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Definition of the profiles of hepatitis C virus patients based on the identification of risky practices in Spain

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Authors´s contribution: José Luis Calleja: Consultant and rapporteur for AbbVie, Gilead Sciences, MSD. Sabela Lens: Advisory Committee or rapporteur for Abbvie, Gilead, Janssen

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and MSD. Miguel Fernández-Bermejo: Rapporteur for Abbvie. Javier Crespo: Advisory Committee for Abbvie, MSD, Gilead and Janssen, and has received a monetary donation from Gilead, Abbvie and MSD.

ABSTRACT

The absolute number of patients infected with the hepatitis C virus and its prevalence in Spain according to risk practices are not precise. The objective of the study was to estimate the current direct-action antiviral candidates, according to risky practices. The exposed population was determined according to each risky practice and age, based on the data obtained in two epidemiological studies and other bibliographic sources. The overall prevalence of positive serology for the Hepatitis C virus according to the analyzed data was 1.1% (41% with an active infection). The most at-risk group are intravenous drug users (60,368-82,454). It is estimated that between 37,387 to 51,065 patients would be infected via sexual transmission, between 55,505 and 75,812 patients following a blood transfusion and around 18,528 to 25,307 patients by socio-family transmission. According to these data, more than half (55-79%) of the subjects with risky practices would have significant fibrosis (≥ F2). It is estimated that more than half a million people have a positive serology for the Hepatitis C virus and 144,191 to 227,773 antiviral treatments are expected in the coming years. The identification of people with risky practices is key to increase the percentage of diagnosed cases.

Key words: Hepatitis C. Direct-action antivirals. Prevalence. Spain.

INTRODUCTION

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The epidemiology of the hepatitis C virus (HCV) infection in Spain has varied due to the mortality associated with HCV and the success achieved with new treatment strategies, among other reasons (Fig. 1). Twenty years ago, the seroprevalence of HCV was estimated between 1-2.6% (1-7) and currently ranges between 0.3% and 1.8%(8-10). The number of patients with an active HCV infection would be about 200,000, which evolves to chronicity in 60-80% of cases (8,9).

At the beginning of the "Strategic Plan for addressing HCV in the National Health System" (11), 100,000 patients were identified in Spanish hospitals that were awaiting treatment with direct-acting antivirals (DAA). Of these, 54% had a fibrosis (F) level equal to or greater than 2 (12). After almost 4 years since its implementation, the application of the Plan has been shown to be an effective decision for Public Health (13,14). All studies agree that there are a high number of undiagnosed patients that could be an important source of new infections. Therefore, there is a need to screen for HCV infection. Performing Universal Screening is cost effective in Spain (15) -oral communication at the 42 Congress of the *Asociación Española para el Estudio del Hígado (AEEH)* (Spanish Association for the Study of the Liver)- and the implementation of diagnostic strategies in a single step would help to reduce the access to treatment time and prevent disease progression (16). The main limitation is that the identification of patients according to risky practices is not available (17). This would allow an efficient screening, prioritizing the detection in those subgroups with risky practices that are more susceptible to infection.

The objective of this study was to estimate the number of patients infected with HCV according to their risky practices, as well as to estimate the level of fibrosis based on data published in 2017.

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MATERIALS AND METHODS

The project was divided into two phases. On one hand, a review of the data obtained in two Spanish epidemiological studies was performed (oral communications and poster 42 Congress AEEH) and the results of these studies are described in table 1. These studies (Catalonia and PrevHep) were used to identify the main transmission routes of HCV in Spain (risky practices) and to estimate the number of patients with viremia susceptible to treatment with DAA. On the other hand, a non-systematic review of the literature was performed to quantify the population and the period of exposure to each infection route and to estimate the age at first infection according to risky practice.

The degree of fibrosis was estimated by applying the "Markov maximum likelihood estimation-MMLE" method developed and validated by Yi et al.(18). According to this method, the transition probabilities for each state are inferred as follows: F0 → F1 (0.117); F1 → F2 (0.085); F2 → F3 (0.120) and F3 → F4 (0.116). To reinforce this model, a meta-analysis was used(19) which included 111 studies and 33,121 patients with chronic HCV infection.

The prevalence of HCV infection was calculated by extrapolating the figures from the two recent epidemiological studies previously mentioned (Catalonia and PrevHep) to the resident population in Spain over 16 years of age in 2016. Except for the "vertical transmission" group that used the under 16 year population. Four risky practices were considered and nosocomial transmission was not considered (9% of the total number of infected patients according to Buti et al.) (15).

In order to obtain a robust analysis, the results were contrasted with the actual results (number of subjects that have received DAA, degree of fibrosis and risky practices) reported from the Hospital Universitario Marqués de Valdecilla (Santander), Hospital Puerta de Hierro Majadahonda (Madrid) and Hospital Clínic (Barcelona).

RESULTS

The results obtained for each of the principal risky practices for HCV infection identified are presented below.

Intravenous drug use

The highest prevalence of intravenous drug use was recorded in people aged 35 to 44 years (20). In these subjects, we estimated that the time of first infection coincided with the first injection (21). Approximately 4.2% of the analyzed population consumed or had injected drugs at some point in their lives (Table 1). The average prevalence of anti-HCV+ serology in drug users estimated in the studies was 9%. We estimated that infection by this route represented 25% of infections. The extrapolation of these figures to Spain is presented in table 2. Other risky practices such as tattoos and/or piercings frequently coexist in intravenous drug users, so there is an overlap. Nonetheless, we do not have any data to quantify the percentage of intravenous drug-using patients who are HCV+ due to tattoos and/or piercings.

Sexual transmission route (risky sexual behaviors)

The prevalence of risky sexual practices in the general population (Table 1) was 6.5%. The average prevalence of anti-HCV+ serology in this subgroup was 3.6%. An estimated 15% of patients with HCV infection in Spain were associated with the sexual transmission route as a risky practice. Table 2 shows the prevalence figures extrapolated to Spain.

History of blood transfusion

This subgroup includes patients with a transmission route as a result of blood transfusions and hemophiliac patients treated with contaminated coagulation factors. The prevalence of this risk factor (Table 1) was 6.6%. The average prevalence of anti-HCV+ serology in a population with a history of blood transfusion is 4.5%. It is estimated that 23% of HCV patients contracted the disease by this route (Table 2).

Socio-familial transmission

Transmission between cohabitants and vertical transmission were included. Insufficient data were available to quantify this risk with certainty, due to the lack of knowledge about risk exposure in the majority of the population. Recent studies quantified the probability of mother-child transmission as 10%, with a lower probability of chronification of the disease (< 5%) (Poster 42 Congress AEEH).

The prevalence of this risk factor (Table 1) was 5.6% for cohabitants. The prevalence of anti-HCV+ serology in this subgroup was 1% (Oral presentation 42 Congress AEEH) and no other figure was available for this study. The estimate of the population with HCV infection in Spain is shown in table 2.

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Number of candidate patients for DAA treatment, according to fibrosis and risk factor

The degree of fibrosis was estimated based on the prevailing risky practice, assuming no degree of overlap, i.e., that each individual has a single risky practice (Table 2). To obtain a comparator, the treatment data were analyzed according to the risky practice of each of the three hospitals mentioned above. Figure 2 shows the extrapolation to the total number of patients treated according to the figures from the Ministry of Health.

Out of the total estimated number of patients, those already treated (according to Ministry figures) were subtracted in order to obtain the number of patients pending treatment (according to fibrosis and risky practice). On average, 54% of patients undergoing antiviral treatment had F2-F4 degree fibrosis. Therefore, it is estimated that in 2017, 55% of the patients pending treatment with DAA would have fibrosis $\geq$ F2 (Table 3). The groups of patients with a previous or current intravenous drug intake and with risky sexual practices have the largest number of patients to be treated.

DISCUSSION

The extrapolation of two epidemiological studies performed in Spain suggests that the overall prevalence of antibodies against HCV is 1.1% and that the prevalence of active infection ranges from 41-56%. The group with the highest risk of active infection is intravenous drug users, followed by those infected via sexual transmission and blood transfusion. The number of patients with an active infection susceptible to treatment with DAA is estimated at 144,191-227,733 (55% in F2-F4). These results will help us in the proper

design of a national screening plan, which will provide differential care based on risky practices and the age of the screening population.

Intravenous drug use is one of the principal risky practices and this group has a higher prevalence of HCV. According to the EDADES 2015 report, the average age when starting is 22 years. In addition, there are a large number of people in harm reduction and rehabilitation programs in Spain for intravenous opiate dependence (around 80,000 people) that receive opioid substitution therapy (22). This population must be included within the group of risky practices for intravenous drug use, even if they no longer use drugs and not as a separate risk group, as suggested in other publications (23). It is also important to mention the increase in inhaled drug use. A high percentage of these users are unaware of the risks involved in exchanging tools that facilitate inhalation, representing a risk of HCV infection (24,25). It would be necessary to conduct more studies in this population to determine the impact on the prevalence of HCV.

In Spain, the average age of first sexual contact is 18 years (26). Most experts believe that the risk of transmission via sexual transmission is low (27). However, higher rates of sexual transmission of HCV are recorded in men who have sex with men, probably due to the concurrence of specific sexual practices more vulnerable to the transmission of the virus. In the same way, ChemSex practices (sessions of sex and drug use) have been associated with the transmission of HCV (28). Recent data from a sample of HIV-positive men who have sex with men indicate that the practice of ChemSex was relatively high among this population. Furthermore, there was a clear association between the practice of ChemSex, high-risk sexual behaviors and the presence of sexually transmitted diseases, including HCV infection (29). The results of this study reflect the male population with HIV so we cannot affirm

whether the results are similar in other populations**.** The population infected by this route could have an advanced stage of fibrosis, although the rate of progression would vary depending on the patient profile.

With regard to infections due to blood transfusions, the number of new cases is very low thanks to the systematic screening of blood donations since 1992 (11). The results reflect a high percentage of patients with F2-F4 due to the long evolution of the infection in this subgroup. In hemophiliac patients, the high prevalence of HCV is explained by the treatment with contaminated coagulation factors between 1974 and 1986. According to the Federación Española de Hemofilia (Spanish Federation of Hemophilia), about 1/3 of hemophiliac patients were infected with HCV (1,200 in 3,050 hemophiliacs). At the beginning of 2017, the vast majority of patients had been treated. In this population, universal screening and the high efficacy of the new treatments have controlled and minimized the risk of transmission.

With regard to the estimate of prevalence among people with piercings and/or tattoos, the average age of the first infection was considered to be 22 years. The regulation of tattoo centers did not start in Spain until the late 1990s. Therefore, tattoos and piercings could have been a major source of HCV transmission. Currently, it remains a significant risk due to the presence of numerous illegal tattooing centers and tattoo artists.

Among the limitations of this study, it should be noted that in order to estimate the current population of HCV-infected patients according to risky practices and level of fibrosis, data from two prevalence studies were extrapolated. Although there are other recent Spanish studies that have estimated the prevalence of HCV serology and viremia, we used the study performed in Catalonia and the PrevHep study as we could access to patient level data.

However, the prevalence of HCV+ viremia used for our study are in line with those reported in recent Spanish studies: 0.14% (18-76 years old) (30), 0.22% (20-80 years old) (31), 0.32% (Ethon cohort) (oral communication 43 Congress AEEH), 0.48% (oral communication 43 Congress AEEH) and 0.49% (25-70 years old) (32).

Other limitations are related to the remarkable degree of overlap between some risky practices and the difficulty in assigning one or another risky practice to HCV infection in a significant number of patients. Furthermore, the discordance between the number of subjects without a decisive risk practice of infection previously published (about 40%, disHCovery study) (15) and our results are well below this figure. Probably, the notable differences in the design of the study explain these results. However, there is no publication so far that analyses the subsidiary population of antiviral treatment based on their risky practices, as in our study. Furthermore, the overall number of patients with active infection may be overestimated in our study as the overlaps among risky practices could not be considered due to the lack of published epidemiological data.

We can conclude that some routes of HCV infection are not relevant or have practically disappeared today. However, the persistence of some risky practices such as the use of intravenous (or even inhaled) drugs, ChemSex, group sex or tattoos and piercings without sanitary guarantees, mean that the risk of HCV infection remains high.

In conclusion, the relevance of various risky practices in the transmission of HCV is demonstrated and draws attention to the advanced stage of fibrosis in a large proportion of the population with active infection. These people will be candidates for treatment with DAAs in the not too distant future.

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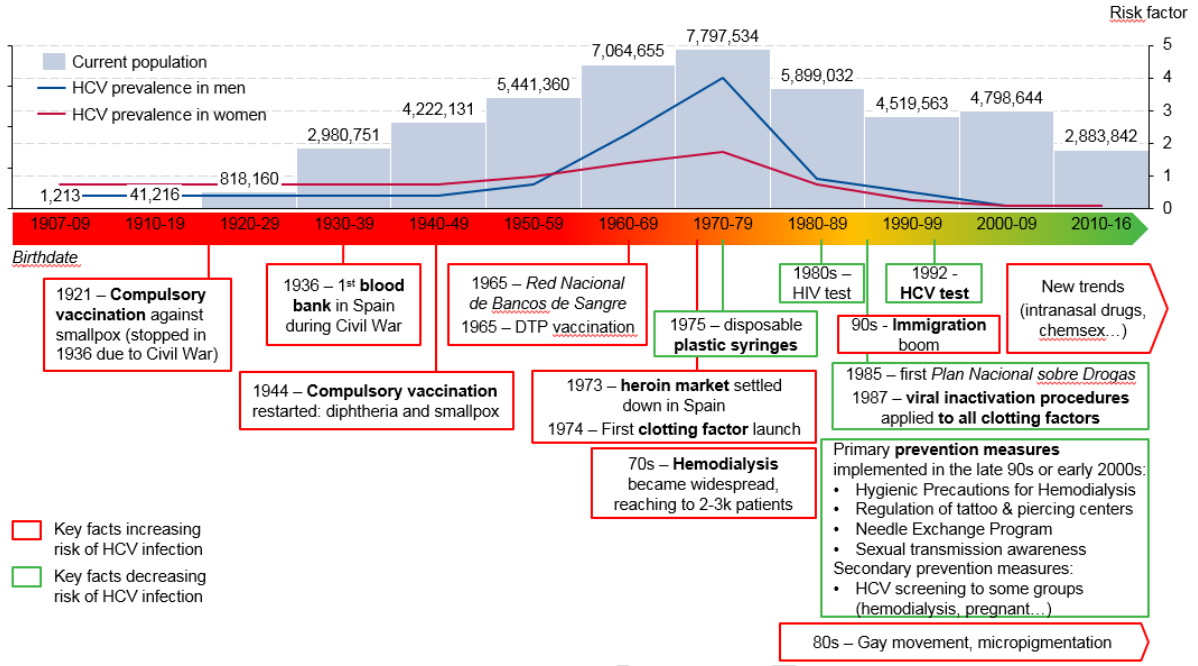
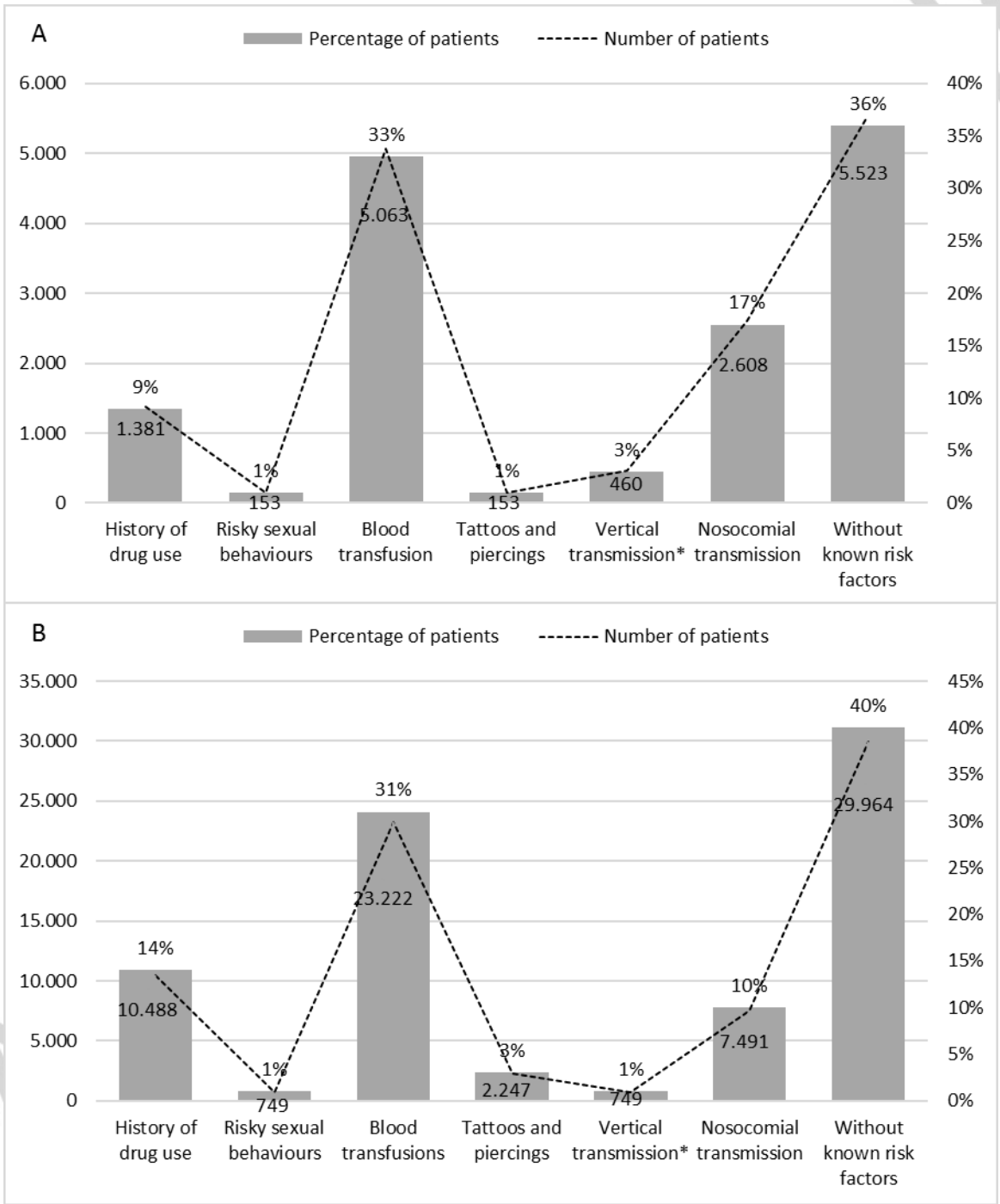
Fig. 1. Evolution of HCV prevalence in Spain.



Abbreviations: DTP: vaccine against diphtheria, tetanus and *Bordetella pertussis* (whooping cough); HCV: hepatitis C virus; HIV: human immunodeficiency virus.

Source: adapted from (9,33).

Fig. 2. Extrapolation of the percentage of patients treated with DAAs based on the degree of fibrosis and the presence or not of risky practices.



*As the only risky practice.
A: F0-F1 patients (17%)[§]; B: F2-F4 patients (83%)[§].

[§]Distribution of those treated by fibrosis stage, according to data available from the SitHepaC registry on the 31st October 2017, from 55,970 patients (PEAHC [Strategic plan for tackling hepatitis C] from November 2017).

Table 1. Characteristics and data of the studies considered for analysis

	Catalonia	**PrevHep**
Sample of patients included	1,921	9,359
Expected sample	4,500	16,285
Design and sample	Telephone contact Conduct of rapid IgG-HCV and HBsAg diagnostic test by finger puncture.	Observational, cross-sectional study (July 2015-Dec 2016) Telephone recruitment of randomized Health Centers. 3,158/4,715 (Madrid), 4,220/6,228 (Cantabria) 1,981/5,342 (Valencia)
HCV+ serology	1.1%	0.15% 20-34 years of age 1.11% 5-49 years of age 1.51% 50-79 years of age 1.1% average*
HCV+ viremia	0.47%	0.15% 20-34 years of age 0.38% 35-49 years of age 0.46% 50-79 years of age 0.36% average*
HCV+ viremia/HCV+ serology	42%	33%
Contact with intravenous/inhaled drugs (SP of anti-HCV+)	2.7% (7.69%)	5.7% (10.30%)
Risky sexual behaviors (SP of anti-HCV+)	6.5% (2.4%)	15.9% (4.80%)
Blood transfusions (SP of anti-HCV+)	9.2% (2.3%)	3.9% (6.60%)
Tattoos and piercings (SP of anti-HCV+)	Tattoos: 7.5% Piercings: 5.2% Both: 4.6%	38.1% (2.5%)

	(2.1%)	
Nosocomial	Surgical procedures: 63.5%	Transfusions, surgery, endoscopy, X-rays, surgical intervention, etc.: 79.7%
Professional	N/A	3.3%
Socio-familial contact**	5.3%	5.9%
% of HCV+ patients unaware of status	52% (11/21)	31% (11/35)

Abbreviations: HBsAg: Hepatitis B surface antigen; HCV: hepatitis C virus; IgG: immunoglobulin G; IQ: surgical intervention; N/A: not available; Rx: X-ray; SP: serological prevalence. *Averages calculated according to INE in July 2016 [consulted in February 2017]. **Family members with a history of HCV, including parents.

Table 2. Estimate of the distribution of patients on the basis of risky practices

Route of infection	Estimated anti-HCV+ patients	% first infection route	Estimate of patients with active infection pre-DAA		Distribution according to fibrosis	
			Minimum (% of viremia over serology 41%)	Maximum (% of viremia over serology 56%)	F0-F1	F2-F4
Intravenous/inhaled drugs	147,239	34%	60,368	82,454	45%	55%
Risky sexual behaviors	91,187	21%	37,387	54,065	32%	68%
Blood transfusions	135,378	30%	55,505	75,812	26%	74%
Socio-familial contact*	23,223	5%	9,521	13,005	40%	60%
Vertical (< 20 years of age)**	45,191	10%	18,528	25,307	21%	79%
Total	*442,218*	*100%*	*244,883*	*334,474*	*36%*	*64%*

Abbreviations: DAA: direct-action antivirals; HCV: hepatitis C virus. *Family members with a history of HCV, including parents. **Bearing in mind a prevalence among women of childbearing age of 0.72% (21) and a probability of transmission and development of chronic infection of 5% (according to the assessment by the committee of experts).

Table 3. Estimation of the number of patients pending treatment based on the risky behavior and the degree of fibrosis

	F0-F1	**F2-F4**	**Total**	**%F2-F4**
History of drug use	17,395-27,474	21,261-33,580	38,656-61,054	47-49%
Risky sexual behaviors	18,092-28,573	22,112-34,923	40,204-63,496	67%
Blood transfusion	0*	12,757-20,148	12,757-20,148	100%
Socio-familial contact (20 years of age or older)	2,783-4,396	3,402-5,373	6,185-9769	50-51%
Vertical transmission (< 20 years of age)	4,871-7,693	5,953-9,402	10,824-17,095	50-51%
Total	*59,146-93,414*	*85,046-134,321*	*144,191-227,733*	*55%*

*According to estimates of fibrosis evolution, all patients with a low stage of fibrosis infected by blood derivative transfusions before 1992 would have been treated, or the progression of the fibrosis is slower in this group.