

Point-of-care testing for hepatitis C virus infection at an Italian dental clinic: portrait of the pilot study population

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SUMMARY

The dental clinic is an appropriate place to promote the prevention of hepatitis C virus (HCV) infection and fast access for care of HCV-positive subjects with new-generation anti-HCV drugs.

This study aimed to determine the socio-demographic profile of subjects screened for HCV virus in a dental clinic to acquire useful information for future campaigns of prevention.

An easy, free-of-charge, screen salivary test was offered to patients referred to the dental clinic of San Raffaele Scientific Research Hospital in Milan, Italy for dental procedures. These patients were also asked to complete an anonymous questionnaire on demographics and risk behaviours.

A total of 1388 of 2097 (66.19%) questionnaires were evaluable. The demographics of the population responding to this initiative was primarily Italians citizen (96.47%), homogeneous gender distribution (55.55%), age over 50 (609 subjects; 43.88%), with high-level education and stable professional positions. 905 subjects (65.20%) were never tested for HCV before. The test showed positive reactivity in 22 cases (1.05%); of these, 21 subjects were known to be HCV-positive, and the test confirmed their status. One subject was newly diagnosed as HCV-positive.

The percentage of subjects who were never tested for HCV infection appears too high (905 subjects, i.e., 65.20%), especially among subjects with high level of education and professions, and among adults over 40 or young people (18-25).

The easy screening test in dental clinic can help raise awareness, promote early diagnosis and prevention, and provide a fast link to care for HCV infection.

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INTRODUCTION

Hepatitis C affects about 170 million people worldwide, of which 1.5 million are in Italy (2% of the Italian population). The World Health Organisation (WHO) is thus working on a global strategy to combat this virus, with the ambitious goal to eliminate the disease, an objective that has now become possible through the availability of new antiviral drugs, which may be administered to all patients infected with hepatitis C virus (HCV). The strategy of the WHO includes a comprehensive package of prevention measures, among which is the "Guidelines for the screening, care and treatment of persons with hepatitis C" that was launched in April 2014, offering guidance to policy-makers and government officials on the prevention of transmission, development of programmes for the screening of people potentially affected by HCV infection, and facilitation of access to care for HCV patients (Calvaruso *et al.*, 2018). The focus is on what can be done to increase patient awareness and

reduce the barriers to treatment. In February 2016, the first European HCV Policy Summit in Brussels developed a programme on the elimination of HCV at the European Union level by 2030, culminating in the presentation of the HCV Elimination Manifesto, and introduced a European Hepatitis Awareness Week as well (Papatheodoridis *et al.*, 2018). According to these guidelines, screening to identify persons with HCV infection is recommended and offered not only to individuals who are part of a population with high HCV prevalence (high-risk people), but also to asymptomatic people who could have contracted the infection, since many years can elapse without any signs or symptoms of the disease, thus to escape the diagnosis of the so-called "submerged infections". These subjects remain asymptomatic for decades after infection, with progression of liver disease and eventually presenting with grave and deadly complications such as liver cirrhosis, liver cancer, and liver failure. In many countries, the majority (in some countries, more than 75%) of people living with viral hepatitis do not know about their infection; many became infected through blood transfusion or other medical procedures years ago when no tests were available. Thus, the early diagnosis of HCV in submerged infections is unusual and the identification of HCV-carriers is occasional in a large part of individuals. Nowadays it is clear that everyone is potentially at risk, as unsafe injections and other invasive procedures can expose individuals to hepatitis C

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virus within and outside the healthcare sector. For these reasons, initiatives aimed to identify a submerged portion of patients among the general population are encouraged. In this field, the use of easy screening tests that can be performed at the site of patient care without the need for a virology laboratory, represents an interesting alternative to classical virological tests performed using serum or plasma obtained by venipuncture, and is now considered a strategic tool (Shivkumar *et al.*, 2012).

The dental clinic is an ideal place to promote the prevention of HCV infection (Gherlone *et al.*, 2016a; Gherlone *et al.*, 2016b) and the linking HCV-positive cases to care, as previously demonstrated in a project conducted by the Department of Infectious Diseases and the Centre for Oral Hygiene and Prevention (IRCCS San Raffaele Scientific Hospital, Milan, Italy) (Parisi *et al.*, 2017). Based on the collected data, this study aimed to determine the socio-demographic profile of subjects screened for HCV infection during this preventive initiative, for the final purpose of acquiring useful information for future screening campaigns. Patient representative groups, namely the Association of People with Hepatitis C (EpaC) and the ANLAIDS-Lombardia Association (Associazione Nazionale Lotta all'AIDS), have promoted the initiative.

MATERIALS AND METHODS

This was a cross-sectional study of the community, conducted under the patronage of the Infectious Diseases Department and the Centre for Oral Hygiene and Prevention, Department of Dentistry, San Raffaele Scientific Institute, in Milan. It was supported by the EpaC Onlus (Associazione onlus contro l'Epatite C) and ANLAIDS-Lombardia associations. The project was conducted at the Oral Hygiene Unit, where hygienists offered a free HCV rapid test before performing routine oral hygiene on patients.

The Oral Hygiene Unit is part of a University Hospital and provides a regimen of solvency for patients who access it. Therefore, there are no services with tickets paid by the Italian National Health System.

In the waiting room of the clinic, each patient can read the brochures to learn about the prevention of HCV infection. To guarantee the privacy of the subjects, the hygienist performed pre-test counselling with each patient in a separate area, and submitted the informed consent form to each subject. After signing the consent form, the subjects performed the test for free and then received their professional oral hygiene treatment.

The test used was the OraQuick ADVANCE® Rapid HCV Antibody Test (OraSure Technologies, Bethlehem, PA), whose sensitivity and specificity in oral mucosal transudate among anti-HCV-seropositive patients is 89.9% and 100%, respectively (Parisi *et al.*, 2016; Pallarés *et al.*, 2018). Details on the methods and results of the screening test were previously reported in a separate article, in which a draft protocol of "best practice" for rapid HCV infection screening was also presented (Parisi *et al.*, 2017).

Subjects who took the test were first asked to complete an anonymous questionnaire, through which it was possible to collect a series of data about their demographic and socio-economic factors and risk behaviours.

The patients were asked to complete the questionnaire very sincerely, given the importance of the data collected. Patients were also asked not to hesitate to request clarifications in case of unclear questions.

In addition, personal counselling on the prevention of HCV infection and sexually transmitted infections was provided by a skilled hygienist involved in the study to subjects who did not take the test. In particular, their reasons for refusing to participate in the screening were also recorded and evaluated.

All these data were collected and evaluated using descriptive statistics methods to identify the socio-demographic profile of subjects that can be obtained by HCV screening in a dental clinic for the final purpose of acquiring useful information for future prevention campaigns.

RESULTS

Among the 2377 informed subjects, 2097 (88.22%) agreed to attend this screening program by signing the informed consent, accepting to be tested and completing the anonymous questionnaire. Among the 2097 completed questionnaires, only 1388 (66.19%) were completely evaluable, while the others were invalidated due to the lack of answers to the majority of the questions.

Characteristics of subjects who refused to participate in the screening program and reasons for refusal

Of the 2377 subjects initially informed, 280 (11.78%) refused to participate in this screening program. All of these subjects were asked the reason for their refusal; however, only 87 subjects (31.07%), mostly female (n=51) agreed to provide reasons for their refusal. Reasons for their refusal are presented in *Figure 1*.

The socio-demographic profile of the subjects responding to this Easy-test initiative

Data extracted from the 1388 valid questionnaires were used to describe the profile of the target customers or population responding to this Easy-test initiative.

The profile of the population responding to this initiative was the following: dominantly Italians (n=1339, 96.47%), homogeneous gender distribution (607 males, 43.73% and 771 females, 55.55%, and 10 missed data, 0.72%), age over 50 years (609 subjects out of 1388, 43.88%), medium/high level of education (high-school level (n=610, 43.95%), graduate (n=463, 33.36%), post-graduate (n=182, 13.11%).

With respect to occupation in stable professional positions, 45 questionnaires had missing data (3.24%), 118 (8.50%) were managers, 215 (15.49%) were self-employed, 341 (24.57%) were employed by others, 192 (13.83%) were in other occupations, 223 (16.07%) were retired, and 37 (2.67%) were ordinary workers. Only 17 (1.22%) were unemployed.

The questionnaire revealed information about high-risk factors for HCV infections. In the whole sample, 501 subjects (36.09%) were at high risk of being infected with HCV for the following reasons: 236 subjects (17.00%) for tattoo or piercings; 99 subjects (7.13%) for blood transfusions, and 166 subjects (11.96%) for risky sexual behaviour. For the other 63.91% of subjects in the present sample, however, it is still plausible that they could belong to risk categories that were not considered in the present survey.

Characteristics of the sub-sample of subjects who had never been tested for HCV before this initiative.

The questionnaire also asked about possible previous experiences of the subjects about HCV diagnostic tests. The

data revealed that 905 (65.20%) subjects (55% females) who had valid completed questionnaires had never been tested for HCV prior to this experience in the dental clinic. This sub-sample of subjects had separate analysis performed on their socio-demographic factors. Data about their age distribution and level of education are showed in Figure 2 and 3, respectively.

The majority of these subjects (n=423, 46.74%) were more than 50 years old. One hundred and eight-two (20.11%) were younger subjects (41-50 years old) and the remaining 300 (33.15%) subjects were under 40 years old, among which 120 subjects were 31 ≤ x ≤ 40 years old (13%); 46 subjects were 26 ≤ x ≤ 30 years old (5%); and 134 subjects were 18 ≤ x ≤ 25 years old (15%).

The 380 of 905 (41.99%) subjects who had never been test-

ed for HCV had a very high level of education (graduate and post-graduate degrees) and 435 (48.07%) subjects had a high school education. Only 90 (9.94%) who had never been tested had a middle school diploma.

With respect to potential high-risk factors among people who had never been tested for HCV infection, 237 (26.19%) subjects displayed a high-risk level for HCV infections, 107 (11.82%) subjects declared practising risky sex, and 130 (14.36%) subjects declared having tattoos or piercings.

Data about appreciation of the initiative

Overall, the initiative was well-liked by the users of the Dental Unit. Almost all subjects (n=1360, 97.98%) answered that the initiative was very useful; 1377 (99.21%)

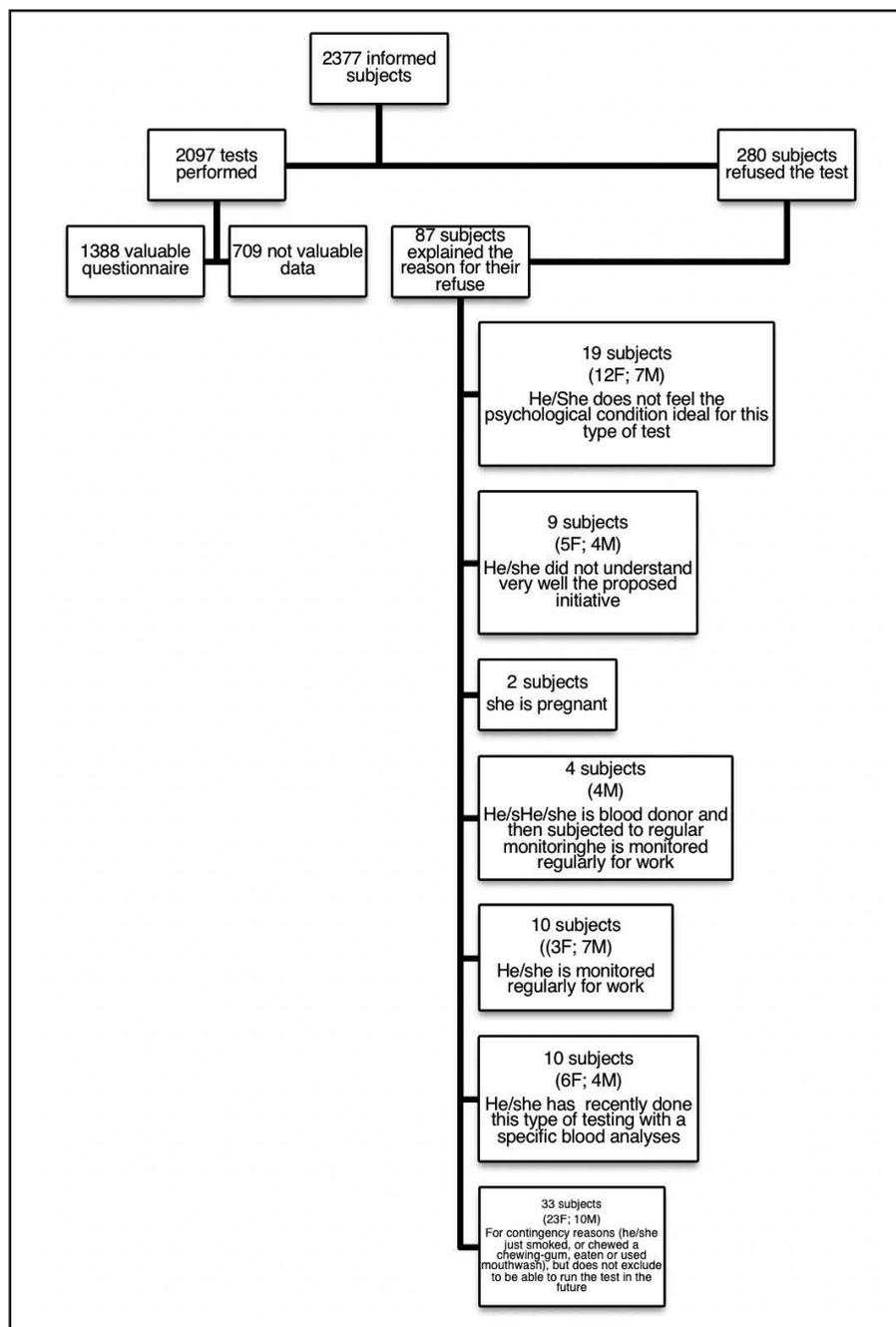


Figure 1 - Flow chart of the data recorded.

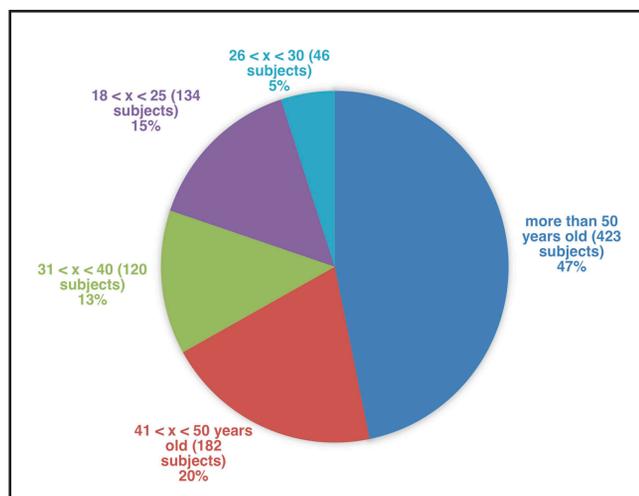


Figure 2 - Age distribution of subjects who had never been tested for HCV before this initiative (905 subjects).

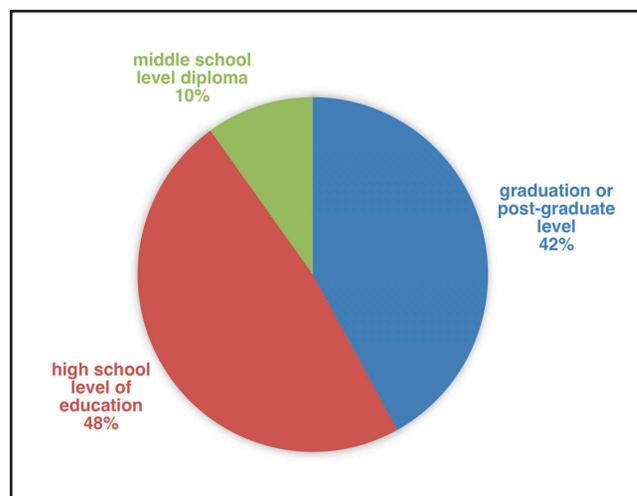


Figure 3 - Education level of subjects who had never been tested for HCV before this initiative (905 subjects)

of subjects declared they were satisfied with the initiative; and 697 (50.62%) declared they were “very satisfied.” Almost all subjects ($n=1359$, 97.91%) indicated that they would recommend this kind of initiative to friends and others while only 29 (2.09%) subjects indicated that they would not.

Interestingly, it was noted that among 107 of the 905 subjects with risky sexual behaviour, 103 subjects declared that they would recommend the test. Among 798 of the 905 subjects who did not indicate risky sexual behaviour, 722 subjects recommended the test. The difference between subjects with and without risky sexual behaviour was statistically significant (chi-square 18, 23; $p=0.001$).

DISCUSSION

Large-scale HCV screening programmes are required to prevent further spread of the infection, to improve access to care in the context of new HCV drug regimens, and to decrease the risk of long-term complications of chronic liver disease (Chevaliez *et al.*, 2016). In this context, the “Easy-test programme” for HCV virus identification represents an interesting alternative to classic virological tests: it is easy to administer, does not require a laboratory for analysis, can be administered by trained personnel not specialised in laboratory medicine, and is highly appreciated by the patient because not invasive.

It is therefore becoming increasingly important to identify the contexts in which to propose these screening tests to the population, together with a widespread information campaign about HCV infection.

Only two pilot projects in this field have been published in the literature: one screening campaign conducted in a group of California pharmacies (Dong *et al.*, 2017) and the other conducted by the present research group in an Italian university dental clinic oral hygiene unit that was a suitable context for proposing this type of screening to the patient (Parisi *et al.*, 2017). The purpose of this study was therefore to determine the socio-demographic profile of the target users who could potentially access this type of screening in a dental clinic, and to evaluate the feasibility and acceptability of this type of preventive campaign in the context of an oral hygiene session.

The majority (88.22%) of the 2377 informed subjects agreed to participate in this screening project by signing the informed consent form, accepting to be tested and completing the anonymous questionnaire. The percentage of positive responses to this initiative was certainly satisfactory, considering that this was the first pilot project of HCV preventive programmes in a unit for oral hygiene. This leads to one to assume that rapid screening on oral fluid can be acceptable, immediate, and consistent with the context of what the oral hygiene session represents for the patient.

The oral hygiene session is intended to predispose the patient to establish a highly trusting relationship with his/her oral hygienist and be willing to receive a 360-degree preventive service, which can certainly include an HCV prevention component (Parisi *et al.*, 2017). In fact, the high level of adherence to this pilot project has allowed the research group to foresee the continuation of this project, which is ongoing, not only in the present Oral Hygiene Unit but also in other dental clinics throughout the Lombardy region.

In the present project, 280 subjects of the 2377 initially informed (i.e., 11.78%) refused to participate in this screening project. All these subjects were asked the reason for their refusal, but only 87 subjects (87 subjects out of 280, i.e., 31.07%), mostly female (51 females out of 87 subjects) agreed to explain the reasons for their refusal. Various hypotheses can be established to explain the refusal by the 11.78% of subjects to participate in the screening. A possible hypothesis is that - dealing in most cases with internal staff of the hospital - they did not want to take this test with colleagues. The majority of subjects who gave a personal reason affirmed that their refusal was due only to contingent factors (for example, they had been drinking, or had used mint substances such as toothpaste, or had chewed something). These substances are not recommended before the test as they could provide false positive results (Pallarés *et al.*). Thus, these subjects had returned to the Oral Hygiene Unit for other visits (each 4–6 months from the previous one) and requested to be tested. They were then referred to the testing point at the San Raffaele Hospital, where the project is still active. Nineteen (22%) subjects indicated that their refusal was due to psycholog-

ical reasons that were—on the basis of their verbal statements during the anamnestic interview with their oral hygienist—*anxiety* due to the stress of waiting for the test response, or to avoid *embarrassing* situations in the event of a positive result. To these subjects, it was a lead time to reflect while waiting for the next visit (scheduled after 4-6 months) to reconsider the opportunity to take the test in the future. Two of these subjects did in fact request the test after 6 months and were referred to the testing point at the San Raffaele Hospital. These data confirm that the dental hygienist is a figure that generally meets the patient periodically and can perform this type of prevention campaign over time, gradually acquiring the consent of patients to participate, including from those subjects who initially refuse the screening test due to *fear* or *embarrassment*. Therefore, the dental clinic context seems more effective than the pharmacy context to convince people, even those who may be initially sceptical, to screen for HCV.

In the present study, the data extracted from the 1388 valid questionnaires were used to describe the profile of the target subjects or population responding to the initiative. From the collected data, the most common profile for subjects who would potentially accept the test is the following: female, Italian nationality, age over 50, with a high level of education (high school diploma, graduate or post-graduate degree), and with a stable job. This profile confirms the known high level of attention and awareness of females regarding prevention and early diagnosis.

The experimental programmes conducted in California pharmacies indicated a different profile of target customers, characterised by high-risk subjects, such as injection drug users, and crack, cocaine or methamphetamine users (Dong *et al.*, 2017). Thus, these two initiatives show profiles of completely different potential users and underline different targets for these preventive campaigns.

The present project also reveals the existence of a large sub-sample (65%, 55% female) consisting of subjects who had never been tested for HCV before. Data about these 905 subjects were analysed separately to identify their socio-demographic characteristics. Among them, 605 (67%) subjects were more than 40 years old. This data probably depends on the fact that in Italy, until a few years ago, tests for the diagnosis of HCV infections were not prescribed assiduously during pregnancy or in the context of occupational medical screenings. For this reason, there could be people over 40 years old who had never been screened for HCV. Presently, however, this type of test is also called for during pregnancy or in the context of occupational medicine. Therefore, HCV screening will become more widespread among young people in the future. In addition, in the future, more attention will be paid to the prevention of HCV, and the spread of the Easy test (the OraQuick HCV rapid test in oral mucosal transudate has a high sensitivity and specificity for detecting active HCV infection (Pallarés *et al.*, 2018)) will facilitate mass screening, becoming more and more widespread also among young people.

However, the present data seem to suggest that nowadays among very young subjects (18-25 years old) there is still little knowledge about transmission, and that the diagnostic test is less common: in the present sample, among subjects 18 to 25, 71% had never been tested for HCV infection. These data therefore confirm that people age 18-25 are undoubtedly little aware of the risk of contracting the virus, and less informed about infection and related pathologies, as well as the possibility of doing diagnostic

Easy-tests. Prevention and information campaigns should intensify their messages to subjects in this age range.

Current information campaigns on the transmission of HCV quite effectively reach the categories most affected by the pathology (i.e., people with low educational level, elderly >70 years old, and in risky situations such as past use of glass syringes, blood transfusion, intravenous drug use, and cohabitation with an anti-HCV positive subject, factors that predict HCV positivity), because among these categories there is greater awareness of the danger of the disease (Andriulli *et al.*, 2018). However, young people, and those more cultured who are apparently not at risk of infection, are not adequately reached by prevention campaigns. Among these categories, it appears that there is still a very high percentage of people who have never performed the diagnostic test.

The easy-test for HCV screening therefore appears to be an effective tool to reach these groups of subjects, who would never have undergone this test if they did not have the opportunity to take it from the dental hygienist.

Despite the prevention campaigns and information that should primarily reach people with an appropriate educational level, the present survey reveals that there is still a significant percentage of highly educated people who still have never been tested for hepatitis C.

In effect, therefore, prevention campaigns must aim to reach everyone, because knowledge of the severity of the disease does not appear to be linked to education level. It cannot be assumed that people with a high education level are the most informed about risks and disease.

In addition, the present data revealed that 237 subjects who never tested belonged to one of the categories considered risky. However, it cannot be excluded that the other 668 who never tested may belong to other risky categories that have not been considered in this pilot project. Since the data from the potentially high-risk factors of the population may be underestimated, as the transmission of HCV infection is not only related to the presence of tattoo, piercing, unprotected risky sex, and blood transfusions, it will be proposed that future questionnaires will include other exposure factors in order to conduct a more complete analysis.

Considering the data obtained, the present initiative therefore appears to be in line with the main world agencies, such as the WHO, that aim to reach and identify at least a part of the submerged share of infection, or that part of the population more or less at high risk of infection which has never been diagnosed (submerged diagnosis).

The present preliminary part of the project, conducted in a dental clinic, can help to reach potential *submerged diagnoses of the infection*, because the appointment is routinely repeated, and the patient meets the operator periodically; therefore, this context is ideal for proposing a 360-degree prevention programme. A possible bias is that the study was done in a university (solvent patients), while the majority of the Italian population is directed to non-university hospitals or private dental offices. In Italy, recent data state that 84-87% of dental visits are made in about 40,000 private offices. Thus, a possible development in this field could be the inclusion of private dental offices in this type of prevention campaign.

With respect to the level of appreciation of the initiative, it was judged more than satisfactory by 98% of the people who joined the initiative. Only 2% of subjects would not recommend the test to relatives or friends because they

judged the traditional test with the blood draw to be more comfortable.

Those subjects who affirmed the practice risky sex and never who took the test were the category of subjects who reported - in a statistically significant percentage when compared to subjects who do not practice risky sex - appreciation for the initiative. That is, for these subjects, the initiative was judged very useful and recommendable.

CONCLUSION

The percentage of positive responses to the initiative was certainly satisfactory, since this was the first experience of this type of pilot prevention programme in the Oral Hygiene Unit.

From the data obtained, it appears that the most common profile of subjects who would potentially accept this initiative is the following: female, Italian nationality, age over 50, with a high level of education (high school diploma, graduate or post-graduate degree), and with a stable job. The percentage of subjects who had never undergone an HCV diagnostic test appears still too high (about 65%) among subjects with high level of education, age over 40, and among very young people (18-25 years old). Therefore, this type of initiative can help raise awareness in these groups of target subjects regarding the early diagnosis and the prevention of HCV infection, and, at the same time, can try to intercept any submerged infections and link them to care.

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