

# Spatial Epidemiology of Hepatitis C Virus Infection in Egypt: Analyses and Implications

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Egypt has the highest hepatitis C virus (HCV) prevalence in the world (14.7%). The drivers of the HCV epidemic in Egypt are not well understood, but the mass parenteral antischistosomal therapy (PAT) campaigns in the second half of the 20th century are believed to be the determinant of the high prevalence. We studied HCV exposure in Egypt at a microscale through spatial mapping and epidemiological description of HCV clustering. The source of data was the 2008 Egypt Demographic and Health Survey. We identified clusters with high and low HCV prevalence and high and low PAT exposure using Kull-dorff spatial scan statistics. Correlations across clusters were estimated, and each cluster age-specific HCV prevalence was described. We identified six clusters of high HCV prevalence, three clusters of low HCV prevalence, five clusters of high PAT exposure, and four clusters of low PAT exposure. HCV prevalence and PAT exposure were not significantly associated across clusters (Pearson correlation coefficient [PCC] = 0.36; 95% confidence interval [CI] -0.12 to 0.71). Meanwhile, there was a strong association between HCV prevalence in individuals older than 30 years of age (who could have been exposed to PAT) and HCV prevalence in individuals 30 years of age or younger (who could not have been exposed to PAT) (PCC = 0.81; 95% CI 0.55-0.93). **Conclusion:** The findings illustrate a spatial variation in HCV exposure in Egypt. The observed clustering was suggestive of an array of iatrogenic risk factors, besides past PAT exposure, and ongoing transmission. The role of PAT exposure in the HCV epidemic could have been overstated. Our findings support the rationale for spatially prioritized interventions. (HEPATOLOGY 2014;60:1150-1159)

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**H**epatitis C virus (HCV), first identified in 1989,<sup>1</sup> is an RNA virus that is primarily transmitted through direct percutaneous exposure to blood, such as through blood transfusions, sharing of needles, and accidental percutaneous occupational exposures common in healthcare workers and dentists.<sup>2</sup> After the discovery of this virus, a flurry of studies around the world was conducted to document its distribution and prevalence in human populations.<sup>3</sup>

It is now well established that HCV is a global health challenge, with an estimated 130-170 million chronic infections (2-3% of the global population).<sup>3,4</sup> An anomaly in the distribution of HCV infection, however, was discovered in Egypt, where the prevalence was ~10-fold higher than that in other countries.<sup>5,6</sup>

The unusual high prevalence in Egypt has stimulated research to identify the factor or factors that contributed to such widespread HCV transmission in this country. Based largely on indirect evidence,<sup>7-12</sup> it was believed that an extensive iatrogenic exposure to HCV occurred during the mass parenteral antischistosomal

*Abbreviations:* CAPMAS, Egyptian Central Agency for Public Mobilization and Statistics; CI, confidence interval; CIA, chemiluminescent microplate immunoassay; EDHS, Egypt Demographic and Health Survey; ELISA, enzyme immunoassay; GIS, Geographical information system; GPS, global positioning system; HCV, hepatitis C virus; PAT, parenteral antischistosomal therapy; PCC, Pearson correlation coefficient; RR, relative risk; RT-PCR, real-time reverse-transcription polymerase chain reaction.

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therapy (PAT) campaigns in Egypt, from as early as 1921, but most intensively during the 1960s and 1970s.<sup>11</sup> These campaigns were phased out across Egypt by the late 1970s and early 1980s.<sup>11</sup>

HCV prevalence levels in Egypt indicate uneven geographic distribution, with higher HCV prevalence found in rural areas compared to urban settings,<sup>13-15</sup> and in Lower Egypt compared to the rest of the country.<sup>11,15</sup> The factors contributing to the spatial heterogeneity are not well understood, but disparity in the intensity of past PAT campaigns has been proposed as a cause of the geographical variation.<sup>10-12,16</sup> A detailed knowledge of the geographical distribution of HCV exposure in Egypt may aid both an elucidation of the drivers of past and present infection transmission and identification of areas with the highest disease burden, where interventions could be prioritized.

Aligned with the concept of “Know your epidemic, know your response,” a successful framework and strategy in HIV control,<sup>17</sup> we studied HCV prevalence in Egypt at a microscale level through spatial mapping and epidemiological description of the clustering of HCV exposure. With the ultimate aim of developing a more effective strategy to control HCV infection transmission in Egypt, and to clarify the potential drivers of HCV transmission, we implemented a novel approach to analyze the geographical and epidemiological differences in areas where the probability of HCV exposure was higher or lower, and in areas where PAT exposure was higher or lower.

## Materials and Methods

**Data Sources.** The main source of data in our study was the Egypt Demographic and Health Survey (EDHS) conducted in 2008,<sup>6</sup> one of the largest nationally representative studies of HCV infection ever implemented. The survey used a stratified three-stage random cluster sampling to enroll more than 19,500 households. The first stage involved selecting primary sampling units such as towns in urban areas and villages in rural areas. The second stage included mapping and household listing,

where the global positioning system (GPS) was used to generate the geographical information system (GIS) dataset that stored the geographical coordinates of each of the EDHS clusters of households. The final stage of the sampling involved the selection of the household sample.

All women and men aged 15-59 present in the sampled households were eligible for the survey, and 11,126 (87.1%) of these individuals agreed to and were given an HCV biomarker test. The HCV testing protocol included an initial round of testing to detect the presence of antibodies against the virus. A third-generation enzyme immunoassay (ELISA), Adlatis EIA-gen HCV Ab kit, was used to test for antibodies against HCV, and then confirmed by a chemiluminescent microplate immunoassay (CIA) when positive.<sup>6</sup> Quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR) was also used at the Egyptian Ministry of Health Central Laboratory for the detection of HCV RNA using the RealTime m2000 system (Abbott Laboratories, Abbott Park, IL).<sup>6</sup> Further methodological details related to specimen handling and laboratory methods employed for the detection of HCV antibody and HCV RNA can be found in El-Zanaty and Way.<sup>6</sup>

We used the dichotomous HCV antibody serological status for each individual as the response outcome in our statistical analyses because of our epidemiological interest in investigating exposure to this virus, rather than chronic infection. HCV prevalence in this article refers strictly to the proportion of individuals who are serologically antibody-positive for HCV. We also used the binary answer to the question: “Ever had received an injection to treat for schistosomiasis” as the measure of PAT exposure. Further details related to the EDHS methodology can be found in El-Zanaty and Way.<sup>6</sup>

**Spatial Cluster Analysis.** We identified spatial clusters of high and low HCV prevalence, as well as spatial clusters of high and low PAT exposure, using a spatial scan statistical analysis,<sup>18</sup> implemented in the SaTScan software.<sup>19,20</sup> Scan statistics are one of the most widely used statistical methods for cluster detection in epidemiology.<sup>21,22</sup> Briefly, scan statistical analysis uses circular windows of varying radii that span the study region to

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identify areas with exposure clustering. Since we aimed to identify localized clusters, a maximum circular window of 30 Km in radius was used for scanning clusters of HCV exposure and PAT exposure. The circular window was varied continuously in both location and radius size. The radius size was varied from 0 Km up to the fixed maximum radius (30 Km), thus creating and testing a large number of distinct potential clusters of diverse sizes. Each potential cluster was tested using a likelihood ratio test to determine the statistical significance against the null hypothesis of spatial randomness. Clusters with  $P < 0.05$ , calculated through Monte Carlo simulations, were identified as statistically significant, and they were analyzed further for additional epidemiological description.

**Cluster Characterization and Correlations.** After a cluster was identified, the strength of the clustering was estimated using the relative risk (RR) of HCV infection within the cluster versus the area outside the cluster. The fraction of the population living within the cluster and HCV prevalence were also estimated for each cluster. Correlation between HCV prevalence and PAT exposure across the identified clusters was determined using Pearson correlation coefficient (PCC). Age-specific prevalence of HCV exposure for each cluster was described. As mentioned above, PAT campaigns were phased out across Egypt by the late 1970s and early 1980s. Therefore, we assumed that those younger than 30 years of age were virtually unexposed to PAT. This age cutoff was then used to assess the association between HCV prevalence in individuals older than 30 years of age (individuals who could have been exposed to PAT) and HCV prevalence in individuals 30 years of age or younger (individuals who could not have been exposed to PAT). The correlation between HCV prevalence in individuals older than 30 years and HCV prevalence in individuals aged 30 years or younger was calculated across the clusters using PCC. These statistical analyses were conducted using SAS v. 9.3.<sup>23</sup>

**Geographical Distribution of HCV Incidence.** We generated a mapping by governorate of the average annual HCV incidence rate experienced by the living Egyptian cohort, using a methodology introduced and developed by Leske et al.,<sup>24</sup> among others,<sup>25</sup> and applied recently by Miller and Abu-Raddad to study HCV incidence in Egypt at the national level.<sup>26</sup> Briefly, the incidence rate was estimated from the age-stratified HCV prevalence per governorate. We assumed that the incidence risk ( $\Pi$ ) was a cumulative probability, ranging from 0 to 1, of HCV infection over a certain period of time, which we took to be a

5-year age range. It follows that the cumulative probability of incident cases for age interval  $x$  is given by

$$\Pi_x = \frac{P_{x+1} - P_x}{D_x},$$

where  $P_x$  is the prevalence proportion for age interval  $x$ ,  $P_{x+1}$  is the prevalence proportion for the next older age group ( $x+1$ ), and  $D_x$  is the range of ages in interval  $x$ .

The total population size for each governorate was obtained from the Egyptian Central Agency for Public Mobilization and Statistics (CAPMAS), based on 2006 census data.<sup>27</sup> To estimate the fraction of the population in each 5-year age group for individuals aged 15-59 in every governorate, we assumed that these proportions were the same as the proportions estimated for the national sample in the EDHS.

GIS analyses, including the production of cartographic displays, were performed with ArcGIS v. 9.2.<sup>28</sup>

## Results

**Spatial Clustering of HCV Infection.** HCV prevalence in responders aged 15-59 years, main outcome in our analysis, was 14.7% (95% confidence interval [CI] 13.9-15.5%). HCV RNA positivity prevalence was 9.8%.<sup>6</sup> We identified six clusters of high prevalence of HCV exposure (Fig. 1A; Table 1): Cluster 1, located at the interface between the governorates of Beni Suef and Minya (HCV prevalence of 33.1%); Cluster 2, Faiyum (23.8%); Cluster 3, Dakahlia (23.4%); Cluster 4, Kafr el-Sheikh (26.5%); Cluster 5, Monufia (22.3%); and Cluster 6, Minya (23.1%). We also identified three clusters of low prevalence of HCV exposure (Fig. 1B): Cluster 7, Alexandria (7.5%); Cluster 8, Cairo (9.4%); and Cluster 9, Luxor (5.8%). Furthermore, 20.8% (95% CI 20.0-21.6%) of the total population of Egypt resided within clusters of high HCV prevalence, whereas 17.6% (95% CI 16.9-18.4%) of the total population resided within clusters of low HCV prevalence.

**Spatial Clustering of PAT Exposure.** The proportion of the population that was ever exposed to PAT was 9.2% (95% CI 8.6-9.7%). We identified five clusters of high PAT exposure (Fig. 1C): Cluster 10, located at the interface between the governorates of Beni Suef and Minya (PAT exposure of 23.9%); Cluster 11, Sohag (19.4%); Cluster 12, Beni Suef (17.1%); Cluster 13, Kafr el-Sheikh (22.3%); and Cluster 14, Asyut (17.8%). In addition, we identified four clusters of low PAT exposure (Fig. 1D): Cluster 15, Cairo

**Table 1. Hepatitis C Virus (HCV) and Parenteral Antischistosomal Therapy (PAT) Clustering Description**

	Cluster	Fraction of the Population Within Cluster (%)	HCV Prevalence (%)	PAT Prevalence (%)	Relative* Risk	P Value
Clusters of high HCV prevalence	1, Beni Suef/Minya	2.6 (2.3-2.9)	33.1 (27.7-38.8)	17.8 (13.5-22.7)	2.4	<0.001
	2, Faiyum	4.1 (3.7-4.5)	23.8 (19.9-30.0)	12.8 (9.9-16.3)	2.0	<0.001
	3, Dakahlia	4.2 (3.8-4.6)	23.4 (19.6-27.5)	9.9 (7.3-13.0)	1.7	<0.001
	4, Kafr el-Sheikh	2.5 (2.2-2.8)	26.5 (21.4-32.1)	14.1 (10.2-18.7)	1.7	<0.001
	5, Monufia	4.6 (4.3-5.1)	22.3 (18.8-26.1)	4.1 (2.6-6.2)	1.6	0.0018
Clusters of low HCV prevalence	6, Minya	2.7(2.4-3.0)	23.1 (18.5-28.4)	9.7 (6.6-13.8)	1.8	0.018
	7, Alexandria	5.5 (5.1-6.0)	7.5 (5.5-9.8)	7.5 (5.5-9.9)	0.5	<0.001
	8, Cairo	2.8 (2.5-3.1)	9.4 (7.7-11.4)	3.7 (2.6-5.0)	0.7	0.011
	9, Luxor	9.3 (8.8-9.9)	5.8 (3.5-9.0)	9.1 (6.1-12.9)	0.4	0.013
Clusters of high PAT exposure	10, Beni Suef/Minya	2.8 (2.5-3.1)	26.8 (21.9-32.1)	24.1 (19.5-29.4)	2.7	<0.001
	11, Sohag	3.4 (3.1-3.7)	9.3 (6.6-12.7)	19.5 (15.6-23.9)	2.2	<0.001
	12, Beni Suef	4.0 (3.6-4.3)	18.0 (14.9-22.3)	17.7 (14.2-21.7)	2.0	<0.001
	13, Kafr el-Sheikh	12.4 (10.5-14.7)	16.5 (10.8-23.8)	22.3 (15.7-30.1)	3.8	<0.001
	14, Asyut	2.3 (2.0-2.6)	9.5 (6.2-13.8)	18.0 (13.4-23.3)	2.0	0.026
Clusters of low PAT exposure	15, Cairo	9.1 (8.6-9.7)	10.6 (8.8-12.7)	2.5 (1.6-3.7)	0.3	<0.001
	16, Alexandria	2.1 (1.9-2.4)	6.7 (4.5-9.6)	3.7 (2.0-6.0)	0.4	<0.001
	17, Monufia	5.3 (5.0-5.8)	20.6 (17.4-24.0)	3.3 (2.0-5.1)	0.4	<0.001
	18, Suez	3.7 (3.4-4.1)	12.2 (8.3-17.0)	0	0.0	<0.001

Includes HCV prevalence, PAT exposure, and P value for each identified cluster using spatial scan statistics. Clusters are organized in descending order starting from the most likely cluster.

\*Relative risk (RR) of HCV exposure for HCV clusters or RR of PAT exposure for PAT clusters.

(PAT exposure 2.5%); Cluster 16, Alexandria (3.6%); Cluster 17, Monufia (3.3%); and Cluster 18, Suez (0%). Furthermore, 13.1% (95% CI 12.5-13.8%) of the total population was located within clusters of high PAT exposure, whereas 20.8% (95% CI 20.0-21.6%) of the total population was located within clusters of low PAT exposure.

**Comparisons Between Clusters of HCV Infection and PAT Exposure and Correlation Between HCV Exposure and PAT Exposure.** Cluster 1-Beni Suef/Minya, which had the largest relative risk of HCV infection (RR = 2.4), and implicitly the largest HCV prevalence (33.1%), overlapped with a cluster of high PAT exposure (Cluster 10). In contrast, PAT exposure in the high HCV prevalence clusters of Faiyum, Dakahlia, and Minya was not statistically significantly different from the national PAT exposure. Moreover, the high PAT exposure clusters of Sohag and Asyut had low HCV prevalence compared to the national level (9.4% and 9.5%, respectively).

Figure 2A illustrates a comparison between HCV prevalence and PAT exposure for each cluster identified by scan statistics. Clusters with high or low HCV prevalence, and clusters with high or low PAT exposure, were scattered, with no evident overall pattern of an association between HCV prevalence and PAT exposure. There was a weak association, and with a broad confidence interval consistent with the null hypothesis of no correlation, between HCV prevalence per cluster and the corresponding PAT exposure

(PCC = 0.36; 95% CI -0.12 to 0.71;  $P = 0.14$ ). There was a high HCV prevalence cluster of 22.3%, located in the governorate of Monufia (Cluster 5), that had also a low PAT exposure of 4.1% (Fig. 2A). Additionally, a cluster of low PAT exposure in the Suez governorate (Cluster 18), which contained no individuals reporting a PAT exposure, had an HCV prevalence of 12.2%, nearly as high as the national HCV prevalence.

**Patterns of Age-Specific HCV Prevalence and Correlation Between HCV Exposure Among the Old and Young.** The analysis of the age-specific prevalence of HCV exposure reflected regional variations among the clusters identified by scan statistics. The influence of PAT on the age distribution of HCV prevalence was evident in Cluster 1-Beni Suef/Minya, which had the largest HCV prevalence and a high PAT exposure. The epidemiological profile observed in this cluster showed a curve where HCV prevalence was low and constant for young individuals followed by a sharp rise for older individuals, indicative of a cohort effect<sup>11</sup> (Fig. 3B). This cohort effect, however, was not observed in other clusters, such as the low PAT exposure clusters (Fig. 3D), where the age-specific HCV prevalence increased steadily with age, indicative of a steady exposure to HCV infection. This pattern of steady increase with age is illustrated in a high HCV prevalence cluster that also had a low PAT exposure (Cluster 5, Monufia; Fig. 3C), and a similar pattern was observed in the other clusters with high HCV prevalence.

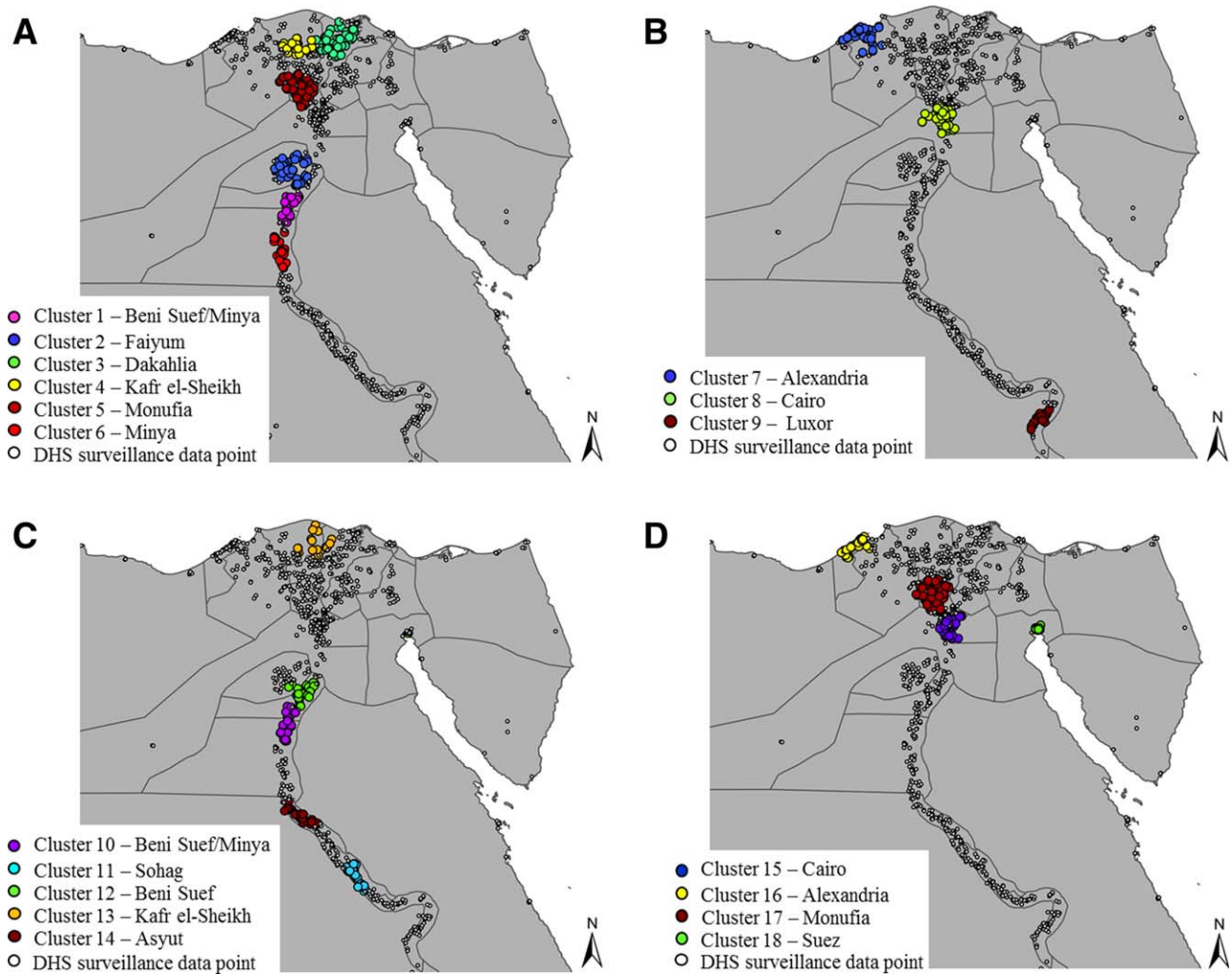


Fig. 1. Geographical distribution of the clusters of high (A) and low (B) hepatitis C virus (HCV) prevalence, and of high (C) and low (D) parenteral antischistosomal therapy (PAT) exposure. The dots indicate locations where the surveys were conducted.

We identified a strong association between HCV prevalence among individuals older than 30 years of age and HCV prevalence in individuals 30 years of age or younger across the clusters of high and low HCV prevalence and high and low PAT exposure (PCC = 0.81; 95% CI 0.55-0.93;  $P < 0.001$ ; Fig. 2B). Figure 2B also highlights the remarkably high HCV prevalence in young individuals in Cluster 1, Beni Suef/Minya (15.4%; 95% CI 10.0-22.5%) and Cluster 6, Minya (14.6%; 95% CI 9.3-21.4%).

**Geographical Pattern of HCV Incidence.** The average annual HCV incidence rate that has been experienced by the living cohort in Egypt ranged from 1.4 cases (95% CI 0.0-4.0) per 1,000 person-years in the governorate of New Valley, to 12.8 cases (95% CI 5.2-18.6) per 1,000 person-years in the governorate of Kafr el-Sheikh (Fig. 4). The largest HCV incidence rate in Egypt was in the governorates of Kafr el-Sheikh (12.8 cases [95% CI 5.2-18.6] per 1,000 person-

years), Dakahlia (11.7 cases [95% CI 6.0-17.3] per 1,000 person-years), Beni Suef (12.5 cases [95% CI 6.7-17.1] per 1,000 person-years), and Faiyum (12.1 cases [95% CI 5.5-17.9] per 1,000 person-years). These regions overlapped with most of the identified high HCV prevalence clusters (Figs. 1A, 3).

Similarly, there was an overlap between regions with low HCV incidence rate, such as the governorates of Alexandria (3.2 cases [95% CI 0.5-10.5] per 1,000 person-years) and Cairo (5.8 cases [95% CI 2.2-11.9] per 1,000 person-years), and the low HCV prevalence clusters.

## Discussion

Egypt has by far the highest national-level HCV prevalence in the world, with more than 14% of the Egyptian adult population having been exposed to the virus.<sup>6,15</sup> This analysis of the spatial distribution of

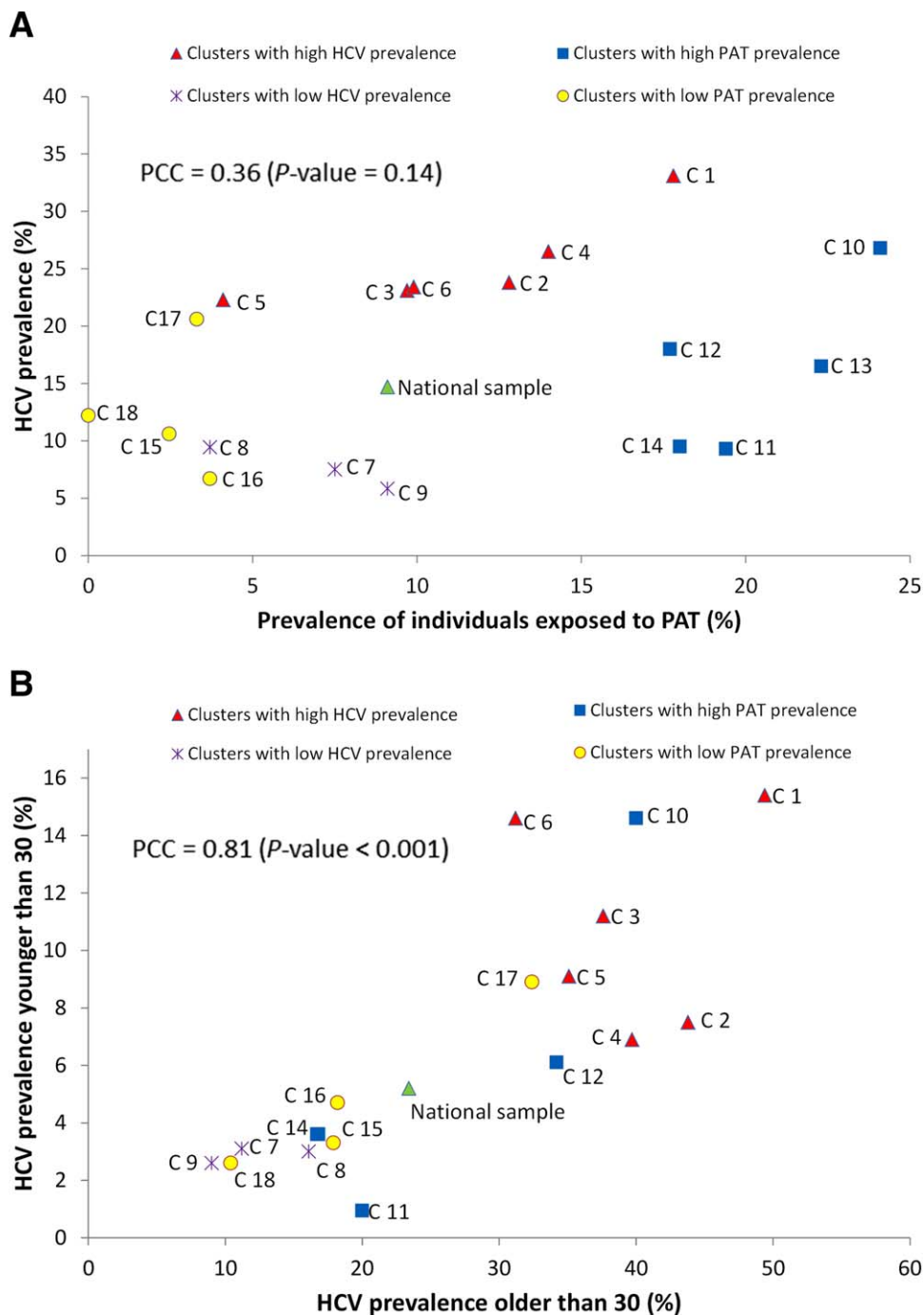


Fig. 2. Comparisons and associations across clusters. (A) Comparison between hepatitis C virus (HCV) prevalence and parenteral anti-schistosomal therapy (PAT) exposure across all HCV exposure or PAT exposure clusters identified in this analysis. (B) Comparison between HCV prevalence among individuals 30 years old and older and HCV prevalence among individuals younger than 30 years in clusters of high and low HCV prevalence and high and low PAT exposure. Correlations were determined using Pearson correlation coefficient (PCC).

HCV exposure suggests a clustered HCV transmission in this country, possibly reflecting microepidemics, or a series of large and small outbreaks of different intensities throughout the previous decades. About 21% of the Egyptian population today resides within clusters of high HCV prevalence, whereas 18% resides in clusters of low HCV prevalence.

Contrary to expectation, our cluster-based analyses suggested a rather weak and statistically not significant association between HCV prevalence and previous PAT exposure (Fig. 2A). Most of the clusters of high

PAT exposure did not geographically overlap with the clusters of high HCV prevalence (Fig. 1). A number of the high HCV prevalence clusters had low PAT exposure, and a number of the high PAT exposure clusters had low HCV prevalence. In Suez, a cluster where there were no reported PAT exposures, nor a history of PAT campaigns, HCV prevalence was nearly as high as the national HCV prevalence. The absence of evidence of a strong association between HCV prevalence and PAT exposure does not support the common belief that PAT exposure is the dominant

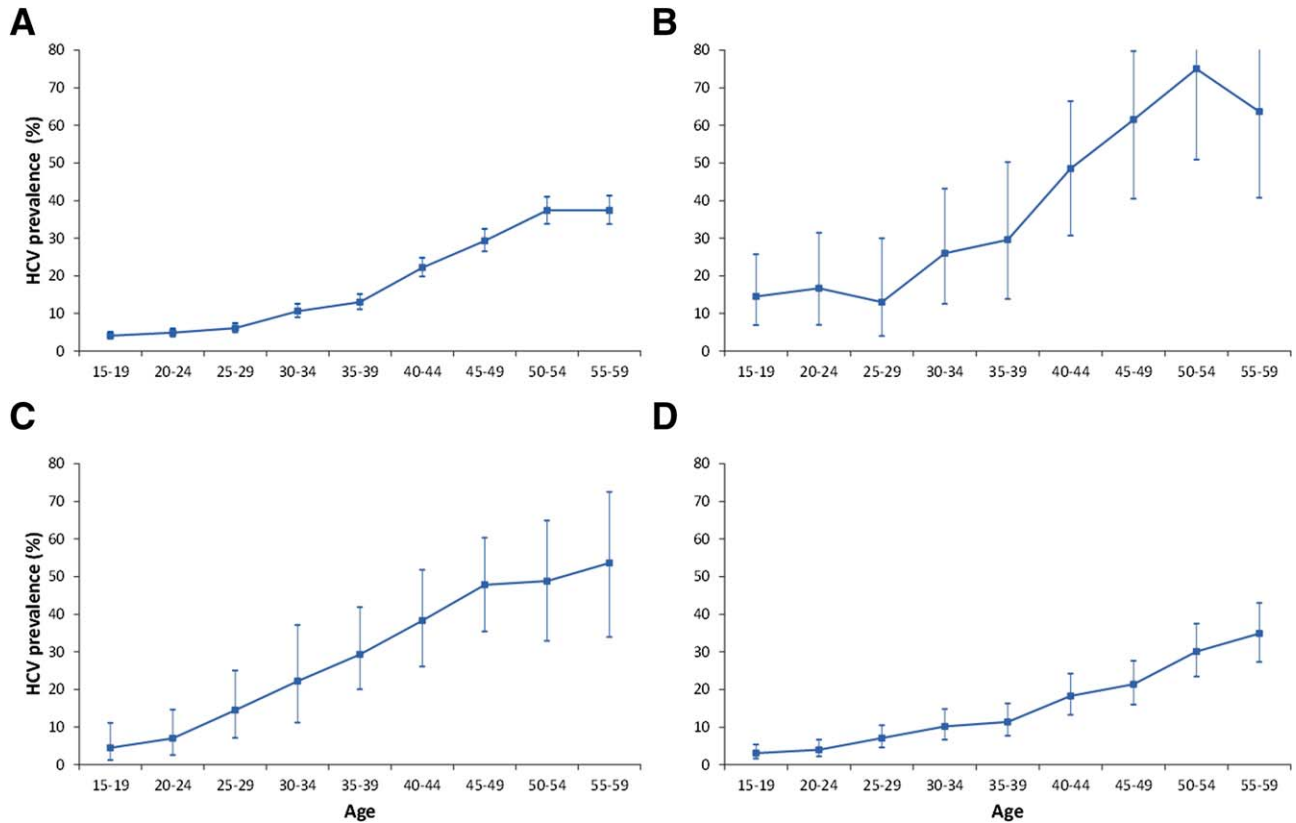


Fig. 3. Patterns of the age-specific prevalence of hepatitis C virus (HCV) infection. Age-specific prevalence of HCV infection in (A) the national sample; (B) the high HCV prevalence Cluster 1, Beni Suef/Minya; (C) the high HCV prevalence Cluster 5, Monufia; and (D) all clusters of low parenteral antischistosomal therapy (PAT) exposure.

determinant of the high HCV prevalence in the Egyptian population. In fact, less than 10% of the EDHS population sample reported an ever exposure to PAT, and less than one-third of those exposed to PAT were actually infected with HCV.

The age-specific prevalence of HCV has been proposed as one of the strongest signatures of the role of the past PAT campaigns in driving HCV infection exposure in Egypt.<sup>11,14</sup> The cluster-based age-specific prevalence analyses support only a partial role for the PAT campaigns. The cohort effect of PAT campaigns can be seen,<sup>11</sup> for example, in the Beni Suef/Minya cluster (Cluster 1). Nonetheless, most clusters do not support a strong cohort effect that is to be expected if PAT exposure was the dominant determinant of the large HCV prevalence in Egypt. Indeed, the largely linear age-specific HCV prevalence across most clusters is consistent with ongoing exposures to HCV infection throughout the life of the living Egyptian cohort (Fig. 3).

The strong association between HCV prevalence among those older than 30 years, and those younger than 30 years, further affirms the interpretation of considerable ongoing HCV incidence in Egypt. This strong association also suggests that PAT campaigns,

though playing a major role in contributing to the reservoir of HCV infection in this country, are only one factor, among others, that contributed to the widespread HCV transmission in this country. PAT campaigns were phased out by the late 1970s and early

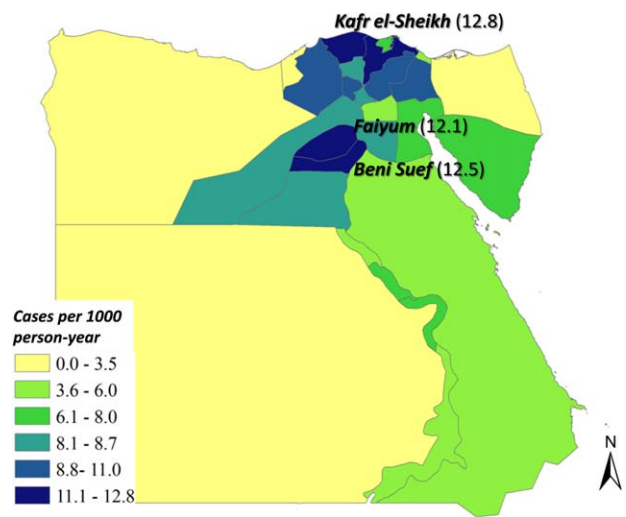


Fig. 4. Geographical distribution of the estimated average annual hepatitis C virus (HCV) incidence rate that has been experienced by the living adult Egyptian cohort.

1980s across Egypt. Those younger than 30 years of age were virtually unexposed to PAT, but their HCV exposure prevalence was strongly associated with that of those who are older than 30 years of age. This finding is consistent with the existence of other modes of exposure to the infection that have facilitated HCV transmission from its large reservoir in the older population, to those younger than 30 years of age, after the end of the PAT campaigns.

Interestingly, even in the Beni Suef/Minya cluster (Cluster 1), the cluster that best supports a strong role for PAT exposure through a manifest cohort effect (Fig. 3B), and by being a cluster of both high HCV prevalence and high PAT exposure (Fig. 1A,C), there is a remarkably high HCV prevalence among those younger than 30 years of age (Fig. 2B). This is further evidence that other modes of exposure have contributed extensively to HCV transmission across Egypt, even in areas where the PAT role was most intense.

The fact that PAT is a major factor, but only one factor among others, to explain the HCV epidemic in Egypt, poses a question about these other modes of exposure. However, with the different kinds of possible specific parenteral exposures, such as different healthcare procedures, and confounders, and the large reservoir of infection, it may be difficult to pinpoint the specific exposures through which persons acquired HCV infection. The cross-sectional design of most available studies, and lack of sufficiently detailed questionnaires, further limits the ability to determine the specific exposure risk factors.<sup>13</sup> For example, statistical analyses of the EDHS data identified several statistically significant formal and informal healthcare exposures at the bivariate level of analysis, but only three of these exposures remained significant at the multivariate level after adjustment for confounders.<sup>13</sup> These three modes of exposure were PAT, female genital mutilation, and blood transfusion; and were not necessarily statistically significant in both urban and rural populations.<sup>13</sup> The odds ratios were also not large, and the proportion of HCV infections attributable to PAT was meager, at ~10%.<sup>13</sup>

Despite the challenge in identifying specific exposures, a recent systematic review of HCV prevalence in Egypt supported a strong role for various exposures in the formal and informal healthcare settings.<sup>15</sup> Multiple studies in Egypt to date have identified medical-care exposures as risk factors for HCV infection such as a history of invasive procedures, hospitalization, blood transfusion, injections, perinatal care, dialysis, and dental work.<sup>8,29-31</sup> Community and informal health provider-related exposures have also been suggested as

risk factors for HCV infection such as male circumcision, female genital mutilation, cauterization, and injections.<sup>8,13,30,32</sup> Mother-to-child transmission may also explain part of the HCV incidence.<sup>33,34</sup> A number of studies have also suggested intrafamilial transmissions and household exposures.<sup>35,36</sup>

Therefore, the totality of the different lines of evidence supports the conclusion that PAT is only one factor among others that determined the high HCV prevalence among the Egyptian population. These lines of evidence include the nature of HCV prevalence and PAT exposure clustering; the at-best mild association between HCV prevalence and PAT exposure across clusters; the largely linear age-specific HCV prevalence in most clusters; the strong correlation between HCV prevalence among older and younger populations across clusters; the volume of studies linking HCV acquisition to formal and informal healthcare procedures and intrafamilial, household, and community exposures; and the small fraction of infections that can be attributed to PAT. Collectively, the data to date suggest that the role of PAT in the HCV epidemic in Egypt may have been overstated and perhaps overshadowed concurrent iatrogenic exposures occurring at the time of the PAT campaigns and thereafter.

PAT exposures may have been only a subset of exposures by which persons acquired the infection during the decades in which PAT was administered. The PAT experience in Egypt is possibly only one manifestation of the limited infection control and blood-borne infection awareness that existed at the time. Although infection control and safety measures have improved steadily since the discovery of the epidemic, the totality of the evidence suggests also that appreciable HCV transmission is likely ongoing up to the present.

Several study limitations may have affected our results. Given the multiple logistical difficulties in conducting DHS studies, some of our measures could have been affected by inherent biases in the data, such as due to response rate or refusal of HCV testing with prior knowledge of acquired infection.<sup>37-39</sup> A potential bias in our study is the GPS displacement process of the EDHS sampling data points, used to preserve the confidentiality of the data points,<sup>40</sup> which could have impacted the precision of the geographical location of the clusters (by a few kilometers at most). Moreover, the EDHS data do not include information regarding patterns of mobility of the interviewed individuals, and it would be challenging to reliably link external information about population mobility with the EDHS data to conduct meaningful analyses. Therefore, we could not incorporate patterns of mobility



and migration, and some people may have been exposed to HCV infection in areas different from their current location.

HCV incidence rates were calculated from the EDHS HCV prevalence, and therefore these estimates reflect averages over lifelong exposures, and should not be interpreted as current HCV incidence rates.<sup>41</sup> Despite all of the above limitations, the DHS studies are among the most methodologically rigorous surveys available globally,<sup>42</sup> and these limitations are not likely to significantly affect our results or their interpretation.

Our study, which used a novel analytical approach implemented on one of the largest nationally representative databases of HCV infection ever assembled, highlights the spatial variation of HCV infection exposure in Egypt. Our results may suggest that spatial clustering of HCV infection exposure could be an intrinsic feature of the epidemiology of this infection, given the nature of the exposures that lead to acquisition. Accordingly, the spatial statistical approach implemented here may be useful for other countries where HCV prevalence is considerable, such as Cameroon, Congo, Gabon, Guinea, Malawi, Mongolia, Pakistan, and Romania.<sup>43</sup> Examination of the geographical patterns of HCV infection exposure in these countries could provide fresh analytical insights about the drivers of infection transmission in generalized epidemics, and may facilitate a targeted strategy for prioritizing control interventions. This is especially relevant with the growing pipeline of highly efficacious and curative, but cost-prohibitive, treatments for HCV infection.<sup>44</sup> A targeted approach focused on settings of most intense HCV transmission will likely be more cost-effective than a broad one at the national level.

In conclusion, our study has illustrated a considerable local variation in HCV infection exposure across Egypt. The exact drivers of such rich and complex epidemiological topography are not certain. However, the observed spatial clustering and the analyses of these clusters indicate an array of iatrogenic risk factors besides past PAT exposure, as well as appreciable ongoing HCV transmission fueled by a large human reservoir of infection. Our findings support program efficiency of spatially targeted prevention strategies in Egypt, which can benefit from the presented characterization of exposure clustering, and the growing availability of highly efficacious treatments for HCV infection.

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