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DOI: 10.17235/reed.2019.6117/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
Alarcón Linares María Esther, Torres Cantero Alberto, Subirá Carme, Ramírez Rubio Oriana, Crespo García Javier, Lazarus Jeffrey, Requena-Méndez Ana. Geographic analysis and estimation of hepatitis C cases in migrant populations living in Spain: is a country-based screening strategy appropriate?. Rev Esp Enferm Dig 2019. doi: 10.17235/reed.2019.6117/2018.

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OR 5177

Geographic analysis and estimation of hepatitis C cases in migrant populations living in Spain: is a country-based screening strategy appropriate?

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Received: 21/12/2018

Accepted: 26/02/2019

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ABSTRACT

Background: Spain needs to increase the number of new known cases in order to achieve the goal of eliminating hepatitis C virus (HCV) by 2030. The aim of this study was to estimate the number of HCV cases among the migrant population in Spain and propose different scenarios for micro-elimination strategies, targeting the most relevant migrant groups.

Methodology: this epidemiological and demographic cross-sectional descriptive study employed a systematic approach to estimate the number of migrants infected by HCV in Spain. Estimates are based on demographic data and details the size of the foreign-born population living in every Spanish province and the anti-HVC+ prevalence rates in their respective countries of origin.

Results: in Spain, there are 100,268 estimated cases of anti-HCV+ among the total adult migrant population who live in the country. The estimated cases of anti-HCV+ among migrants from moderate-high endemic countries with a prevalence of ≥ 2%, > 3%, > 4% and > 5% are 48,979, 48,029, 24,176 and 15,646, respectively. The anti-HCV+ endemic countries (≥ 2%) that contribute to the highest number of estimated cases in Spain are Romania, Italy, Pakistan, Ukraine, Senegal, Russia and Nigeria. The autonomous communities with the highest prevalence and number of estimated anti-HCV+ cases among migrant population are Catalonia, Valencian Community, Madrid and Andalusia, respectively.

Conclusion: these data show the need to establish HCV screening strategies for the migrant population in Spain and, particularly, in the most affected areas. The strategy should target those migrant communities with a higher prevalence and a higher number of estimated cases, such as people from Eastern Europe, Sub-Saharan Africa and Pakistan.

Key words: Hepatitis C. Prevalence. Migrants. Screening.

INTRODUCTION

According to the World Health Organization (WHO), there are 71 million viremic cases of hepatitis C virus (HCV), equivalent to approximately 1% of the world population (1-3). The United Nations' Sustainable Development Goals (2015) committed to combat viral hepatitis and, in 2016, the WHO set a concrete date for the elimination of viral hepatitis by 2030 (4). Access to new and effective antiviral treatments has been one of the main impulses for the WHO and all its member states in order to set their sights on elimination (5).

According to the latest official data published by the Spanish Ministry of Health (6), the preliminary data from the last national seroprevalence study in the general population is 0.80%. Several other HCV seroprevalence surveys at the regional level provide similar data: Navarra 0.83% (95% CI: 0.64-1.05%) (7), Basque Country 0.7% (95% CI: 0.3-1.2%) (8), Valencia 1.14% (95% CI: 0.73-1.55%) (9), Ethon-cohort (Valencia, Cantabria and Madrid) 1.23% (10) and Catalonia 1.1% (11). According to data

published by the Spanish Government (6), more than 117,000 people with HCV have been treated with the new direct acting antiviral (DAA) drugs in Spain as of the end of 2018. Even after this notable achievement by the Spanish National Health System, there are further challenges for the design of targeted and efficient secondary prevention programs that are capable of diagnosing undetected cases. Furthermore, new studies highlight the risk of "diagnostic burn-out" and there is a need to change the current screening strategies in order to reach more people and the goal of hepatitis C elimination in Spain (12).

In Spain, the screening recommendations for HCV are laid out in the "Strategic Plan for Tackling Hepatitis C in the Spanish National Health System" (13). The different risk groups are defined as people who inject drugs (PWID), people living with HIV (PLWH), men who have sex with men (MSM) and people with tattoos or piercings, among others. Nevertheless, migrants from countries with a moderate or high prevalence of HCV are not included in these screening recommendations.

The strategy of the WHO is to eliminate this disease and promote the screening for HCV in at risk groups, such as immigrants from countries with an endemicity of 2-5% or higher (2,14). In addition, other countries such as the United Kingdom, Ireland and Canada offer opportunistic screening programs and/or campaigns to detect new cases among the immigrant populations arriving from endemic countries (15-17).

In Spain, there are more than six million immigrants from more than 100 countries (18). The European Centre for Disease Prevention and Control (ECDC) made a first approach with demographic data from 2013. This study estimated that there were more than 50,000 chronic cases among immigrants in Spain, when considering only the top 10 countries that contributed to the greatest number of cases. However, there are no data for the estimated case distribution among the 17 autonomous communities (AC) and 50 Spanish provinces.

Due to the lack of data and comprehensive epidemiological studies in Spain, and based on the ECDC's study approach, this study aimed to report an estimated figure of migrants with anti-HCV+ and viremic HCV in Spain. Furthermore, four different screening strategy scenarios were proposed according to the threshold of prevalence being considered.

METHODS

This is a descriptive cross-sectional study that used demographic data of the foreign-born population stratified by country of birth for each of the 50 Spanish provinces and two autonomous cities (Ceuta and Melilla). These were obtained from the National Statistics Institute (INE) on the 1st of January of 2016 (18). The study population included the adolescent/adult migrant population defined as those ≥ 15 years/old who were born in countries other than Spain (including both foreign and nationalized Spanish citizens). The limit of ≥ 15 years old was established based on a meta-analysis and also on the ECDC's report, which calculated and established the country anti-HCV+ prevalence for a population ≥ 15 years-old (19,20). The prevalence of anti-HCV+ for every country was obtained from the ECDC technical report, which assesses the epidemiological data of hepatitis in immigrants in the European Union (EU) (19). The number of infected or anti-HCV+ cases among immigrants in every province was estimated from both sources with the assumption that the HCV prevalence in each country of birth is the probability of being infected within each group of migrants.

Qualitative variables included: country of origin (INE supplies population data for 112 individual countries of origin of foreign-born population) excluding Andorra, province (50 + 2 provinces and Ceuta and Melilla) and autonomous community (17 + 2, including the Canary Islands and Ceuta and Melilla) (18). Quantitative variables were immigrant population with anti-HCV+ and immigrant population with RNA+.

The population with HCV-RNA+ (or chronic hepatitis C infection, referring to viremic infection) was calculated as 70% of anti-HCV+ cases, assuming that virus elimination in 30% of anti-HCV+ of cases (19,20). A spatial analysis was carried out by province using the program QGIS (version 2.10.1, Pisa). The immigrant population variable is represented by choropleths and the intensity of the color indicates the size of the population. A proportional point symbol was used to represent the estimated anti-HCV+ cases. The base cartography of the provinces comes from DIVA-GIS, which is a free computer program for mapping and geographic data analysis (21). The HCV prevalence (lower and upper limit) in every country was multiplied by the immigrant population who lived in every province in order to calculate the number of HCV cases

among immigrant population in every province of Spain. A moderate-high prevalence country was defined as those with an anti-HCV+ prevalence ≥ 2% based on the range established by the WHO recommendations (range between 2%-5%) (14).

The number of immigrants who could benefit from HCV screening was calculated for four different scenarios (scenario A, B, C or D). Every scenario used a different prevalence threshold ≥ 2%, ≥ 3%, ≥ 4% or ≥ 5%, respectively. The prevalence of the country of origin determines if the person is included or excluded from the screening program. The total estimated cases in each scenario are calculated as the sum of the estimated cases for all countries that fulfil the set threshold criteria. The average HCV prevalence for the population in each scenario was calculated as the total number of estimated cases of HCV included in the scenario divided by the total population included in the scenario.

RESULTS

Accordingly, 5,741,108 immigrant residents ≥ 15 years old from the 112 countries were included in the study (2016). Among those, 3,887,293 people (67.8%) were foreign and 1,853,815 people (32.2%) were nationalized Spanish citizens. There were 100,268 estimated HCV cases among the adolescent/adult migrant population (range between 55,453 and 141, 847 immigrants). The average HCV prevalence in the adolescent/adult migrants was estimated to be 1.75% (0.96- 2.47%). The number of RNA+ or chronic estimated cases in migrants is 70,187. Catalonia had the highest absolute number of estimated HCV cases in migrants, followed by Madrid and the Community of Valencia (Table 1).

Analysis by different screening scenarios at a national level

The hypothetical scenario of the HCV screening program for migrants has a ≥ 2% prevalence threshold. Among the 1,234,104 migrants living in Spain from countries meeting this requirement, 48,979 people are estimated to be anti-HCV+ (34,285 chronic hepatitis C cases). The estimated average anti-HCV+ prevalence for this group is 3.97%. Results of the other screening scenarios are shown in table 2.

Figure 1 shows the proportion of migrants in Spain who would benefit from a

screening program according to each assumption. A hypothetical screening program, with scenario A at the national level would allow 48.8% of the total population of adult migrants with anti-HCV+ to benefit from the screening program. The proportions for all scenarios are also shown in figure 1.

Analysis by different screening scenario and country of origin

The 15 countries with the highest contribution of estimated infected cases, without considering the anti-HCV+ prevalence, would be Romania, Morocco, Italy, Pakistan, Ecuador, Argentina, Colombia, Ukraine, Senegal, Russia, Nigeria, Venezuela, China, Peru and Brazil (in decreasing order).

Figure 2 shows the 44 countries with the highest contribution of estimated infected cases, considering the anti-HCV+ prevalence (in a decreasing order of anti-HCV+ prevalence). This figure also shows the position of the country with regard to the relationship between their anti-HCV+ prevalence with the anti-HCV+ prevalence in the general population in Spain. People from countries with a prevalence of < 2% would not be included in any scenario of screening such as Morocco, Ecuador or Colombia. Countries such as Albania, Gambia, Israel, Latvia or Thailand would be included in a screening program under scenario A (prevalence ≥ 2%). However, they would be excluded in other scenarios.

Analysis by different screening scenarios and autonomous community (AC)

Only the results for scenarios A, C and D are shown due to the fact that the difference between scenario A and B is only 950 cases (0.94%). The number of adult migrant population included in scenario A (from countries with an anti-HCV+ prevalence ≥ 2%) for every AC and the number of estimated anti-HCV+ cases (and its lower and upper limit) is shown in table 1. Data for every AC for migrants from countries with an HCV prevalence ≥ 4% and ≥ 5% (scenario C and D, respectively) are also shown in table 1.

Spatial analysis by screening scenarios and provinces

Figure 3 shows the distribution of the migrant adult population among the 52 provinces in Spain and the estimated number of HCV+ cases in every province. Each

map (A, B, C and D) shows the estimated number of HCV+ cases for each screening scenario, respectively. With regard to screening scenario A, Madrid has the highest number of estimated cases (8,679), followed by Barcelona (7,101), Valencia (3,356), and Alicante (2,526). These provinces maintain the same ranking, even under other scenario conditions.

Analysis by country of origin and province

The results of the number of estimated anti-HCV+ cases by country of origin and province are shown in table 3.

DISCUSSION

Our study estimates that approximately 100,000 immigrants are anti-HCV+ in Spain, 70,000 estimated viremic cases with an average anti-HCV+ prevalence of 1.7%. However, the number of people treated and with a potentially eliminated infection should also be considered. According to a prevalence study conducted in the Navarre population, 7% of all anti-HCV+ cases are migrants (7). Considering that all migrants would have equally accessed treatment in Spain, we estimate that 8,222 migrants have been treated for HCV (7% of 117,452 treated people in Spain) and therefore have been cured. Thus, a total of 61,778 migrants would potentially benefit from a screening program.

We could consider different threshold cut-offs for establishing high HCV endemicity, (2, 3, 4 or 5%) and building a scenario (A, B, C or D, respectively) for screening based on an individual country-based risk strategy. For example, if a threshold of ≥ 2% was established (scenario A), the screening would be offered to adult people from countries with a prevalence ≥ 2%, in the absence of other risk factors. In this case, about half of the estimated anti-HCV+ cases in the migrant population (48,000 people) could be potentially diagnosed. Nevertheless, if the strategy targeted migrants from countries with ≥ 3% anti-HCV+ prevalence (B), this scenario would result in almost no differences to ≥ 2% (A) and is further substantially reduced in the targeted migrants from countries with a ≥ 4% (C) or ≥ 5% anti-HCV+ prevalence (D). Therefore, the two last scenarios would probably not target the countries most represented in migrant

communities in Spain.

The strategies targeting migrants from > 2% or 3% HCV prevalence countries would have a greater number of anti-HCV+ cases. However, further cost-effectiveness studies in Spain should evaluate the most efficient scenario to reach the 2030 elimination goal objective, considering the cost of the program and the limited available resources. New screening targets and different strategies to increase the number of unknown anti-HCV+ are needed (22). Researchers warn that Spain and other countries, although they effectively diagnose and treat HCV, may have problems eliminating the epidemics due to "diagnostic burnout". This is the stage where no more newly diagnosed people are available for treatment (12).

Migrants have been identified as important sub-groups that should be specifically addressed as part of the hepatitis C efforts and micro-elimination activities (23). To address HCV among migrants in Spain, the following three micro-elimination strategies are proposed.

Micro-elimination tailored strategy based on country of birth

The high-risk migrant groups living in Spain were identified based on the HCV prevalence of the country of origin among the immigrant population who lived in Spain. Considering the country of origin of these high-risk groups, some of the endemic countries with the highest number of estimated cases in Spain are Romania, Italy, Pakistan, Ukraine and Senegal. The countries with a higher prevalence and therefore a higher probability of being infected with HCV in Spain are Egypt (anti-HCV+ prevalence: 15%) and Cameroon (11%). However, these two countries contribute very little to the total estimated cases in Spain due to a low number of people from these countries living in Spain.

The high contribution of Italians to the burden of HCV cases in migrants is due to the high number of Italian people living in Spain and also due to the traditionally high HCV prevalence in this country. This may be related to previous intravenous drug and nosocomial transmission, among others. Migration movements may have also been partially responsible for the high prevalence, particularly in the last two decades where the incidence in autochthonous population has decreased. Active surveillance is

needed to better understand if the incoming migrants could modify the current epidemiological trends in the host population in Italy (24).

Micro-elimination strategy based on geographically defined areas

In our study, the distribution of estimated cases among different regions was assessed, highlighting the heterogeneity between the different AC. There was a greater accumulation of estimated cases in Catalonia, followed by Madrid, the Community of Valencia and Andalusia regions. The provinces of Madrid, Barcelona, Valencia, Alicante and Malaga have a higher number of estimated anti-HCV+ cases, in comparison to their neighboring provinces. Each region should provide resources and target the migrant communities at higher risk, which will depend on their context of immigration.

Strategies with a province, autonomic or State administrative level

The geographical distribution of positive cases also depends on the country of origin. Accordingly, the number of anti-HCV+ estimated cases from Romania is homogeneously distributed across all provinces in Spain, while cases in the Pakistani population are mainly found in the eastern Spanish provinces. It is remarkable that the province of Barcelona alone has 50% of the total estimated anti-HCV+ cases of people from Pakistan.

As every AC in Spain has its own Autonomous Health System and some AC are more affected than others, we recommend establishing prevention and control policies for hepatitis C that are targeted towards sub-populations that require more attention, after studying and understanding the immigrant context in every province.

However, a national or state screening program should also be proposed for migrants from a particular origin that are more homogeneously distributed across Spain, for example Romania. It should be highlighted that if such a measure was implemented that only targeted the Romanian immigrant population (with a prevalence of 3.2% in the country of origin), 19,200 estimated anti-HCV+ cases (13,400 viremic cases) could benefit from this screening. This would result in 40% of the total estimated cases among immigrants from endemic countries (≥ 2%). These data are comparable to the estimations of the ECDC of approximately 14,800 viremic cases amongst Romanians in

Spain (19).

However, a possible limitation in our study, which seems to be a controversial issue, is the percentage of viral clearance in relation to anti-HCV+. Although many studies have established that around 70% are viremic cases (19,20), recent preliminary data (from the national seroprevalence survey, performed at primary health centers [6]) report a marked reduction in this percentage. Nevertheless, these low figures should be studied and updated, detailing when they are available (6).

The ECDC recognized in its report (2016) that the use of HCV prevalence in the country of origin is a limitation for the calculation of estimated cases (19). Likewise, this assumption is also considered as the main limitation of our study. Although it could be justified by the lack of any other epidemiologic study at the national level that provides prevalence data by country of origin. In fact, only a few studies exist in Spain that consist of small cohorts followed by Tropical Diseases Hospital Units, which could overestimate the prevalence in these groups (25-27). On the other hand, seroprevalence surveys that target the Spanish general population are not usually representative of the immigrant groups and/or the results by country are not often available (7,8,28). Moreover, our data can benefit from the design of new studies that sample immigrates in Spain to confirm that the country HCV prevalence is similar to that of the people that have migrated. A recent systematic review and meta-analysis aimed to estimate HCV infection prevalence of migrants living in Spain, with different prevalence surveys conducted in our country in different regions (29). This study calculated the HCV prevalence in immigrants based on 26 studies conducted either at the community or primary care level or in maternity hospitals. However, pooled prevalence data are not provided that are separated by country of origin, there is only data by continent of origin, when available. This includes migrants from European countries such as those at high or moderate risk of HCV infection and those with the highest pooled prevalence (7.1%) among Sub-Saharan African migrants (3.1%) and lowest among Latin American migrants (0.2%). This meta-analysis concluded that the prevalence in the immigrant population was 1.6% (CI 95%: 0.8-3.0%), which is comparable to our global result of 1.75% (range: 0.96-2.47%). This study also reported a mean age of the cases studied as younger than 40 years old in the immigrant

population. This is in contrast to the mean age of the highest risk population in Spain, which was suggested by studies conducted in the general Spanish population as those born between 1955 and 1975 (30). Therefore, a screening scenario that targets the highest risk population in Spain could not include most of the cases in migrants.

Furthermore, our segregated figures by countries and small geographic areas also allow for comparisons in the expected burden of cases and the number of diagnosed/undiagnosed cases in our health services. In addition, the possible barriers to access the screening program could be identified in every region. It is well known that immigrants underutilize health services in comparison with the general population (31), even in countries with more permissive health care access laws for documented/undocumented immigrants. Other social-cultural barriers may be complex and have effects on accessing care (32).

The Spanish National Strategy of hepatitis C calls every AC to action to take measures on the Hepatitis C Prevention and Control programs. Furthermore, the immigrant population from endemic countries are not explicitly mentioned in the HCV screening national protocol (13). This could offer a great opportunity to add this target population in order to reach the goal of hepatitis C elimination in Spain. Viral hepatitis cannot be eliminated without reaching this population.

The data from our study may help to identify which groups of immigrants could benefit greatly from local screening programs since it reports data of the distribution of HCV cases among immigrants by region and province. Thus, providing useful information for each AC surveillance health system in order to facilitate the design of tailored HCV programs. Further studies that assess the HCV prevalence in migrants living in the different Spanish areas, the acceptability of HCV screening programs among migrants, or a cost-effectiveness analysis of these strategies in the context of each Autonomous Health System are necessary before implementing a screening program in migrant populations from high-endemic countries.

CONCLUSIONS

This study determined HCV estimated cases among migrants, demonstrating that they are an important group in order to address the elimination efforts. Targeted screening

efforts, which are based on subgroups according to the country of origin and the place of residence are needed to engage this population in prevention, treatment and care within Spain.

Note to the editor: analysis by Autonomous Community and countries with anti-HCV+ prevalence ≥ 2% can be consulted on-line in an extra-supplement (17 extra tables).

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Table 1. Immigrant population (≥ 15 years old) and estimated number of anti-HCV+ cases among the total migrant population and for the population that could enter the screening program in the scenarios C and D, from countries with an HCV+ prevalence ≥ 2%, ≥ 4% and ≥ 5%, in every autonomous community

Table 2. Immigrant population and number of estimated anti-HCV+ cases and CHC cases for every group at risk depending on the scenario of the screening program

Meeting the requirement for the scenario	Total population of adult immigrants	Estimated number of adult immigrants with anti-HCV+	Estimated number of adult immigrant with chronic hepatitis C (OR ARN+):	Estimated anti-HCV+ average prevalence
A	1,234,104	48,979	34,285	3.97%
B	1,193,641	48,029	33,620	4.02%
C	460,166	24,176	16,923	5.25%
D	260,239	15,646	10,952	6.01%

Scenario A: migrants from countries with an anti-HCV+ prevalence ≥ 2%, who could benefit from a screening program. Scenario B: migrants from countries with an anti-HCV+ prevalence ≥ 3%, who could benefit from a screening program. Scenario C: migrants from countries with an anti-HCV+ prevalence ≥ 4%, who could benefit from a screening program. Scenario D: migrants from countries with an anti-HCV+ prevalence ≥ 5%, who could benefit from a screening program.

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Table 3. Immigrant adult population and estimated number of anti-HCV+ in people from countries with an anti-HCV+ prevalence > 2-3% in every province in Spain (contribution is less with 100 people in every province)

Fig. 1. Different scenarios for a hypothetical opportunistic hepatitis C screening programme in immigrants from endemic countries depending on the set threshold of prevalence. Scenario A: proportion of estimated anti-HCV+ cases who could enter the screening (Yes/No), setting the threshold at ≥ 2%. Scenario B: proportion of estimated anti-HCV+ cases who could enter the screening (Yes/No), setting the threshold at ≥ 3%. Scenario C: proportion of estimated anti-HCV+ cases who could enter the screening (Yes/No), setting the threshold at ≥ 4%. Scenario D: proportion of estimated anti-HCV+ cases who could enter the screening (Yes/No), setting the threshold at ≥ 5%.

Fig. 2. Scenarios A, B, C and D for a hypothetical HCV screening programme: countries included in every scenario based on the HCV prevalence in each country of origin and the number of HCV cases in every origin.

Fig. 3.