in 19% (200/1053) of patients. The origin of the patients was not reported in 10% (105/1053) of patients. After a one-year follow-up from diagnosis, only 55% (579/1053) of the total number of patients had visited a specialist requesting the determination of viraemia, after a median of 70 days (IQR 35-128). The prevalence of active infection was 77% in these patients for whom determination of



HCV RNA was requested.

The prospective phase started with the establishment of the diagnosis of active infection and the warning message for referral (reflex cohort). During the inclusion period (September 2017 to February 2018), a total of 623 patients were admitted to the study, 74% (461/623) men, with a mean age of 52 years (IQR 46-59). The request had been made from PC in 64% (399/623) of these patients, from the hospital itself in 17% (106/623) of patients and from other centres in 18% (112/623) of patients. In 1% (6/623) of patients the origin of the patients was not reported. The prospective phase included more men and patients who were referred from primary care. After 9.5 months follow-up, only 17% (106/623) out of the total number of patients have not visited a specialist for treatment assessment after a median of 52 days (IQR 28-86). The prevalence of active infection found in the prospective study was 63%. Thirteen percent of non-viraemic patients, in whom the infection had resolved spontaneously, were referred to a specialist in hepatology/infectious disease for treatment. In patients from addiction centres, prisons and/or others, the referral rates for treatment assessment were 43% (86/200) and 55% (62/112), after median times of 121 days (IQR 62-189) and 88 days (IQR 40-176) in the retrospective and prospective phases, respectively.

Table 1 summarises the baseline characteristics of the patients included in both study phases. Figure 1 and table 2 shows the frequency data and time to referral in both phases of the study, overall and based on the source.

## **DISCUSSION**

In Spain, traditional diagnosis of HCV infection involves the detection of HCV antibodies, after which the patient has to await a new request of the physician responsible for initiating treatment to investigate the viraemia. This strategy entails significant inefficiencies in the management of HCV infection, because it fails to identify patients who should be referred to a specialist to be evaluated for treatment initiation. Reflex testing is an alternative that might improve the shortcomings of traditional diagnosis (20,21).

In our study, we managed to implement reflex testing in 18 hospitals in Andalusia. Accordingly, we overcame some of the barriers that were raised in the initial survey: we achieved consensus between microbiologists, hepatologists and infectious disease specialists, after drafting a consensus document endorsed by the three Andalusian societies involved (22), an initiative that was then rolled out to the national societies involved (23). We facilitated access in those hospitals in which the methodology for determination of viral load was not available, through point-of-care methodology (23). Finally, we managed to help resolve the administrative barriers, supporting the proposal of the Ministry of Health regarding reflex testing as one of the basic goals for all Andalusian clinical management units with microbiology services (24).

Our results confirm those presented in the pilot study previously conducted in other hospitals in Spain (Granada and Santiago de Compostela) (19). The introduction of reflex testing, in conjunction with warning messages for referral, have resulted in an increase in the number of patients evaluated for antiviral treatment, from 55% (579/1053) after one year of follow-up in the retrospective phase to 83% (517/623) in the prospective phase. Furthermore, as in the previous study, the time in which the patients were evaluated was also reduced, from a median of 70 days (IQR 35-128) with the traditional method to a median of 52 days (IQR 28-86) when reflex testing was introduced. Both changes, that is, the increase in the percentage of patients referred to the specialist and the reduction in time, were statistically significant ( $p < 0.01$ )

Individualised analysis of the referral according to the source has shown a larger number of losses to follow-up in patients from prisons and/or addiction centres compared to those from primary care and hospitals. Consistently with other authors (23-25), these patients constitute some of the primary foci in which HCV transmission remains active. Our findings support the need to implement measures to encourage access of these patients to treatment.

In the retrospective phase of our study, the infection had resolved spontaneously in 23% of patients that were referred to the specialist. The implementation of reflex testing managed to obviate unnecessary visits, because patients who have cleared the infection are therefore not referred to the specialist, with the consequent cost saving. In our study, reflex testing avoided overloading specialist clinics with patients who had already cleared the infection spontaneously.

Our study has several limitations. First of all, we cannot state that improvement in linkage to care is exclusively due to the reflex testing strategy because there are some uncontrolled variables, such as the time frame of the two phases, that may have had some effect on the results, because knowledge and interest in the treatment of HCV might be currently larger than in 2016. Secondly, although unlikely, this study should be replicated in the rest of Spain, since there could be uncontrolled biases associated with the Andalusian region. Finally, core antigen determination was used for the reflex testing instead of HCV RNA in 2 out of the 18 participating hospitals. Although the core antigen has lower sensitivity than HCV RNA for low viraemia (the antigen may not be detected in up to 1% of HCV RNA-positive patients), several studies and guidelines have demonstrated its usefulness for the identification of patients with active HCV infection (26,27,28).

In summary, in our study, we used a methodology that has led to the implementation of reflex testing in southern Spain. We have also confirmed data from the previous pilot study, showing that the implementation of reflex testing has a real impact on the HCV treatment cascade, enabling a larger number of patients to be

correctly diagnosed and evaluated for treatment, thereby contributing to the elimination of hepatitis C.

## **FUNDING SOURCES**

None

## **DECLARATION OF INTERESTS**

The authors have no conflict of interest to declare.

## **AUTHOR CONTRIBUTIONS**

All authors have contributed to the work and have seen and approved the current submission.

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Table 1. Demographic characteristics of patients included in the study.

	Retrospective phase (n=1053)	Prospective phase (n=623)	p
Age, years, median (IQR)	52 (45-59)	52 (46-59)	ns
Sex (men), n (%)	727 (69)	461 (74)	<0.01
Source PC, n (%)	569 (54)	399 (64)	<0.01
Source HC, n (%)	179 (17)	106 (17)	ns
Other institutions*, n (%)	200 (19)	112 (18)	ns

IQR: interquartile range; PC: Primary care; HC: Hospital care; ns: Non-significant;

\*Prisons/addiction centres

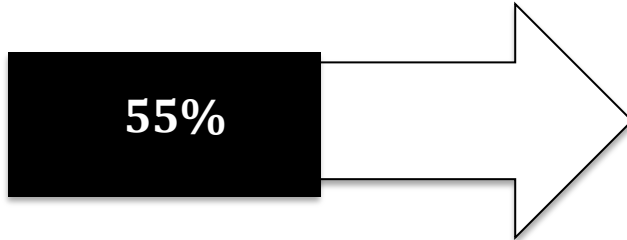
Table 2. Patient referral rates during the retrospective and prospective phases of the study.

	Retrospective phase (n=1053)				p	Prospective phase (n=623)			
	Total	PC	HC	Others*		Total	PC	HC	Others*
Non-referral, n (%)	474/1053 (45%)	290/569 (51%)	82/179 (46%)	114/200 (57%)	<0.01	106/623 (17%)	76/399 (19%)	28/106 (26%)	50/112 (45%)
Days to referral, median (IQR)	70 (35-128)				<0.01	52 (28-86)			

PC: Primary care; HC: Hospital care; \*Prisons/addiction centres

Figure 1. Percentage of patients that were referred to specialist physicians for the evaluation of treatment initiation in both phases of the study: a) retrospective (pre-reflex) and b) prospective (post-reflex), after the implementation of reflex testing.

**A) Retrospective phase: pre-reflex cohort**



**B) Prospective phase: post-reflex cohort**

